Girls and Renal Scarring as Risk Factors for Febrile Urinary Tract Infection after Stopping Antibiotic Prophylaxis in Children with Vesicoureteral Reflux

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Abstract

Purpose

To clarify the incidence of and risk factors for febrile urinary tract infection in children with persistent vesicoureteral reflux (VUR) after the discontinuation of continuous antibiotic prophylaxis (CAP), retrospective chart review was performed.

Patients and Methods

Among children with primary VUR at 10 years of age or younger at presentation, those who had persistent VUR despite conservative management with CAP and who were subsequently followed after discontinuation of CAP were included. Kaplan-Meier curve and Cox's proportional hazard regression model were used for evaluation of the incidence of and risk factors for febrile urinary tract infection (fUTI) after stopping CAP.

Results

Among 144 children (99 boys and 45 girls), fUTI developed in 34. The 5-year fUTI-free rate after discontinuation of CAP was 69.4%. On multivariate analyses, girls (p=0.008) and abnormalities on nuclear renal scans (p=0.0019), especially focal defect (p=0.0471), were significant factors for fUTI. Although the fUTI-free rate was not different between children who had no or 1 risk factor, it was significantly lower in children with 2 risk factors than in those with no or 1 risk factor.

Conclusions

The present study revealed that girls and abnormal renal scan, especially focal defect, are risk factors for fUTI. Active surveillance without CAP for persistent VUR seems to be a safe option for children with no or 1 risk factor. Prophylactic surgery or careful conservative follow-up may be an option for girls with abnormal renal scan results if VUR persists under CAP.

Key words

vesicoureteral reflux, continuous antibiotic prophylaxis, febrile urinary tract infection, risk factor

Funding: None

Conflicts of interest

The author(s) declare that they have no competing interests.

Ethical standards

This study has been approved by the institutional review board. The institutional review board approved protocol number is 017-0197. The need for written informed consent was waived because this study was conducted by retrospective chart review.

Authors' contribution

Michiko Nakamura contributed to conception and design, data analysis, and manuscript writing/editing. Kimihiko Moriya was involved in conception and design, data collection, data analysis, and critical revision of the manuscript for scientific and factual content. Masafumi Kon and Yoko Nishimura collected and analyzed the data. Hiroki Chiba and Takeya Kitta critically revised the

manuscript for scientific and factual content. Nobuo Shinohara supervised the study.

Introduction

Vesicoureteral reflux (VUR) is associated with an increased risk for febrile urinary tract infection (UTI). The principle of management for children with VUR is to prevent febrile UTI and to protect renal function because sterile reflux alone does not induce renal scarring and spontaneous resolution of VUR is expected with time.

According to the American Urological Association guidelines published in 2010, conservative management with continuous antibiotic prophylaxis (CAP) is recommended as the initial management for children with primary VUR, especially in infancy[1]. Although conservative management with CAP is indicated for almost children with VUR, there are no uniform guidelines for the subsequent management of children with persistent VUR who have no recurrent febrile UTI under CAP. Our strategy for such children is basically active surveillance. First, CAP is indicated for all children with VUR. If no recurrent UTI is observed under CAP, CAP is discontinued regardless of the persistence of VUR or successful toilet training. Then, they are followed while continuing bladder and bowl management, if necessary.

Previously, we reported the risk factors for breakthrough UTI during CAP in children with primary VUR diagnosed at younger than 1 year old[2]. Moreover, we reviewed the incidence and risk factors for febrile UTI after early discontinuation of CAP in children in whom VUR was initially detected during infancy[3]. However, VUR is sometimes found in older children. Thus, it is important to clarify the risk factors for febrile UTI after stopping CAP among

children of varying ages with persistent VUR in clinical practice. We hypothesized that the risk factors for febrile UTI after discontinuation of CAP differ from those for VUR in infancy.

In the present study, we investigated the incidence and significant predictive factors for the risk for febrile UTI after stopping CAP. As we continue active surveillance for management of primary VUR for all children with persistent VUR after stopping CAP regardless of grade unless their guardians request surgical management or to continue CAP, this study presents the outcomes of active surveillance in clinical practice.

