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# Long-term outcomes, including fetal and neonatal prognosis, of renal oligohydramnios: a retrospective study over 22 years

--Manuscript Draft--

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| Abstract: | Objective<br><br>To assess the long-term outcome of renal oligohydramnios and risk factors for fetal, neonatal, and postneonatal death.<br><br>Study design<br><br>This retrospective cohort study included fetuses with prenatally detected renal oligohydramnios between 2002 and 2023. Patients who were lost to follow-up were excluded. Fetal, neonatal, and long-term outcomes were evaluated, and their risk factors were analyzed.<br><br>Results<br><br>Of 131 fetuses with renal oligohydramnios, 46 (35%) underwent a termination of pregnancy, 11 (8%) had an intrauterine fetal death, 26 (20%) had a neonatal death, nine (7%) had a postneonatal death, and 39 (30%) survived. Logistic regression analyses showed that an earlier gestational age at onset (odds ratio 1.16, 95% confidence interval (CI) 1.01–1.37) was significantly associated with intrauterine fetal death, and anhydramnios (odds ratio 12.7, 95% CI 1.52–106.7) was significantly associated with neonatal death as a prenatal factor. Although neonatal survival rates for bilateral renal agenesis, bilateral multicystic dysplastic kidney (MCDK), and unilateral MCDK and contralateral renal agenesis were lower than for other kidney diseases, one case of bilateral renal agenesis and two of bilateral MCDK survived with fetal intervention. Kaplan–Meier overall survival rates were 57%, 55%, and 51% for 1, 3, and 5 years, respectively. In the Cox proportional hazards model, birth weight <2000 g (hazard ratio 7.33, 95% CI 1.48–36.1) and gastrointestinal comorbidity (hazard ratio |

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| | 4.37, 95% CI 1.03–18.5) were significant risk factors for postneonatal death.<br><br>Conclusion<br><br>Long-term survival of renal oligohydramnios is a feasible goal and its appropriate risk assessment is important. |
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12 March 2024

Paul Graham Fisher, MD, Editor-in-Chief

Thomas R. Welch, MD, Associate Editor

*The Journal of Pediatrics*

Dear Drs. Fisher and Welch:

Please find enclosed our manuscript titled "**Long-term outcomes, including fetal and neonatal prognosis, of renal oligohydramnios: a retrospective study over 22 years**" which we would like to be considered for publication as an Original Article in *The Journal of Pediatrics*. Our previous manuscript (manuscript no: 2024224) which was submitted to *The Journal of Pediatrics* on January 30, 2024 was rejected on February 5, 2024, with a recommendation to expand the report to include long-term outcomes. We appreciate this opportunity and have accordingly changed the study design, so would like to resubmit the manuscript after its revision.

Renal oligohydramnios (also known as Potter's syndrome/sequence) tends to be considered a disorder with a uniformly poor prognosis, as indicated by the high rate of pregnancy termination (29%–61%). This is due to the lack of evidence for prenatal prediction of poor prognosis and information on the long-term outcome of fetuses with renal oligohydramnios.

We performed a retrospective cohort study on prenatal, neonatal, and long-term outcomes of fetuses with prenatally detected renal oligohydramnios at our institution over 22 years. We also analyzed the risk factors for intrauterine fetal death (IUFD), neonatal mortality, and postneonatal mortality, respectively. Of 131 fetuses, 46 (35%) underwent termination of pregnancy, 11 (8%) had IUFD, 26 (20%) had neonatal death, 9 (7%) had postneonatally death, and 39 (30%) were alive. The logistic regression analysis identified an earlier gestational age at onset as a significant risk factor for IUFD, and anhydramnios was a significant risk factor for neonatal death as a perinatal factor. Overall survival rates were 57, 55, and 51% in 1, 3, 5 years from birth, respectively. The Cox proportional hazards model showed that the birth weight <2000 g and gastrointestinal comorbidity were the significant risk factors for postneonatal death. In conclusion, accurately assessing primary renal disease and risk factors for predicting the prognosis in each individual case, rather than considering renal oligohydramnios as a disease with a uniformly poor prognosis, is important. Long-term survival of renal oligohydramnios is a feasible goal, even in severe cases such as bilateral renal agenesis and bilateral renal MCDK, with recent improvements in neonatal medicine and the advent of fetal interventions. These results could be useful in counseling the families of these

fetuses.

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We hope that you will find our manuscript suitable for publication in *The Journal of Pediatrics* and hope to hear from you at your convenience.

Sincerely,

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# Long-term outcomes, including fetal and neonatal prognosis, of renal oligohydramnios: a retrospective study over 22 years

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**Key words**: Potter syndrome, fetal intervention, renal agenesis, congenital anomalies of the kidney and urinary tract, lower urinary tract obstruction

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**Data Sharing Statement:** Deidentified individual participant's data will not be made available.

**Abstract**

**Objective:** To assess the long-term outcome of renal oligohydramnios and risk factors for fetal, neonatal, and postneonatal death. **Study design:** This retrospective cohort study included fetuses with prenatally detected renal oligohydramnios between 2002 and 2023. Patients who were lost to follow-up were excluded. Fetal, neonatal, and long-term outcomes were evaluated, and their risk factors were analyzed. **Results:** Of 131 fetuses with renal oligohydramnios, 46 (35%) underwent a termination of pregnancy, 11 (8%) had an intrauterine fetal death, 26 (20%) had a neonatal death, nine (7%) had a postneonatal death, and 39 (30%) survived. Logistic regression analyses showed that an earlier gestational age at onset (odds ratio 1.16, 95% confidence interval (CI) 1.01–1.37) was significantly associated with intrauterine fetal death, and anhydramnios (odds ratio 12.7, 95% CI 1.52–106.7) was significantly associated with neonatal death as a prenatal factor. Although neonatal survival rates for bilateral renal agenesis, bilateral multicystic dysplastic kidney (MCDK), and unilateral MCDK and contralateral renal agenesis were lower than for other kidney diseases, one case of bilateral renal agenesis and two of bilateral MCDK survived with fetal intervention. Kaplan–Meier overall survival rates were 57%, 55%, and 51% for 1, 3, and 5 years, respectively. In the Cox proportional hazards model, birth weight <2000 g (hazard ratio 7.33, 95% CI 1.48–36.1) and gastrointestinal comorbidity (hazard ratio 4.37, 95% CI 1.03–18.5) were significant risk factors for postneonatal death. **Conclusion:** Long-term survival of renal oligohydramnios is a feasible goal and its appropriate risk assessment is important.

## Introduction

Potter syndrome is a disorder with a poor prognosis and is characterized by bilateral renal agenesis and pulmonary hypoplasia due to renal oligohydramnios [1]. Similar conditions can also be caused by severe congenital kidney disorders other than bilateral renal agenesis, such as polycystic kidney, hypoplastic kidney, dysplastic kidney, including multicystic dysplastic kidney (MCDK), obstructive uropathy, and renal tubular dysplasia, also known as "Potter sequence" [2,3]. The neonatal mortality rate in patients with bilateral renal agenesis is 100% in the absence of fetal intervention [4], whereas the severity of other renal diseases varies widely. However, renal oligohydramnios tends to be considered a disorder with a uniformly poor prognosis, as indicated by the high rate of pregnancy termination (29%–61%) and palliative care [5-12]. This results from a lack of evidence for the prenatal prediction of poor prognosis and information about the long-term outcome of fetuses with renal oligohydramnios.

Although several studies have investigated the predictive factors for perinatal mortality, the results are controversial and vary between reports [8,10-14]. Additionally, the long-term outcome and risk factors for postneonatal death remain unknown. The clarification of long-term outcome, including fetal and neonatal prognosis, and risk factors for a poor outcome in Potter syndrome/sequence has implications for selecting a termination of pregnancy (TOP), and is also important for counseling as well as early transfer to a treatable facility. Long-term outcomes, including perinatal prognosis, may have changed following recent improvements in neonatal medicine, the management of kidney failure for neonates, and the advent of fetal interventions. In particular, fetal intervention is the only approach reported to improve the survival of fetuses with bilateral renal agenesis, although many questions remain about its efficacy in this indication [4,15-18].

The present study investigated the prenatal, neonatal, and long-term outcomes of fetuses with prenatally detected renal oligohydramnios, which is the main cause of Potter syndrome/sequence, at our institution over 22 years. We also analyzed the risk factors for intrauterine fetal death (IUFD), neonatal mortality, and postneonatal mortality separately because their causes differ.

## Methods

### *Study design, site, and participants*

This retrospective cohort study included fetuses with prenatally detected renal oligohydramnios between 1 March 2002 and 31 October 2023 at the National Center for Child Health and Development. All fetuses with prenatally detected renal oligohydramnios were included. Patients who were lost to follow-up were excluded from this study.

### *Data collection*

The following data were collected from the medical records to determine the clinical course of the patients: maternal age, onset of oligohydramnios and megacystis, presence of anhydramnios, fetal intervention, birth information, primary renal diagnosis and associated anomalies, long-term outcome, including prenatal and neonatal outcome, kidney outcome, medical care, and Pediatric Cerebral Performance Category Scale score [19] at the last follow-up.

### *Outcome*

Primary endpoints were overall survival after fetal, neonatal, and postneonatal death. The secondary endpoint was kidney failure. Additionally, the risk factors for fetal, neonatal, and postneonatal mortality were analyzed separately.

***Definitions***

Oligohydramnios was defined as an amniotic fluid index of ≤5 cm or maximum vertical pocket of <2 cm. Anhydramnios was defined as an amniotic fluid index of 0 cm or maximum vertical pocket of <1 cm [7]. Renal oligohydramnios was defined as oligohydramnios associated with congenital kidney disease with the exclusion of other causes of oligohydramnios. Megacystis was defined as a longitudinal bladder diameter of ≥7 mm in the first trimester (<14 weeks of gestation). Megacystis was defined as an enlarged bladder and hydronephrosis diagnosed by fetal medicine specialists after the first trimester because there is no clear definition of megacystis in the second (between 14 and 27 weeks' gestation) and third trimesters (>28 weeks' gestation) [20]. TOP is allowed by law under a term limit of 22 weeks in Japan. The primary renal disease was classified into the 7 following groups: bilateral renal agenesis (classic Potter syndrome), bilateral MCDK, unilateral MCDK and contralateral renal agenesis, autosomal recessive polycystic kidney disease (ARPKD) (subtype I of Potter syndrome), hypoplastic/dysplastic kidney (subtype II of Potter syndrome), obstructive uropathy (subtype IV of Potter syndrome), and others (e.g., renal tubular dysgenesis) [21]. Although subtype III is due to autosomal dominant polycystic kidney disease, no patients had this disease in this study. Hypoplastic/dysplastic kidney included unilateral MCDK and contralateral hypoplastic/dysplastic kidney, and unilateral renal agenesis and contralateral hypoplastic/dysplastic kidney. Bilateral MCDK and unilateral MCDK and contralateral renal agenesis were classified separately and independently from bilateral hypoplastic and dysplastic kidneys (subtype II) owing to the

complete absence of kidney function. Obstructive uropathy included posterior urethral valves, urethral atresia, urethral stricture, and bilateral hydronephrosis. If obstructive uropathy and hypoplastic/dysplastic kidney coexisted, patients were classified as having obstructive uropathy. However, when bilateral renal agenesis, bilateral MCDK and, unilateral MCDK and contralateral renal agenesis were associated with obstructive nephropathy, they were not included in obstructive nephropathy. Major congenital complications included some syndromes (e.g., VATER association, prune belly syndrome, and multiple malformation syndrome), and organ involvement required surgery (e.g., anal atresia, esophageal atresia, atresia of the intestine, congenital heart disease, and myelomeningocele). Hearing loss, coloboma, genital anomalies, vertebral malformations, finger anomalies, mild liver fibrosis, and congenital heart disease not requiring surgery were not included in the major congenital complications of the study because they were not directly associated with death.

***Facility standards and strategy for kidney failure***

TOP was provided with parental consent after appropriate information and counseling. Amnioinfusion was performed with parental consent in cases of renal oligohydramnios at ≤30 weeks' gestation in the absence of chromosomal abnormalities, placental insufficiency, or premature rupture of membranes. Ultrasound-guided fetal vesicoamniotic shunting was performed in fetuses with lower urinary tract obstruction with oligohydramnios, with a good fetal urine scan, and with parental consent at <30 weeks' gestation. Neonatal care was provided after extensive antenatal counseling on resuscitation at birth and goals of care.

***Statistical analysis***

Continuous variables are expressed as the median and range and categorical variables as the number (%). Normally distributed continuous variables were compared using the t-test, and

non-normally distributed variables were compared using the Mann–Whitney U test. Categorical variables were compared using the $\chi^2$ test. The risk factors for IUFD and neonatal death were evaluated by multivariate analyses using a logistic regression. The overall survival rate and survival rate for births excluding patients who died in the neonatal period were analyzed by the Kaplan–Meier method to evaluate the time until the occurrence of primary and secondary endpoints. Risk factors for postneonatal death were evaluated by multivariate analyses using the log-rank test and Cox proportional hazard analysis. In the Kaplan–Meier estimates of kidney survival, patients who died were censored at the time of death. A 2-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed with the JMP software package for Macintosh, 14.2 (SAS Institute Japan, Tokyo, Japan).

### *Ethics*

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare, Japan. The study protocol was approved by the Institutional Ethics Committee of the National Center for Child Health and Development (approval number: 2022−158). In accordance with the above-mentioned guidelines, informed consent was not required for participation in the study.

## Results

### *Prenatal characteristics*

During the study period, 178 fetuses with renal oligohydramnios fulfilled the inclusion criteria at our center. Of these, 47 fetuses who were lost to follow-up for outcome were

excluded from the study. Of 131 fetuses, 46 (35%) underwent TOP, 11 (8%) had IUFD, and 74 (56%) were live born (Figure 1). Of the 74 births, 26 (35%) patients died in the neonatal period and nine died in the postneonatal period.

The median gestational ages of TOP and IUFD were 20 weeks (interquartile range [IQR], 18-21 weeks) and 18 weeks (IQR, 15-35 weeks), respectively. Table I shows the prenatal characteristics of the study cohort. Associated anomalies were present in 41% of fetuses. Major congenital complications were present in 30%. The most common major complication was anal atresia in 33 (19%) fetuses. Autopsies were performed in 13 fetuses in the TOP group and in only 1 in the IUFD group. Associated anomalies in live-born cases are shown in Table II. Anal atresia was also the most common major complication in live-born fetuses (n=19, 25%). VATER association (n=7) and prune belly syndrome (n=5) were among the most common anomalies. Twenty-one patients underwent fetal intervention.

***Prenatal outcome and risk factors for IUFD***

Of the 85 fetuses without TOP, 11 (13%) had IUFD. A comparison of prenatal characteristics between patients with IUFD and live-born patients is shown in Table I. Seven fetuses with obstructive uropathy and 4 with bilateral renal agenesis had IUFD, whereas none with other renal disease had IUFD. After adjusting for maternal age, megacystis, and major congenital complications, the logistic regression analysis showed that an earlier gestational age at the onset of renal oligohydramnios (odds ratio 1.16, 95% confidence interval [CI] 1.01-1.37, P=0.031) was significantly related to IUFD (Table IIIA).

***Neonatal outcome and risk factors for neonatal death***

Of the 74 births, 26 (35%) patients died in the neonatal period. Of these, 17 died within 24 h of birth and 24 died within 48 h of birth. The causes of neonatal death were respiratory

failure due to pulmonary hypoplasia in 24 cases, hemorrhage from umbilical cord ulcers in 1 case, and kidney failure in 1 case.

A comparison between survivors in the neonatal period and those with neonatal death is shown in Table IV. The neonatal survival rate for bilateral renal agenesis (n=1/3, 33%), bilateral MCDK (n=2/6, 33%), and unilateral MCDK and contralateral renal agenesis (n=0/7, 0%) were lower than for renal tubular dysgenesis (n=3/3, 100%), bilateral hypoplastic/dysplastic kidney (n=13/14, 93%), ARPKD (n=10/12, 83%), and obstructive nephropathy (n=21/29, 72%). The logistic regression analysis showed that anhydramnios (odds ratio 12.7, 95% confidence interval (CI) 1.52-106.7, P=0.019) was a significant risk factor for neonatal death after adjusting for maternal age, gestational age at onset, and megacystis (Table IIIB). In a logistic regression analysis including postnatal factors, a low Apgar score at 5 min (odds ratio 1.83, 95% CI 1.30-2.88, P<0.001) was significantly related to neonatal death (Table IIIC).