Patients and Methods

We retrospectively reviewed the medical charts of children with primary VUR at 10 years of age or younger at presentation at our hospital who were born between January 2001 and December 2016. Primary VUR was confirmed in VCUG. Initial VCUG was performed in patients with febrile UTI and/or severe hydronephrosis. CAP was indicated for all children with VUR as our management strategy for VUR. Follow-up VCUG was performed when no recurrent UTI is observed under CAP after 2 years old for infants at diagnosis, or 1 year later after febrile UTI for children at 1 year of age or older at diagnosis. When persistent VUR was detected, we inform the outcome of follow up VCUG, risk of febrile UTI after stooping CAP based on our previous study and risk of antimicrobial resistance under CAP. Then we usually stop CAP unless the guardians rejected stopping CAP or request surgical management, and followed the children while continuing bladder and bowel management if necessary. Subsequent VCUG was indicated at the time of febrile UTI or the physician’s/guardian’s preference. Of these children, those who had persistent VUR despite conservative management with CAP and who were subsequently followed after discontinuation of CAP were included in the present study.

The severity of VUR was classified into 5 grades according to the International Reflux Study in children[4], and high-grade VUR was defined as grade IV and V. In patients with bilateral VUR, the reflux grade was documented on the more severe side. Those with underlying abnormalities, such as neurogenic bladder, urethral valve, ectopic ureter, the exstrophy-epispadias

complex, and ureterocele, were excluded from the current study. Febrile UTI was characterized as significant pyuria on urinalysis associated with a fever greater than 38.0°C, malaise, flank pain, and/or significant bacteriuria. Significant pyuria and bacteriuria were defined as more than 10 white blood cells per high power field and as the growth of more than 100,000 colony-forming units per ml of single uropathogen by urine culture. Urine samples for urinalysis and culture were collected by clean catch in toilet trained children and using catheterization or collecting bags in children not yet toilet trained. Abnormal findings on dimercapto-succinic acid (DMSA) scan were defined as a focal defect or global atrophy with a split renal function of less than 40%. We performed DMSA renal scans with routine single-photon emission computerized tomography (SPECT) at presentation for patients without a history of UTI, or at 3 months or later for patients with febrile UTI. Constipation was defined as infrequent or difficult evacuation of the bowels for which laxatives were required. Breakthrough UTI under CAP is our absolute indication for surgery. However, when the guardians rejected surgical management, we continued conservative management. Such children were also included in the present study.

Regular intervals of follow-up visits included urinalysis and/or ultrasonography were varied depending on gender, age and duration after stopping CAP. It was about 3 months for 1 to 2 years after cessation of CAP and about 6 months for 1 to 2 years thereafter, subsequently regular follow-up visits at 1 or 2-year intervals were recommended until puberty. If children had febrile UTI during follow-up, the DMSA renal scan was performed 3 months or later after UTI to decide the following management. If not febrile UTI, the DMSA renal

scan was done routinely at intervals of several years.

We analyzed the incidence of and risk factors for febrile UTI after discontinuation of CAP. The febrile UTI-free time was calculated from date of stopping CAP to the date of the first febrile UTI during active surveillance, date of anti-reflux surgery, confirmation of VUR resolution, or last contact with patients without febrile UTI. JMP®pro version 14 was used for all statistical analyses. Kaplan-Meier curve was used to evaluate the febrile UTI-free rate. Statistical analyses were performed using Cox's proportional hazard regression model and the log-rank test. $P<0.05$ was considered significant.

This study was approved by our institutional ethics committee (No. 017-0197).

Results

Of 234 children in whom primary VUR was detected at 10 years old or younger, conservative management with CAP was indicated for 223 children. Since 49 children, 23 still under CAP and 26 treated surgically before stopping CAP, were excluded from the current study, 174 children were subsequently followed until follow up VCUG. As a spontaneous resolution of VUR was confirmed at the time of stopping CAP in 26 and 4 children were lost to follow-up just after stopping CAP, a total of 144 children with persistent VUR who were followed after stopping CAP were included in the present study (Figure1).

The patient characteristics were shown in Table 1. The present study enrolled 99 boys and 45 girls. The median age at first presentation was 8.8 months old. The presenting symptom was mainly febrile UTI (90%). On initial VCUG, bilateral VUR was identified in 81 children (56%) and high-grade VUR was noted in 68 (47%). Among 139 children who underwent DMSA scintigraphy after presentation, 78 (56%) had abnormal findings. Of these 78 children, 32 had only focal defect, 34 had only global atrophy and 12 had both. The median age at stopping CAP was 25 months old and the median follow-up period after stopping CAP was 5.1 years. High-grade VUR was detected in 49 children (34%) at the time of stopping CAP.