Of the 21 patients with fetal intervention, 17 survived to the neonatal period, including 1 with bilateral renal agenesis and 2 with bilateral MCDK. The remaining 4 patients died in the neonatal period owing to lung hypoplasia within the first 2 days of life. The detailed clinical course of 21 patients with fetal intervention is shown in Table V.

***Long-term outcome and risk factors for postneonatal death***

According to Kaplan–Meier estimated overall survival rates for 74 births (Figure 2A), 1, 3, and 5-year survival rates were 57%, 55%, and 51%, respectively. According to the Kaplan–Meier estimated survival rate for 48 births after excluding patients who died in the neonatal period (Figure 2B), 1, 3, and 5-year survival rates were 87%, 82%, and 78%, respectively.

A comparison between survivors and those with postneonatal death is shown in Table VI. Log-rank tests showed that a birth weight <2000 g (P<0.001, Figure 2C), postnatal

anuria (*P*=0.008, Figure 2D), and gastrointestinal comorbidity (P=0.002, Figure 2E) were significantly associated with postneonatal death. The Cox proportional hazards model showed that a birth weight <2000 g (hazard ratio 7.33, 95% CI 1.48–36.1, P=0.014) and gastrointestinal comorbidity (hazard ratio 4.37, 95% CI 1.03–18.5, P=0.046) were significant risk factors for postneonatal death after adjusting for male sex and postnatal anuria (Table IIID). The causes of postneonatal death were peritonitis in three cases, cholangitis associated with ARPKD in three cases, respiratory failure in two cases, and liver failure in one case.

***Kidney outcome***

None of the 26 patients with neonatal death were started on dialysis. Of the 48 patients without neonatal death, 16 (33%) (bilateral renal agenesis, n=1/1; bilateral MCDK, n=2/2; ARPKD, n=5/9; bilateral hypoplastic/dysplastic kidney, n=4/13; obstructive uropathy, n=1/20; renal tubular dysgenesis, n=3/3) required dialysis during the neonatal period. Of them, 13 patients required dialysis within the first 7 days of life. During the observation period, 30 (63%) (bilateral renal agenesis, n=1/1; bilateral MCDK, n=2/2; ARPKD, n=6/9; bilateral hypoplastic/dysplastic kidney, n=7/13; obstructive uropathy, n=11/20; renal tubular dysgenesis, n=3/3) progressed to kidney failure. According to the Kaplan–Meier estimated kidney survival rate for 48 births after excluding patients who died in the neonatal period (Figure 2F), 1, 3, and 5-year kidney survival rates were 43%, 37%, and 27%, respectively. At the last follow-up, 14 patients had received a kidney transplantation, seven were receiving peritoneal dialysis, two were on hemodialysis, and seven had died.

***Medical care and Pediatric Cerebral Performance Category Scale score at the last follow-up***

Medical care of the 39 patients who were alive at the last observation was as follows: two were tracheostomized, one was on oxygen, 12 were receiving tube feeding, eight had developed a vesicocutaneous fistula, and six had a colostomy. No child was on a ventilator. Pediatric Cerebral Performance Category Scale scores were 1 (n=20), 2 (n=12), 3 (n=4), 4 (n=2), and 5 (n=1).

**Discussion**

In the present retrospective cohort study, we evaluated long-term outcomes and associated risk factors for IUFD, neonatal death, and postneonatal death in fetuses with prenatally detected renal oligohydramnios. Of 131 fetuses, 46 (35%) underwent a TOP, 11 (8%) had IUFD, 26 (20%) experienced neonatal death, nine (7%) had a postneonatal death, and 39 (30%) survived. Logistic regression analysis identified early gestational age at onset as a significant risk factor for IUFD, and anhydramnios was shown to be a significant risk factor for neonatal death as a perinatal factor. Overall survival rates were 57%, 55%, and 51% at 1, 3, and 5 years from birth, respectively. The Cox proportional hazards model showed that a birth weight <2000 g and gastrointestinal comorbidity were significant risk factors for postneonatal death. These results may have important implications for decisions on TOP and active neonatal care.

Of all 85 fetuses excluding those with TOP in the present study, 11 (13%) had IUFD. The percentage of IUFD in the present study is consistent with that in previous studies (6%–17%) [7-12]. Of the 11 fetuses with IUFD, 7 had obstructive uropathy and 4 had bilateral renal agenesis, while there were no deaths in fetuses with bilateral hypoplastic/dysplastic kidney or polycystic kidney. The logistic regression analysis with adjustment for maternal age showed that an earlier gestational age at onset was significantly

related to IUFD. Associated anomalies and chromosomal abnormalities are more common in fetuses with megacystis who are diagnosed in the first trimester of pregnancy and have a worse prognosis than those diagnosed in the second or third trimester [22,23]. In the present study, the median gestational age at onset in fetuses with megacystis in the IUFD group was 15 weeks. Although chromosomal testing was not performed in this study, fetuses with obstructive nephropathy and bilateral renal agenesis at early onset may have been progressed to IUFD owing to chromosomal abnormalities.

Postnatally, 26 (35%) of the 74 births resulted in neonatal death. The neonatal mortality rates after birth ranged from 26% to 64% in previous large studies of oligohydramnios [7,8,11-14]. They are also similar to previous reports showing that neonatal death is often due to respiratory failure associated with lung hypoplasia [7-14]. The gestational age at onset, early onset of oligohydramnios, a lower birth weight, associated anomalies, and the best oxygen index on the first day of life were reported to be factors associated with neonatal or neonatal death [8,10-14,22], although many of these results were based on univariate analyses because of the rarity of the disease [8,10,12,13,22]. Mehler et al. found that the gestational age at onset (<28 weeks) and best oxygen index at the first day were predictors of survival to hospital discharge in a logistic analysis [14]. There was no significant difference in the gestational age at onset between survivors and patients with neonatal death in the present study. In fact, of 51 fetuses with a gestational age at onset of less than 28 weeks, 30 survived. We found that a low Apgar score at 5 min was significantly associated with neonatal death in the logistic regression analysis including postnatal factors. These results may reflect severe respiratory and circulatory failure due to lung hypoplasia at birth. In the logistic regression analysis restricted to prenatal factors, anhydramnios was significantly related to neonatal death. Our results are consistent with the common assumption that a fetus born with anhydramnios is expected to have a fatal outcome [24].

More importantly, the neonatal prognosis greatly differed depending on the primary renal disease. The neonatal survival rate in patients with bilateral renal agenesis, bilateral MCDK, and unilateral MCDK and contralateral renal agenesis was lower than that in patients with other Potter sequences in our study. It is speculated that these renal diseases are largely associated with anhydramnios [4, 24, 25].

To the best of our knowledge, this study is the first report showing the long-term prognosis of renal oligohydramnios. One, 3, and 5-year survival rates for 48 births (excluding patients who died in the neonatal period) were 87%, 82%, and 78%, respectively. This shows that survival rates after the neonatal period, especially after the age of 1 year, can be relatively high even in the most severe forms of kidney disease such as bilateral renal agenesis and bilateral MCDK. In a previous systematic literature review, the neonatal mortality rate in patients with bilateral renal agenesis was 100% in the absence of fetal intervention [4] Recently, two cases of long-term survival with fetal treatment in patients with bilateral renal agenesis have been reported [15,16]. Notably, the development and growth of these patients were normal at the last follow-up [16]. In the present study, approximately half of the children were at grade level on the Pediatric Cerebral Performance Category Scale. Furthermore, medical care such as tube feeding, vesicourethral fistulas, and colostomy was required in some patients at the last observation; oxygen administration and tracheostomy were rarely required, and none of the patients required a ventilator. Although fetal treatment and year (2002–2012 vs 2013–2022) were not significantly associated with neonatal mortality in this study, one case of bilateral renal agenesis and two cases of bilateral MCDK survived with fetal intervention since 2019. A multicenter study of serial amnioinfusions to prevent pulmonary hypoplasia in cases of early pregnancy renal anhydramnios, the Renal Anhydramnios Fetal Therapy (RAFT) trial [17], is ongoing and results are awaited.

The most common causes of postneonatal death were peritonitis and cholangitis associated with ARPKD. Log-rank tests showed that a birth weight <2000 g, postnatal anuria, and gastrointestinal comorbidity were significantly associated with postneonatal death. Anal atresia was the most common major complication in the present study. Abdominal surgery can cause later dialysis flow problems because of intra-abdominal adhesions, while bowel resection may lead to ultrafiltration failure from a decreased peritoneal surface area [26]. Therefore, the establishment of peritoneal dialysis is greatly affected by gastrointestinal complications. Based on the criteria for hemodialysis at our institution, we classified patients into two groups by birth weight, using 2000 g as the cutoff, and found a significant difference in postneonatal death between the two groups. Thus, in children whose body size does not enable hemodialysis, difficulties with peritoneal dialysis may have a significant impact on life expectancy, although this effect may vary depending on the facility's hemodialysis criteria for birth weight. While we did not find postnatal anuria to be significantly associated with postneonatal death in the Cox proportional hazards model, it is an important factor in the establishment of peritoneal dialysis because it affects the break-in period from catheter insertion to dialysis initiation, with a shorter break-in period increasing the risk of peritoneal leaks and peritonitis [27]. Furthermore, cholangitis in ARPKD is a serious complication [28].

Of the 48 neonates without neonatal death, 30 progressed to kidney failure, including 16 who required dialysis during the neonatal period. Although the kidney outcome of renal oligohydramnios is poor [29], it is important to note that some cases did not require kidney replacement therapy. The neonatal kidney outcome also appeared to be better in patients with obstructive nephropathy (1/20; 5%) than in other kidney diseases, while there was no difference in long-term kidney outcome between patients with obstructive nephropathy (n=11/20; 55%), ARPKD (6/9; 67%), and bilateral hypoplastic/dysplastic kidney (n=7/13; 54%) .

The present study had several limitations. First, this was a single-center retrospective study at a tertiary center with pediatric nephrology, neonatal medicine, and pediatric intensive care in Japan. Second, sex and associated anomalies, especially in fetuses with IUFD, were not adequately evaluated in our study. The reason for this inadequate evaluation is that patients who had TOP in other institutions after the diagnosis of IUFD in our institution were included. Additionally, their assessment may have been inadequate because an autopsy was only performed in 1 case in the IUFD group. Third, TOP is not allowed after a term limit of 22 weeks in Japan. An earlier gestational age at onset was significantly related to IUFD. Therefore, aborted fetuses may be more severe cases, and the incidence of IUFD may be higher if they are not aborted.

In conclusion, accurately assessing primary renal disease and risk factors for predicting the prognosis in each individual case, rather than considering renal oligohydramnios as a disease with a uniformly poor prognosis, is important. Long-term survival in patients with renal oligohydramnios is a feasible goal, even in severe cases such as those with bilateral renal agenesis and bilateral renal MCDK, with recent improvements in neonatal medicine and the advent of fetal interventions. These results could be useful in counseling the families of these fetuses.

**Abbreviations:** ARPKD, autosomal recessive polycystic kidney disease; CI, confidence interval; IUFD, intrauterine fetal death; MCDK, multicystic dysplastic kidney; TOP, termination of pregnancy

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**References**


1. Potter EL. Bilateral renal agenesis. J Pediatr 1946;29:68-76.
2. Bain AD, SCOTT JS. Renal agenesis and severe urinary tract dysplasia: a review of 50 cases, with particular reference to the associated anomalies. Br Med J 1960;1:841-6.
3. Curry CJ, Jensen K, Holland J, Miller L, Hall BD. The Potter sequence: a clinical analysis of 80 cases. Am J Med Genet 1984;19:679-702.
4. Thomas AN, McCullough LB, Chervenak FA, Placencia FX. Evidence-based, ethically justified counseling for fetal bilateral renal agenesis. J Perinat Med 2017;45:585-94.
5. Huber C, Shazly SA, Blumenfeld YJ, Jelin E, Ruano R. Update on the Prenatal Diagnosis and Outcomes of Fetal Bilateral Renal Agenesis. Obstet Gynecol Surv 2019;74:298-302.
6. Aulbert W, Kemper MJ. Severe antenatally diagnosed renal disorders: background, prognosis and practical approach. Pediatr Nephrol 2016;31:563-74.
7. Peipert JF, Donnenfeld AE. Oligohydramnios: A Review. Obset Gynecol Surv 1991;46:325-39.
8. Grijseels EW, van-Hornstra PT, Govaerts LC, Cohen-Overbeek TE, de Krijger RR, Smit BJ, et al. Outcome of pregnancies complicated by oligohydramnios or anhydramnios of renal origin. Prenat Diagn 2011;31:1039-45.
9. Nagase H, Ishikawa H, Nishikawa T, Kurosawa K, Itani Y, Yamanaka M. Prenatal management of the fetus with lethal malformation: from a study of oligohydramnios sequence. Fetal Pediatr Pathol 2011;30:145-9.
10. Goto T, Sugiura T, Awaya R, Ueda H, Mizutani E, Ito K, et al. Survival of fetuses with severe oligohydramnios. Clin Exp Obstet Gynecol 2016;43:341-4.
11. Spiro JE, Konrad M, Rieger-Fackeldey E, Masjosthusmann K, Amler S, Klockenbusch W, et al. Renal oligo- and anhydramnios: cause, course and outcome--a single-center study. Arch Gynecol Obstet 2015;292:327-36.

12. Mehler K, Gottschalk I, Burgmaier K, Volland R, Büscher AK, Feldkötter M, et al. Prenatal parental decision-making and postnatal outcome in renal oligohydramnios. Pediatr Nephrol 2018;33:651-9.
13. Klaassen I, Neuhaus TJ, Mueller-Wiefel DE, Kemper MJ. Antenatal oligohydramnios of renal origin: long-term outcome. Nephrol Dial Transplant 2007;22:432-9.
14. Mehler K, Beck BB, Kaul I, Rahimi G, Hoppe B, Kribs A. Respiratory and general outcome in neonates with renal oligohydramnios--a single-centre experience. Nephrol Dial Transplant 2011;26:3514-22.
15. Bienstock JL, Birsner ML, Coleman F, Hueppchen NA. Successful in utero intervention for bilateral renal agenesis. Obstet Gynecol. 2014;124:413-5.
16. Sheldon CR, Kim ED, Chandra P, Concepcion W, Gallo A, Su S, et al. Two infants with bilateral renal agenesis who were bridged by chronic peritoneal dialysis to kidney transplantation. Pediatr Transplant 2019;23:e13532.
17. Atkinson MA, Jelin EB, Baschat A, Blumenfeld YJ, Chmait RH, O'Hare E et al. Design and Protocol of the Renal Anhydramnios Fetal Therapy (RAFT) Trial. Clin Ther 2022;44:1161-71.
18. Miller JL, Baschat AA, Atkinson MA. Fetal Therapy for Renal Anhydramnios. Clin Perinatol 2022;49:849-62.
19. Zaritsky A, Nadkarni V, Hazinski MF, Foltin G, Quan L, Wright J et al. Recommended Guidelines for Uniform Reporting of Pediatric Advanced Life Support: The Pediatric Utstein Style; Statement for Health Care Professionals from the Task Force of the American Academy of Pediatrics, the American Heart Association, and the European Resuscitation Council. Pediatrics 1995;96:765-79.
20. Capone V, Persico N, Berrettini A, Decramer S, De Marco EA, De Palma D, et al. Definition, diagnosis and management of fetal lower urinary tract obstruction: consensus

of the ERKNet CAKUT-Obstructive Uropathy Work Group. Nat Rev Urol 2022;19:295-303.

21. Kostov S, Slavchev S, Dzhenkov D, Strashilov S, Yordanov A. Discordance for Potter's Syndrome in a Dichorionic Diamniotic Twin Pregnancy-An Unusual Case Report. Medicina (Kaunas) 2020;56:109.
22. Bornes M, Spaggiari E, Schmitz T, Dreux S, Czerkiewicz I, Delezoide AL, et al. Outcome and etiologies of fetal megacystis according to the gestational age at diagnosis. Prenat Diagn 2013;33:1162-6.
23. Fievet L, Faure A, Coze S, Harper L, Panait N, Braunstein D, et al. Fetal megacystis: etiologies, management, and outcome according to the trimester. Urology 2014;84:185-90.
24. Jelin EB, Hooper JE, Duregon E, Williamson AK, Olson S, Voegtline K, et al. Pulmonary hypoplasia correlates with the length of anhydramnios in patients with early pregnancy renal anhydramnios (EPRA). J Perinatol 2021;41:1924-9.
25. Balasundaram M, Chock VY, Wu HY, Blumenfeld YJ, Hintz SR. Predictors of poor neonatal outcomes in prenatally diagnosed multicystic dysplastic kidney disease. J Perinatol 2018;38:658-64.
26. Qureshi MA, Maierean S, Crabtree JH, Clarke A, Armstrong S, Fissell R et al. The Association of Intra-Abdominal Adhesions with Peritoneal Dialysis Catheter-Related Complications. Clin J Am Soc Nephrol 2024, Online ahead of print.
27. Nada T, Kamei K, Sato M, Nishi K, Ogura M, Ito S. Risk factors for early dialysate leakage around the exit site after catheter placement in pediatric peritoneal dialysis: a single-center experience. Clin Exp Nephrol 2023;27:791-9.