During follow-up, febrile UTI developed in 34 children. The median age of the first febrile UTI after stopping CAP was 50 months old (Inter Quartile Range (IQR) 27.1-70.8), and the median duration after stopping CAP was 16.8 months (IQR 1.28-29.4). The febrile UTI-free rate at 1 year, at 2 years and at 5 years after

discontinuation of CAP were 88.3%, 82.8% and 69.4%, respectively (Figure 2).

Nineteen of 34 children with febrile UTI after stopping CAP underwent surgical correction of VUR (17 by ureteral reimplantation by open procedure and 2 by endoscopic injection of Dextranomer/Hyaluronic acid Copolymer (Deflux®)), whereas the remaining 15 children did not undergo surgery because their guardians rejected surgical corrections and requested to continue active surveillance. Of 34 children with febrile UTI after stopping CAP, DMSA scan was performed in 31. Among them, new focal defect developed in 9 children.

The risk factors for febrile UTI in children with persistent VUR after stopping CAP are summarized in Table 2. On univariable analysis, a significantly higher rate of febrile UTI after the discontinuation of CAP was found in girls (Hazard ratio (HR); 3.46, 95% confidence interval (95%CI); 1.56-7.80, p=0.002) and in children in whom VUR was detected during infancy (HR; 0.38, 95%CI; 0.17-0.86, p=0.020). Children with abnormal findings on DMSA scan had a significantly higher rate of febrile UTI (HR; 2.27, 95%CI; 1.01-5.40, p=0.047). On multivariable analyses, girls (HR; 5.47, 95%CI; 2.01-16.24, p=0.001) and abnormal findings on DMSA scans (HR; 4.46, 95%CI; 1.70-13.21, p=0.002) were significant risk factors for febrile UTI.

Among 144 patients, 139 children who had DMSA scan as initial evaluation were stratified into 3 groups by the number of these risk factors (girl and abnormal findings on DMSA scans) they had. The number of children who had 0, 1, or 2 risk factors was 34, 89, or 16, respectively. The febrile UTI-free rate at 1 year, at 2 years and at 5 years after discontinuation of CAP were 97.1%, 97.1% and 84.0% with no risk factors, 88.3%, 85.3% and 74.4% with 1 risk factor,

and 67.0%, 40.2% and 16.7% with 2 risk factors, respectively (Figure 3). The febrile UTI-free rate was not different between children with 0 or 1 risk factor. However, it was significantly lower in patients with 2 risk factors, girls with abnormal findings on DMSA scans, than in those with no or 1 risk factor ($p<0.0001$). When findings of abnormal DMSA scans were divided into 2 categories, focal defect or global atrophy, the focal defect was identified as a significant risk factor on univariate and multivariate analysis whereas global atrophy was not (table 3). When stratified by the number of these risk factors (girl and focal defect on DMSA scans) in the same way as above, the number of children with 0, 1, or 2 risk factors was 66, 59, or 14, respectively. The febrile UTI-free rate at 1 year, at 2 years and at 5 years after discontinuation of CAP were 95.4%, 93.3% and 78.8% with no risk factors, 86.0%, 79.4% and 70.7% with 1 risk factor, and 54.2%, 31.0% and 20.6% with 2 risk factors, respectively (Figure 4). The febrile UTI-free rate was also significantly lower in patients with 2 risk factors, than in those with no or 1 risk factor ($p<0.0001$).

Discussion

The present study revealed that approximately 70% children with persistent VUR were free from febrile UTI for 5 years after stopping CAP, and that girls and abnormal findings on DMSA scans, especially focal defect, are risk factors for febrile UTI after the discontinuation of CAP. Additionally, the rate of febrile UTI was significantly higher in children with 2 risk factors than in those with no or 1 risk factor.

One of the most important goals in the management of VUR is the prevention of the progression of renal damage. Conservative management with CAP is widely accepted due to possibility of spontaneous resolution of VUR with time[5-7], effectiveness of CAP for preventing recurrent UTI in children with or without VUR[8-11], and no difference in the rate of developing new renal scarring between surgical and conservative management with CAP, although surgery reduces the risk of febrile UTI[12]. Therefore, we performed conservative management with CAP as the initial management of primary VUR for all children with any grade of VUR. As our strategy for the management of primary VUR was basically active surveillance regardless of gender, age, or grade of VUR, the outcome of the present study was minimally biased in terms of patient selection though some referral bias might exist. In addition, we extended the inclusion criteria to children up to 10 years old at presentation, thus our results may closely reflect clinical practice.

Should CAP be continued for children who have no recurrent UTI with persistent VUR until resolution? The period of continuing CAP for children with

persistent VUR is controversial. Although there have been no prospective studies regarding the duration of CAP or appropriate timing of stopping CAP for children with persistent VUR, some retrospective reports demonstrated the safety of and risk factors for cessation of CAP for toilet-trained children[13-15]. In addition, we previously reviewed the incidence of and risk factors for febrile UTI after early discontinuation of CAP in children in whom VUR was initially detected during infancy[3]. Our observational study demonstrated the safety of stopping CAP for children with persistent VUR even before toilet training was completed. When compared to CAP group in RIVUR study[8], 2-year UTI free rate in the present study were much higher in patient with no risk factor, almost similar with 1 risk factor and much lower with 2 risk factors. These findings suggest that by stratified with risk factors for febrile UTI, stopping CAP for patients with persistent VUR and no UTI under CAP would be a safe option for the management of primary VUR regardless of the status of toilet training, and that administration of CAP until resolution of VUR would be unnecessary for selected children with persistent VUR.

The present study and other previous studies[13-15] reported that the median duration from stopping CAP to febrile UTI was as early as less than 2 years and that febrile UTI was uncommon after 5 years from stopping CAP. Although the appropriate duration of CAP and optimal timing of stopping CAP remain unclear, stopping CAP after an exact administration duration may be a safe option, especially for patients with no or 1 risk factor, because risk of febrile UTI was 2.9 or 14.7% at 2 years after stopping CAP as demonstrated in the present study. Patients should be followed carefully after stopping CAP especially

for patients with 2 risk factors because febrile UTI often develops during the early period after stopping CAP, and because timely evaluation and treatment can minimize the formation of renal scarring even when UTI develops[3,16,17].

In the current study, two risk factors for febrile UTI after stopping CAP, girls and abnormal renal scan, were identified. One possible explanation as to why febrile UTI after stopping CAP is associated with gender, as demonstrated in previous studies, is that UTI develops more frequently in girls than in boys after infancy, which may have an anatomical basis[17,18]. Another possible explanation is that girls have a higher incidence of bladder and bowel dysfunction (BBD)[19,20]. Although BBD is thought to be a factor for developing UTI and disturbing the spontaneous resolution of VUR[14,19,20], BBD is usually diagnosed after toilet training. As many pre-toilet trained children were included in this retrospective study, we were unable to accurately evaluate the bladder and bowel status. In addition, many of the patients included in this study were followed from infantile period, prophylactic bladder management including timed void was performed at the time of toilet training because BBD was a known risk factor for febrile UTI. Accordingly, assessment of naïve bladder function or micturition habit was difficult in this cohort. The gender difference in the rate of febrile UTI after stopping CAP may be related to gender differences in the bladder and bowel status. In our previous study, gender was not a risk factor for febrile UTI[3]. Because the rate of boys with VUR detected during infancy was higher than girls in Japan[21], the rate of girls in our previous study was fewer than present study (13% vs 31%)[3]. Due to expansion of the inclusion criteria up to 10 years old in the present study, we could reveal that girl is a risk factor of febrile UTI after

discontinuation of CAP.

Another risk factor for febrile UTI after stopping CAP is abnormal renal scan, especially focal defect. Previous studies demonstrated abnormal findings on DMSA scans as a factor predicting breakthrough UTI [2,22-24]. Focal defect on DMSA is recognized as acquired renal cortical damage induced by previous febrile UTI. BBD is recognized to be a risk factor for developing UTI, which is a cause of acquired renal damage after birth. Previous study demonstrated that the children who have 2 febrile UTI have a substantially higher risk of renal scarring compared with children with a single febrile UTI[25]. The exact reason as to why abnormal findings on DMSA scans are related to febrile UTI is unknown. However, we speculated that abnormal findings on DMSA scans reflect bladder dysfunction retained, and that abnormal DMSA findings were related to febrile UTI after stopping CAP in the current study.