28. Inoki Y, Nishi K, Osaka K, Kaneda T, Akiyama M, Sato M et al. Complications and prognosis of patients diagnosed with autosomal recessive polycystic kidney disease in neonatal period. CEN Case Rep 2023, online ahead of print.
29. Nishi K, Uemura O, Harada R, Yamamoto M, Okuda Y, Miura K, et al. Early predictive factors for progression to kidney failure in infants with severe congenital anomalies of the kidney and urinary tract. Pediatr Nephrol 2023;38:1057-66.

**Figure Legends**

**Figure 1.** Flow diagram of the patients' outcomes.

IUFD, intrauterine fetal death; TOP, termination of pregnancy.

**Figure 2.** A. Kaplan–Meier estimated overall survival rates for 74 births. B. Kaplan–Meier estimated survival rate for 48 births after excluding patients who died in the neonatal period. C. Kaplan–Meier curves for the time to death according to the birth weight <2000 g. D. Kaplan–Meier curves for the time to death according to the postnatal anuria. E. Kaplan–Meier curves for the time to death according to the gastrointestinal comorbidity. F. Kaplan–Meier estimated kidney survival rate for 48 births after excluding patients who died in the neonatal period.

Table

**Table I. Prenatal characteristics of patients with renal oligohydramnios and comparison between patients with IUFD and live-born patients**

| | All patients (n=131) | TOP (n=46) | IUFD (n=11) | Live born (n=74) | P value* |
|---|---|---|---|---|---|
| Maternal age (years) | 32 (30–36) | 33 (32–37) | 31 (28–36) | 32 (29–36) | 0.79 |
| Sex | | | | | |
| Male | 76 (73) | 23 (79) | 1 (100) | 52 (70) | 1.00** |
| Female | 25 (24) | 5 (17) | 0 (0) | 20 (27) | |
| Ambiguous | 3 (3) | 1 (3) | 0 (0) | 2 (3) | |
| No data*** | 27 | 17 | 10 | 0 | |
| GA at initial onset (weeks) | 17 (15–22) | 16 (15–17) | 15 (13−25) | 21 (16–26) | 0.12 |
| ≤13 weeks | 15 (12) | 6 (13) | 4 (36) | 5 (7) | |
| 14–27 weeks | 102 (81) | 40 (87) | 6 (55) | 56 (81) | |
| ≥28 weeks | 9 (7) | 0 (0) | 1 (9) | 8 (12) | |
| No data*** | 5 | 0 | 0 | 5 | |
| GA at onset of ROH (weeks) | 19 (16–26) | 17 (16–18) | 17 (14−25) | 24 (20–28) | 0.011 |
| ≤13 weeks | 1 (1) | 0 (0) | 1 (9) | 0 (0) | |
| 14–27 weeks | 105 (84) | 45 (100) | 9 (82) | 51 (74) | |
| ≥28 weeks | 19 (15) | 0 (0) | 1 (9) | 18 (26) | |
| No data*** | 6 | 1 | 0 | 5 | |
| Megacystis | 57 (44) | 22 (48) | 7 (64) | 28 (38) | 0.19 |
| GA at onset of megacystis (weeks) | 15 (13–17) | 14 (13–16) | 13 (12–15) | 16 (14–24) | |
| ≤13 weeks | 14 (28) | 6 (27) | 3 (43) | 5 (20) | |
| 14–27 weeks | 40 (72) | 16 (73) | 4 (57) | 20 (80) | |
| ≥28 weeks | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| No data*** | 3 | 0 | 0 | 3 (0) | |
| Anhydramnios | 83 (63) | 26 (57) | 6 (55) | 51 (69) | 0.49 |
| Renal disease | | | | | 0.003 |
| Bilateral renal agenesis | 12 (9) | 5 (11) | 4 (36) | 3 (4) | |
| Bilateral MCDK | 13 (10) | 7 (15) | 0 (0) | 6 (8) | |
| MCDK + contralateral renal agenesis | 8 (6) | 1 (2) | 0 (0) | 7 (9) | |
| Hypoplastic/dysplastic kidney | 22 (17) | 8 (17) | 0 (0) | 14 (19) | |
| Obstructive uropathy | 58 (44) | 22 (48) | 7 (64) | 29 (39) | |
| ARPKD | 15 (11) | 3 (7) | 0 (0) | 12 (16) | |
| RTD | 3 (2) | 0 (0) | 0 (0) | 3 (4) | |
| Associated anomalies | 54 (41) | 13 (28) | 3 (27) | 38 (51) | 0.20 |
| Major congenital complications | 39 (30) | 10 (21) | 3 (27) | 26 (35) | 0.74 |
| Bilateral renal anomalies | 130 (99) | 46 (100) | 11 (100) | 73 (99) | 1.00 |
| Fetal intervention | 21 (16) | 0 (0) | 0 (0) | 21 (28) | 0.06 |
| Amnioinfusion only | 14 (11) | 0 (0) | 0 (0) | 14 (19) | |
| Vesicoamniotic shunting only | 3 (2) | 0 (0) | 0 (0) | 2 (3) | |
| Both | 4 (3) | 0 (0) | 0 (0) | 4 (5) | |
| Year | | | | | 0.09 |
| 2002–2012 | 52 (40) | 20 (43) | 7 (63) | 25 (34) | |
| 2013–2022 | 79 (60) | 26 (57) | 4 (36) | 49 (66) | |

Data are n (%) or median (interquartile range).

ARPKD, autosomal recessive polycystic kidney disease; gestational age, GA; IUFD, intrauterine fetal death; MCDK, multicystic dysplastic kidney; ROH, renal oligohydramnios; RTD, renal tubular dysgenesis; TOP, termination of pregnancy.

*Comparison between the IUFD group and live-born group.

**Sex was compared between male and female patients.

***Included patients who had an abortion in another institution after IUFD was diagnosed in our institution.

**Table II. Associated anomalies in live-born cases**

| | Patients who died neonatally (n=26) | Patients who died postneonatally (n=9) | Survivors (n=39) |
|---|---|---|---|
| **Major complications** | | | |
| Gastrointestinal comorbidity | 17 | 6 | 12 |
| Esophageal atresia | 4 | 0 | 1 |
| Anal atresia* | 8 | 2 | 9 |
| Intestinal obstruction/stricture/atresia | 4 | 3 | 1 |
| Malrotation of the intestine | 3 | 0 | 1 |
| Hirschsprung's disease | 1 | 1 | 0 |
| Congenital heart disease (severe) | 2 | 0 | 4 |
| Pulmonary atresia | 1 | 0 | 0 |
| Tetralogy of Fallot | 1 | 0 | 3 |
| Atrioventricular septal defect | 0 | 0 | 1 |
| Thoracic hypoplasia | 0 | 0 | 1 |
| Myelomeningocele | 1 | 0 | 1 |
| Persistent cloaca | 3 | 0 | 7 |
| Complete urorectal septum malformation | 2 | 0 | 0 |
| **Minor complications** | | | |
| Hearing loss | 0 | 0 | 4 |
| Ear malformations | 0 | 0 | 2 |
| Coloboma | 0 | 1 | 1 |
| Liver fibrosis | 7 | 1 | 4 |
| Congenital heart disease (mild, moderate) | 5 | 1 | 9 |
| Patent ductus arteriosus | 3 | 1 | 4 |
| Arterial septal defect | 0 | 0 | 4 |
| Pulmonary valve stenosis | 2 | 0 | 1 |
| Pulmonary hypertension | 0 | 2 | 0 |
| External genitalia abnormalities | 0 | 3 | 9 |
| Internal genitalia abnormalities | 0 | 1 | 1 |
| Vertebral malformation | 0 | 1 | 3 |
| Spinal cord lipoma | 0 | 0 | 2 |
| Finger anomalies | 0 | 1 | 1 |
| Bladder extrophy | 0 | 0 | 1 |
| Others | 5** | 0 | 5*** |
| **Syndrome** | | | |
| VATER/VACTERL association | 4 | 1 | 2 |
| Prune berry syndrome | 0 | 2 | 3 |
| Branchio-oto-renal syndrome | 0 | 0 | 1 |
| Renal coloboma syndrome | 0 | 1 | 0 |
| Caudal regression syndrome | 1 | 0 | 0 |
| Turner syndrome | 0 | 0 | 1 |
| Megacystis-microcolon-intestinal hypoperistalsis syndrome | 0 | 1 | 0 |
| 17q12 deletion | 0 | 0 | 1 |
| PAX2 mutation | 0 | 0 | 1 |
| 49XXXXY syndrome | 0 | 0 | 1 |

*Cases with persistent cloaca and complete urorectal septum malformation were included.
**Ventricular enlargement (n=1), knee joint bone defects (n=1), rectovesical fistula (n=1), and lower limb defect (n=2).
***Biliary dilatation (n=1), intestinal failure (n=1), hepatic hemangioma (n=1), cerebellar venous malformation (n=1), and intestinal duplication (n=1).