Of note, we found that patients with 2 risk factors, girls and abnormal DMSA scan, especially focal defect, had an increased risk of febrile UTI after stopping CAP. Stratification of risk of febrile UTI by risk factors is beneficial in clinical practice. Although active surveillance without CAP seems to be a reasonable option for patients with no or 1 risk factor, careful follow-up, which include advices to have proper elimination habit and timely examination and management when they have high fever which is possibly due to UTI, is necessary for patients with 2 risk factors if conservative management is planned to continue. On the other hand, prophylactic surgery may be an option for these patients.

Several limitations of the present study should be addressed. This study

was retrospective. Another potential weakness of this study is that we were unable to accurately evaluate the status of bladder and bowel function in all children because many pre-toilet trained children were included. And due to retrospective nature, standardized evaluation of bladder or bowel function was not performed during follow up to estimate the presence or absence of BBD at the time of regular visit. Accordingly, the condition of evacuation could not be included in the items for statistics. Moreover, as VCUG was not performed subsequently after stopping CAP unless some adverse event like febrile UTI developed, some children whose VUR spontaneously resolved during follow-up after stopping CAP may have been included in the present study.

Although our study had these limitations, it was suggested that risk stratification by the risk factors identified in the present study will be valuable in clinical practice, which will improve the prognosis of children of varying ages with persistent VUR after stopping CAP.

In conclusions, the present study revealed that approximately 70% of patients with persistent VUR were free of febrile UTI for 5 years after stopping CAP, and that girls and abnormal findings on DMSA scintigraphy, especially focal defect, are risk factors for febrile UTI after stopping CAP. Patients both with these factors had a significantly higher rate of febrile UTI than those with no or 1 risk factor. Accordingly, more careful follow-up or prophylactic surgery before recurrent UTI should be indicated in these high-risk patients. On the contrary, active surveillance after stopping CAP may be a safe option for children with no or 1 risk factor.

References

1. Peters CA, Skoog SJ, Arant BS, Copp HL, Elder JS, Hudson RG, Khoury AE, Lorenzo AJ, Pohl HG, Shapiro E, Snodgrass WT, Diaz M (2010) Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol 184 (3):1134-1144. doi:10.1016/j.juro.2010.05.065
2. Nakamura M, Moriya K, Mitsui T, Tanaka H, Nonomura K (2009) Abnormal dimercapto-succinic acid scan is a predictive factor of breakthrough urinary tract infection in children with primary vesicoureteral reflux. J Urol 182 (4 Suppl):1694-1697. doi:10.1016/j.juro.2009.03.070
3. Moriya K, Mitsui T, Kitta T, Nakamura M, Kanno Y, Kon M, Nishimura Y, Shinohara N, Nonomura K (2015) Early discontinuation of antibiotic prophylaxis in patients with persistent primary vesicoureteral reflux initially detected during infancy: outcome analysis and risk factors for febrile urinary tract infection. J Urol 193 (2):637-642. doi:10.1016/j.juro.2014.08.007
4. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE (1985) International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol 15 (2):105-109
5. Estrada CR, Passerotti CC, Graham DA, Peters CA, Bauer SB, Diamond DA, Cilento BG, Borer JG, Cendron M, Nelson CP, Lee RS, Zhou J, Retik AB, Nguyen HT (2009) Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. J Urol 182 (4):1535-1541. doi:10.1016/j.juro.2009.06.053
6. Schwab CW, Wu HY, Selman H, Smith GH, Snyder HM, Canning DA (2002)

Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. J Urol 168 (6):2594-2599. doi:10.1097/01.ju.0000037530.11361.8b

7. Knudson MJ, Austin JC, McMillan ZM, Hawtrey CE, Cooper CS (2007) Predictive factors of early spontaneous resolution in children with primary vesicoureteral reflux. J Urol 178 (4 Pt 2):1684-1688. doi:10.1016/j.juro.2007.03.161
8. Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, Kropp BP, Skoog SJ, Nelson CP, Moxey-Mims M, Chesney RW, Carpenter MA (2014) Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 370 (25):2367-2376. doi:10.1056/NEJMoa1401811
9. Brandström P, Jodal U, Sillén U, Hansson S (2011) The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. J Pediatr Urol 7 (6):594-600. doi:10.1016/j.jpurol.2011.05.006
10. de Bessa J, de Carvalho Mrad FC, Mendes EF, Bessa MC, Paschoalin VP, Tiraboschi RB, Sammour ZM, Gomes CM, Braga LH, Bastos Netto JM (2015) Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. J Urol 193 (5 Suppl):1772-1777. doi:10.1016/j.juro.2014.10.092
11. Lee T, Park JM (2017) Vesicoureteral reflux and continuous prophylactic antibiotics. Investig Clin Urol 58 (Suppl 1):S32-S37. doi:10.4111/icu.2017.58.S1.S32
12. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux

Study Group (1987). Br Med J (Clin Res Ed) 295 (6592):237-241

13. Cooper CS, Chung BI, Kirsch AJ, Canning DA, Snyder HM (2000) The outcome of stopping prophylactic antibiotics in older children with vesicoureteral reflux. J Urol 163 (1):269-272; discussion 272-263
14. Leslie B, Moore K, Salle JL, Khoury AE, Cook A, Braga LH, Bägli DJ, Lorenzo AJ (2010) Outcome of antibiotic prophylaxis discontinuation in patients with persistent vesicoureteral reflux initially presenting with febrile urinary tract infection: time to event analysis. J Urol 184 (3):1093-1098. doi:10.1016/j.juro.2010.05.013
15. Kitchens DM, Herndon A, Joseph DB (2010) Outcome after discontinuing prophylactic antibiotics in children with persistent vesicoureteral reflux. J Urol 184 (4 Suppl):1594-1597. doi:10.1016/j.juro.2010.04.020
16. Al-Sayyad AJ, Pike JG, Leonard MP (2005) Can prophylactic antibiotics safely be discontinued in children with vesicoureteral reflux? J Urol 174 (4 Pt 2):1587-1589; discussion 1589
17. Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, Tekgül S, Urology EAo, Urology ESfP (2015) Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol 67 (3):546-558. doi:10.1016/j.eururo.2014.11.007
18. Shaikh N, Morone NE, Bost JE, Farrell MH (2008) Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J 27 (4):302-308. doi:10.1097/INF.0b013e31815e4122
19. Koff SA, Wagner TT, Jayanthi VR (1998) The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and

urinary tract infections in children. J Urol 160 (3 Pt 2):1019-1022

20. Chen JJ, Mao W, Homayoon K, Steinhardt GF (2004) A multivariate analysis of dysfunctional elimination syndrome, and its relationships with gender, urinary tract infection and vesicoureteral reflux in children. J Urol 171 (5):1907-1910. doi:10.1097/01.ju.0000120288.82950.a2
21. Nakai H, Kakizaki H, Konda R, Hayashi Y, Hosokawa S, Kawaguchi S, Matsuoka H, Nonomura K, Shimada K, Kawamura T, Prospective Study Committee of Reflux Nephropathy Forum Jp (2003) Clinical characteristics of primary vesicoureteral reflux in infants: multicenter retrospective study in Japan. J Urol 169 (1):309-312. doi:10.1097/01.ju.0000042766.09295.72
22. Yamazaki Y, Shiroyanagi Y, Matsuno D, Nishi M (2009) Predicting early recurrent urinary tract infection in pretoilet trained children with vesicoureteral reflux. J Urol 182 (4 Suppl):1699-1702. doi:10.1016/j.juro.2009.03.020
23. Mingin GC, Nguyen HT, Baskin LS, Harlan S (2004) Abnormal dimercapto-succinic acid scans predict an increased risk of breakthrough infection in children with vesicoureteral reflux. J Urol 172 (3):1075-1077; discussion 1077
24. Loukogeorgakis SP, Burnand K, MacDonald A, Wessely K, De Caluwe' D, Rahman N, Farrugia MK (2020) Renal scarring is the most significant predictor of breakthrough febrile urinary tract infection in patients with simplex and duplex primary vesico-ureteral reflux. J Pediatr Urol 16 (2):189.e181-189.e187. doi:10.1016/j.jpurol.2019.11.018
25. Shaikh N, Haralam MA, Kurs-Lasky M, Hoberman A (2019) Association of Renal Scarring With Number of Febrile Urinary Tract Infections in Children. JAMA Pediatr. doi:10.1001/jamapediatrics.2019.2504

Legends to illustrations

Figure 1: Inclusion criteria

Figure 2: Febrile UTI free-rate after stopping CAP

The 5-year febrile UTI-free rate was 69.4%.

Figure 3: Febrile UTI free-rate after stopping CAP based on risk factors (girl and abnormality on DMSA scan)

The rate of febrile UTI was significantly higher in children with 2 risk factors than in those with no or 1 risk factor.

Figure 4: Febrile UTI free-rate after stopping CAP based on risk factors (girl and focal defect on DMSA scan)

The rate of febrile UTI was significantly higher in children with 2 risk factors than in those with no or 1 risk factor.

Tables and their legends

Table 1: Patients characteristics

Table 2: The risk factors for febrile UTI after discontinuation of CAP

Table 1: Patients characteristics

		No. of patients	Median ± SD	IQR
Gender	male	99		
	female	45		
Gestational age (weeks)			39 ± 1.49	38, 40
Premature birth (<37 weeks)		9/123		
Birth weight (g)			3108 ± 429.0	2761, 3350.5
Low birth weight (<2500 g)		17/132		
Age at presentation (months)			8.81 ± 28.08	4.96, 31.5
Presenting symptom	UTI	130*		
	abnormality on USG	18*		
	other	2		
< 1 year old at first examination		100/144		
Constipation		23/139		
Age at first VCUG (months)			7.3 ±25.3	4.0, 15.8
VUR grade at initial examination	1	12		
	2	24		
	3	40		
	4	45		
	5	23		
Bilateral VUR		81/144		
Age at final VUCG (months)			25.8±27.3	23.6, 57.4
VUR grade at final examination	1	24		
	2	26		
	3	45		
	4	33		
	5	16		
Treatment of phimosis		8/90		
Abnormal findings on DMSA scan		78/139		
	Focal defect	44**/139		
	Globall atrophy	46**/139		
Breakthrough UTI before stopping CAP		20/144		
Age at stopping CAP (months)			24.96 ± 24.30	24.0, 41.5
CAP period (months)			16.46 ± 9.39	12.0, 20.9
CAP < 1 year		35/144		
Stopping CAP < 2 years old		40/144		
Follow-up after stopping CAP (years)			5.08 ± 3.65	2.51, 8.25

*: 6 patients had both UTI and abnormal USG as presenting symptoms

**: 12 patioents had both focaldefect and global atopphy

Table 2: The risk factors for febrile UTI after discontinuation of CAP

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender (F/M)	**3.46**	**1.56-7.80**	**0.0024**	**5.47**	**2.01-16.24**	**0.0008**
Premature birth	0.38	0.020-2.23	0.3237			
Low birth weight (<2500 g)	1.05	0.29-3.27	0.9329			
Presenting symptom (UTI)	1.96	0.50-13.02	0.3633			
Presenting symptom (abnormality on USG)	0.61	0.14-2.01	0.4430			
Constipation	0.60	0.17-1.76	0.3733			
< 1 year old at first examination	**0.38**	**0.17-0.86**	**0.0196**	0.87	0.32-2.41	0.7829
High-grade VUR at first examination	0.85	0.39-1.84	0.6779			
High-grade VUR at final examination	1.56	0.70-3.45	0.2724			
Bilateral VUR	0.98	0.45-2.15	0.9606			
Abnormal findings on DMSA scan	**2.27**	**1.01-5.40**	**0.0471**	**4.46**	**1.70-13.21**	**0.0019**
Treatment of phimosis	0.72	0.037-4.51	0.7622			
CAP < 1 year	2.06	0.88-4.75	0.0964	1.99	0,71-5.47	0.1861
Breakthrough UTI before stopping CAP	0.32	0.049-1.19	0.0948	0.44	0.06-1.87	0.2852
Stopping CAP < 2 years old	0.75	0.29-1.77	0.5219			

Table 3: The risk factors for febrile UTI after discontinuation of CAP

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Gender (F/M)	**3.46**	**1.56-7.80**	**0.0024**	**3.34**	**1.37-8.36**	**0.0082**
Premature birth	0.38	0.020-2.23	0.3237			
Low birth weight (<2500 g)	1.05	0.29-3.27	0.9329			
Presenting symptom (UTI)	1.96	0.50-13.02	0.3633			
Presenting symptom (abnormality on USG)	0.61	0.14-2.01	0.4430			
Constipation	0.60	0.17-1.76	0.3733			
< 1 year old at first examination	**0.38**	**0.17-0.86**	**0.0196**	0.82	0.31-2.21	0.6937
High-grade VUR at first examination	0.85	0.39-1.84	0.6779			
High-grade VUR at final examination	1.56	0.70-3.45	0.2724			
Bilateral VUR	0.98	0.45-2.15	0.9606			
Focal defect on DMSA scan	**2.44**	**1.09-5.47**	**0.0295**	**2.39**	**1.01-5.71**	**0.0471**
Global atrophy on DMSA scan	1.60	0.71-3.54	0.2546			
Treatment of phimosis	0.72	0.037-4.51	0.7622			
CAP < 1 year	2.06	0.88-4.75	0.0964	1.66	0.62-4.39	0.3091
Breakthrough UTI before stopping CAP	0.32	0.049-1.19	0.0948	0.48	0.07-2.03	0.3474
Stopping CAP < 2 years old	0.75	0.29-1.77	0.5219			