**Table III. Multivariable analysis of IUFD and neonatal death.**

| **(A)** Logistic regression analysis of IUFD in 85 patients after excluding those with termination of pregnancy | | | |
|---|---|---|---|
| | Multivariate analysis | | |
| Factors | OR | 95% CI | P value |
| Maternal age | 0.99 | 0.86–1.15 | 0.94 |
| Earlier GA at onset of ROH | 1.16 | 1.01–1.37 | 0.031 |
| Megacystis | 1.66 | 0.36–8.07 | 0.52 |
| Major congenital complications | 0.54 | 0.10–2.33 | 0.42 |
| **(B)** Logistic regression analysis of neonatal death in 74 live-born patients (Prenatal factors only) | | | |
| | Multivariate analysis | | |
| Factors | OR | 95% CI | P value |
| Maternal age | 0.93 | 0.83–1.04 | 0.22 |
| Earlier GA at onset of ROH | 1.03 | 0.93–1.16 | 0.59 |
| Megacystis | 1.29 | 0.38–4.39 | 0.68 |
| Anhydramnios | 12.7 | 1.52–106.7 | 0.019 |
| **(C)** Logistic regression analysis of neonatal death in 74 live-born patients (Prenatal and Postnatal factors) | | | |
| | Multivariate analysis | | |
| Factors | OR | 95% CI | P value |
| Maternal age | 0.96 | 0.83–1.11 | 0.60 |
| Earlier GA at onset of ROH | 1.00 | 0.86–1.16 | 0.99 |
| Anhydramnios | 4.03 | 0.40–41.0 | 0.20 |
| Birth weight | 1.00 | 0.997–1.001 | 0.43 |
| Associated anomalies | 0.33 | 0.07–1.51 | 0.14 |
| Low Apgar score | 1.80 | 1.33–2.69 | <0.001 |
| **(D)** Cox proportional hazard analysis of death after neonatal period in 48 births, excluding patients who died in the neonatal period | | | |
| | Multivariate analysis | | |
| Factors | HR | 95% CI | P value |
| Male sex | 1.38 | 0.13–14.5 | 0.78 |
| Birth weight <2000 g | 7.33 | 1.48–36.1 | 0.014 |
| Postnatal anuria | 3.88 | 0.84–18.0 | 0.08 |
| Gastrointestinal comorbidity | 4.37 | 1.03–18.5 | 0.046 |

CI, confidence interval; GA, gestational age; HR, hazard ratio; IUFD, intrauterine fetal death; OR, odds ratio; ROH, renal oligohydramnios.

**Table IV. Comparison of characteristics between survivors in the neonatal period and patients with neonatal death who were live born**

| | Patients with neonatal death (n=26) | Survivors in the neonatal period (n=48) | P value |
|---|---|---|---|
| Prenatal information | | | |
| Maternal age (years) | 31 (26–34) | 33 (30–37) | 0.047 |
| GA at initial onset (weeks) | 22 (17–25) | 21 (16–26) | 0.91 |
| ≤13 weeks | 1 (4) | 4 (9) | |
| 14–27 weeks | 23 (88) | 33 (77) | |
| ≥28 weeks | 2 (8) | 6 (14) | |
| No data | 0 | 5 | |
| GA at onset of ROH (weeks) | 24 (20–27) | 25 (17–28) | 0.62 |
| ≤13 weeks | 0 (0) | 0 (0) | |
| 14–27 weeks | 21 (81) | 30 (70) | |
| ≥28 weeks | 5 (19) | 13 (30) | |
| No data | 0 | 5 | |
| Megacystis | 11 (42) | 17 (35) | 0.62 |
| Anhydramnios | 25 (96) | 26 (54) | <0.001 |
| Fetal intervention | 4 (15) | 17 (35) | 0.10 |
| Amnioinfusion only | 1 (4) | 13 (27) | |
| Vesicoamniotic shunting only | 1 (4) | 1 (2) | |
| Both | 2 (8) | 2 (4) | |
| Postnatal information | | | |
| Male sex | 19/24* (79) | 33 (69) | 0.41 |
| Gestational age (weeks) | 36 (34–37) | 36 (34–37) | 0.69 |
| Birth weight (g) | 2336 (1943–2589) | 2486 (2101–2743) | 0.20 |
| Apgar score at 1 min | 2 (1–4) | 6 (3–8) | <0.001 |
| Apgar score at 5 min | 4 (2–6) | 8 (6–8) | <0.001 |
| Renal disease | | | <0.001 |
| Bilateral renal agenesis | 2 (8) | 1 (2) | |
| Bilateral MCDK | 4 (15) | 2 (4) | |
| MCDK + contralateral renal agenesis | 7 (9) | 0 (0) | |
| Hypoplastic/dysplastic kidney | 1 (4) | 13 (27) | |
| Obstructive uropathy | 9 (35) | 20 (42) | |
| ARPKD | 3 (12) | 9 (19) | |
| RTD | 0 (0) | 3 (6) | |
| Associated anomalies | 11 (42) | 27 (56) | 0.33 |
| Major congenital complications | 8 (31) | 18 (38) | 0.62 |
| Bilateral renal anomalies | 26 (100) | 47 (98) | 1.00 |
| Neonatal treatment | | | |
| Oxygen | 25 (96) | 48 (100) | 0.35 |
| Ventilator | 14 (54) | 39 (81) | 0.017 |
| Inotrope | 14 (54) | 34 (71) | 0.20 |
| Year | | | 0.13 |
| 2002–2012 | 12 (46) | 13 (27) | |
| 2013–2022 | 14 (54) | 35 (73) | |

Data are n (%) or median (interquartile range). *The sex was ambiguous in 2 patients.

ARPKD, autosomal recessive polycystic kidney disease; GA, gestational age; MCDK, multicystic dysplastic kidney; ROH, renal oligohydramnios; RTD, renal tubular dysgenesis.

## Table V. Detailed clinical course of 21 patients with fetal intervention

| Case | Sex | Year | Renal disease | GA of onset (weeks) | | Fetal intervention | | | | | | | | Complication (weeks) | Duration of anhydramnios (GA in weeks) | Neonatal outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Institution | Amnioinfusion | | | | | Shunt | | | | |
| | | | | ROH | Anhydramnios | | Amnioinfusion | Timing of initial infusion (weeks) | Times | Volume of fluid infused (mL) | Timing of last infusion (weeks) | Shunt | Timing (weeks) | | | |
| 1 | M | 2009 | OU | 15 | 22 | Ours | − | − | − | − | − | VAS | 17 | − | 22–39 | Death |
| 2 | M | 2019 | BM | 23 | 24 | Ours | + | 25 | 1 | 1000 | 25 | RAS | 25, 26 | − | 24, 31–36 | Death |
| 3 | F | 2021 | HK/DK | 19 | 28 | Ours | + | 28 | 1 | 1000 | 28 | − | − | PPROM (28) | 28–34 | Death |
| 4 | M | 2022 | OU | 25 | − | Ours | + | 27 | 3 | 750–800 | 31 | − | − | PPROM (31) | − | Death |
| 5 | F | 2003 | OU | 17 | 27 | Ours | + | 28 | 1 | 500 | 28 | NAS | 28 | PPROM (29) | 27–28 | Alive |
| 6 | M | 2005 | OU | 28 | 29 | Ours | + | 28 | 1 | 250 | 28 | − | − | − | 29–36<br>29–31 | Alive |
| 7 | M | 2005 | OU | 17 | NA | Other | + | 17 | 3 | NA | NA | − | − | − | NA | Alive |
| 8 | M | 2008 | OU | NA | NA | Other | + | NA | 9 | NA | NA | − | − | NA | NA | Alive |
| 9 | M | 2009 | OU | 17 | NA | Other | + | 23 | 11 | NA | 31 | VAS | NA | − | NA | Alive |
| 10 | M | 2016 | OU | 24 | 25 | Ours | − | − | − | − | − | VAS | 18, 20, 25, 30 | − | 25 | Alive |
| 11 | M | 2017 | OU | 16 | − | Other | + | 19 | 4 | 400–450 | 34 | VAS | 19, 22 | − | − | Alive |
| 12 | F | 2018 | HK/DK | 15 | NA | Other | + | 21 | NA | NA | 27 | − | − | NA | NA | Alive |
| 13 | M | 2019 | BM | 17 | NA | Other | + | 23 | 8 | NA | 35 | − | − | NA | NA | Alive |
| 14 | M | 2019 | OU | 27 | 27 | Ours | + | 27 | 2 | 850–1000 | 30 | − | − | − | 27, 35 | Alive |
| 15 | M | 2020 | ARPKD | 26 | − | Ours | + | 27 | 7 | 1000 | 36 | − | − | PPROM (36) | − | Alive |
| 16 | F | 2021 | OU | 16 | 16 | Ours | − | − | − | − | − | VAS | 20 | − | 16–17 | Alive |
| 17 | M | 2022 | ARPKD | 28 | 29 | Other | + | 30 | 2 | 700–950 | 30 | − | − | PPROM (30) | 29, 30–31 | Alive |
| 18 | M | 2022 | HK/DK | 21 | − | Other | + | 22 | 9 | NA | 32 | − | − | PPROM (32) | − | Alive |
| 19 | M | 2022 | OU | 20 | 25 | Ours | + | 25 | 6 | 500–800 | 31 | − | − | PPROM (31) | 25 | Alive |
| 20 | M | 2023 | BRA | 15 | 19 | Ours | + | 20 | 7 | 200–1000 | 32 | − | − | − | 19, 33–35 | Alive |
| 21 | M | 2023 | BM | 22 | 24 | Ours | + | 24 | 10 | 200–850 | 35 | − | − | − | 23–24, 36–37 | Alive |

ARPKD, autosomal recessive polycystic kidney disease; BM, bilateral multicystic dysplastic kidney; BRA, bilateral renal agenesis; F, female; GA, gestational age; M, male; HK/DK, hypoplastic/dysplastic kidney; RAS, renal pelvis-amniotic shunt; NA, not available; OU, obstructive uropathy; PPROM, preterm premature rupture of membranes; ROH, renal oligohydramnios; VAS, vesicoamniotic shunting

**Table VI. Comparison of characteristics between survivors and patients who died after neonatal period**

| | Patients who died after neonatal period (n=9) | Survivors (n=39) | P value |
|---|---|---|---|
| Prenatal information | | | |
| GA at onset of ROH (weeks) | 24 (19–26) | 26 (17–30) | 0.44 |
| Megacystis | 2 (22) | 15 (38) | 0.46 |
| Anhydramnios | 5 (56) | 21 (54) | 1.00 |
| Fetal intervention | 5 (56) | 12 (32) | 0.25 |
| Postnatal information | | | |
| Male sex | 8 (89) | 25 (64) | 0.24 |
| Gestational age (weeks) | 32 (31–36) | 36 (34–37) | 0.007 |
| Birth weight (g) | 1998 (1542–2680) | 2490 (2250–2758) | 0.17 |
| ≥2000 g | 4 (44) | 35 (90) | 0.007 |
| <2000 g | 5 (56) | 4 (10) | |
| Apgar score at 1 min | 3 (2–7) | 6 (4–8) | 0.08 |
| Apgar score at 5 min | 7 (4–8) | 8 (7–8) | 0.12 |
| Renal disease | | | 0.62 |
| Bilateral renal agenesis | 0 (0) | 1 (3) | |
| Bilateral MCDK | 0 (0) | 2 (5) | |
| MCDK + contralateral renal agenesis | 0 (0) | 0 (0) | |
| Hypoplastic/dysplastic kidney | 3 (33) | 10 (26) | |
| Obstructive uropathy | 2 (22) | 18 (46) | |
| ARPKD | 3 (33) | 6 (15) | |
| RTD | 1 (11) | 2 (5) | |
| Postnatal anuria | 5 (56) | 9 (23) | 0.10 |
| Associated anomalies | 6 (67) | 21 (54) | 0.71 |
| Major congenital complications | 4 (44) | 14 (36) | 0.71 |
| Gastrointestinal comorbidity | 5 (56) | 10 (26) | 0.11 |
| Kidney replacement therapy | 7 (78) | 23 (59) | 0.45 |
| Year | | | 1.00 |
| 2002–2012 | 2 (22) | 11 (28) | |
| 2013–2022 | 7 (78) | 28 (72) | |
| Observational period (months) | 5.1 (1.9–23.4) | 60.1 (25.3–107.6) | <0.001 |

Data are n (%) or median (interquartile range).

ARPKD, autosomal recessive polycystic kidney disease; GA, gestational age; MCDK, multicystic dysplastic kidney; ROH, renal oligohydramnios; RTD, renal tubular dysgenesis.

Figure 1



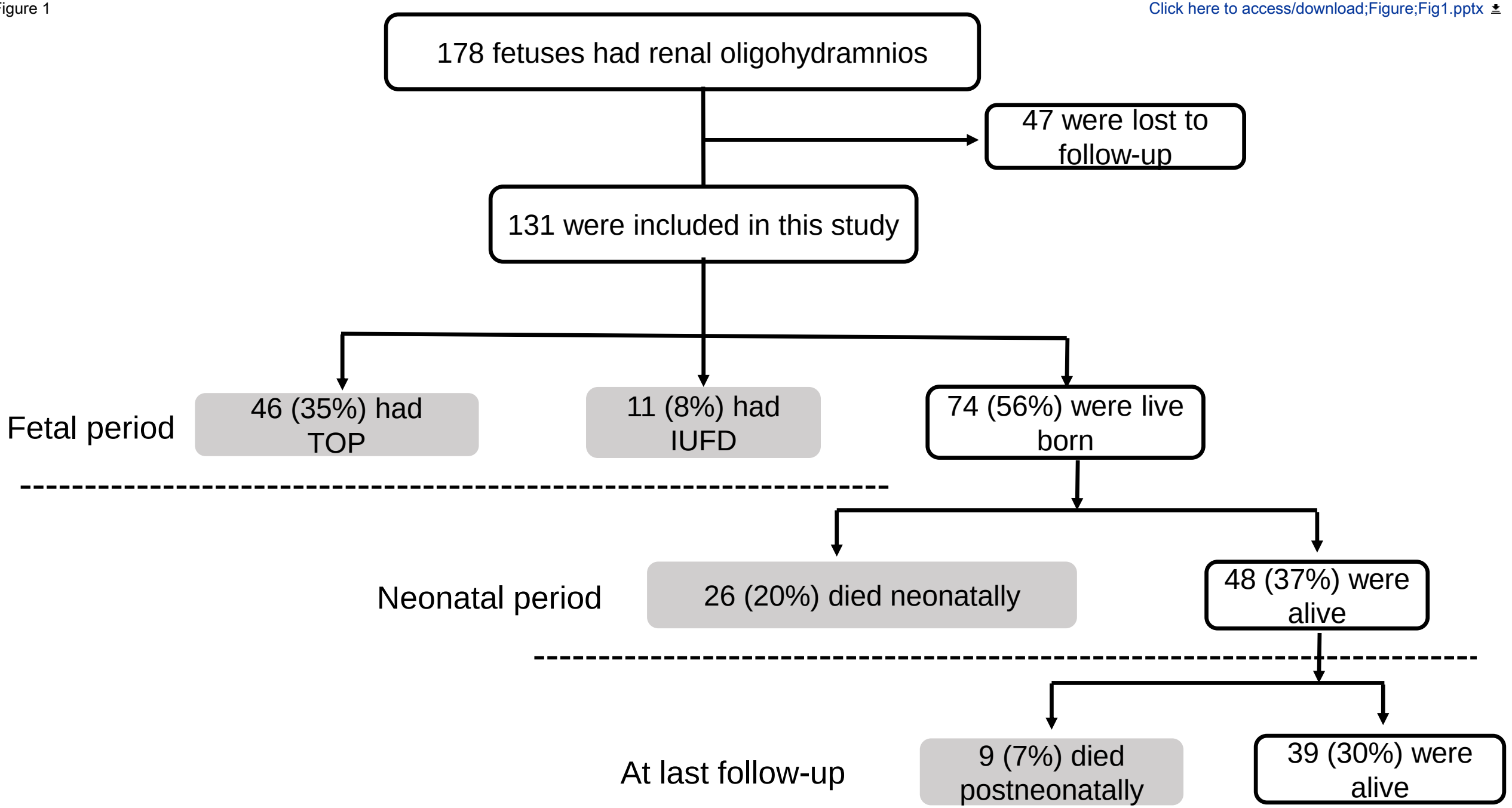
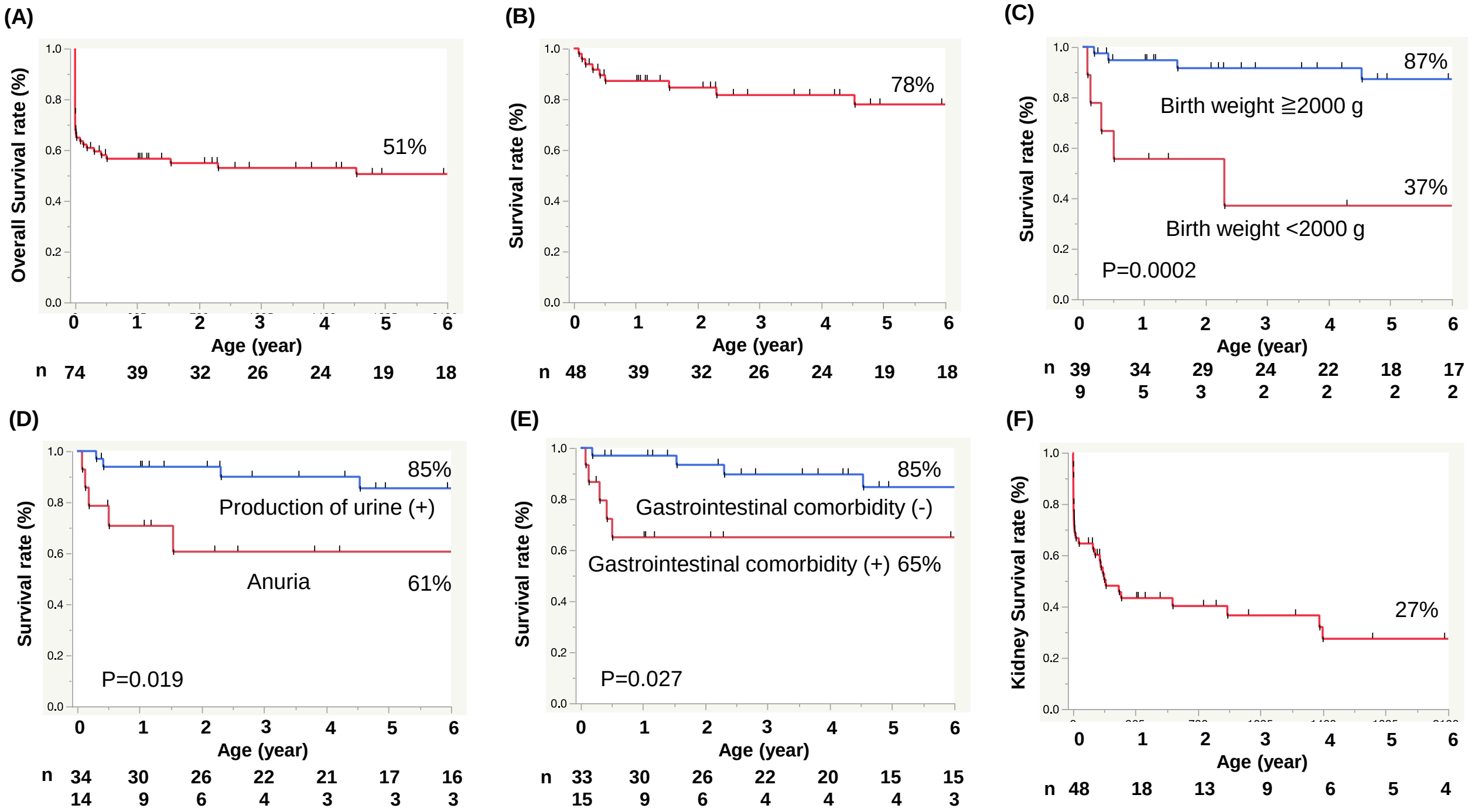


Figure 2

Click here to access/download;Figure;Fig2.pptx



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# Certificate of Editing

Edited Provisional Title

Long-term outcomes, including fetal and neonatal prognosis, of renal oligohydramnios: a retrospective study over 22 years

Client name and institution

Kentaro Nishi, National Center for Child Health and Development

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Graphic Abstract

# Long-term outcomes, including fetal and neonatal prognosis, of renal oligohydramnios: a retrospective study over 22 years

Graphical Abstract

**Objective**: To assess the long-term outcome of renal oligohydramnios and risk factors for fetal, neonatal, and postneonatal death.

## DESIGN & OUTCOMES:

178 fetuses with Renal oligohydramnios

47 lost to Follow-up

TOP, termination of pregnancy
IUFD, intrauterine fetal death

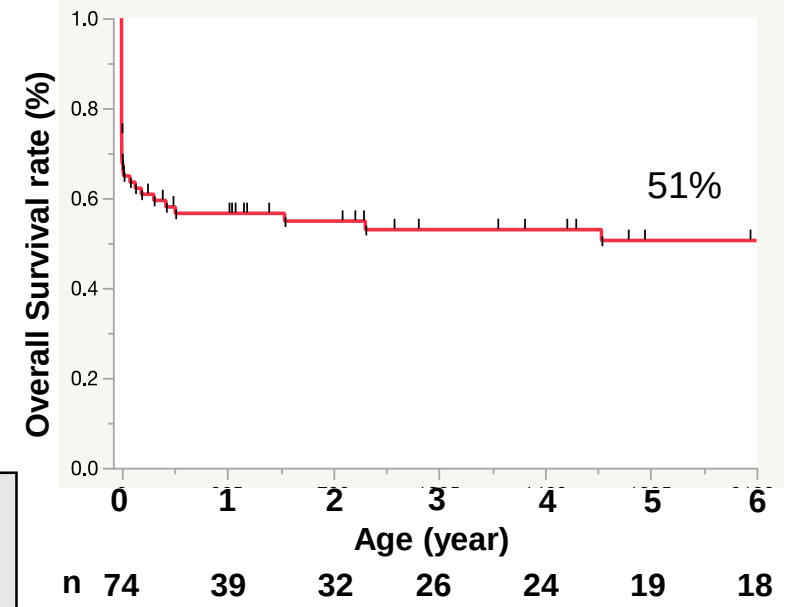
- 46 (35%) TOP
- 11 (8%) IUFD
- 26 (20%) Neonatal death
- 9 (7%) Postneonatal death
- 39 (30%) Alive

Risk Factors*
- **Earlier gestational age at onset**
  OR: 1.16
  95%CI: 1.01-1.37

Risk Factors*
- **Anhydramnios**
  OR: 12.7
  95%CI: 1.52-106.7

Risk Factors**
- **Birth weight <2000 g**
  HR: 7.33, 95%CI: 1.48-36.1
- **gastrointestinal comorbidity**
  HR: 4.37, 95%CI: 1.03-18.5

**Kaplan–Meier estimated survival rates for 74 births.**




* Logistic regression analyses
**Cox proportional hazards model

## CONCLUSION:

Long-term survival of renal oligohydramnios is a feasible goal and its appropriate risk assessment is important.

Nishi et al. 2024

The Journal of Pediatrics

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1,2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3,4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3,4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4-6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6-7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5-7 |
| Study size | 10 | Explain how the study size was arrived at | NA |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6,7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6,7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | NA |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | 4 |
| | | (*e*) Describe any sensitivity analyses | 7 |

Continued on next page

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7,8 |
| | | (b) Give reasons for non-participation at each stage | 7,8 |
| | | (c) Consider use of a flow diagram | Fig.I |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7,8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table I |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Table VI |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | 8-10 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | NA |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | NA |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-10 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 8-11 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 1 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.