Figure 1: Inclusion criteria

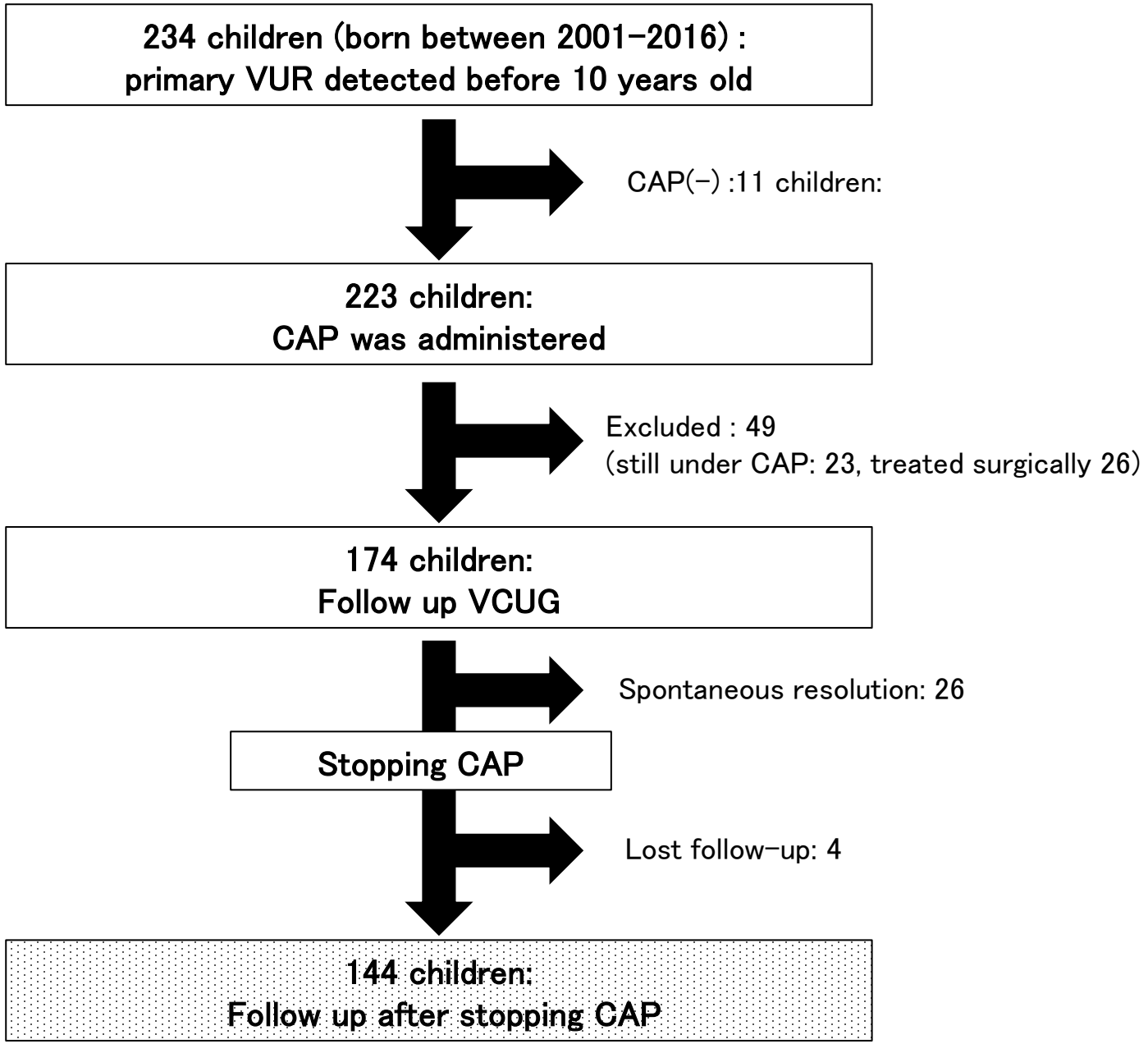
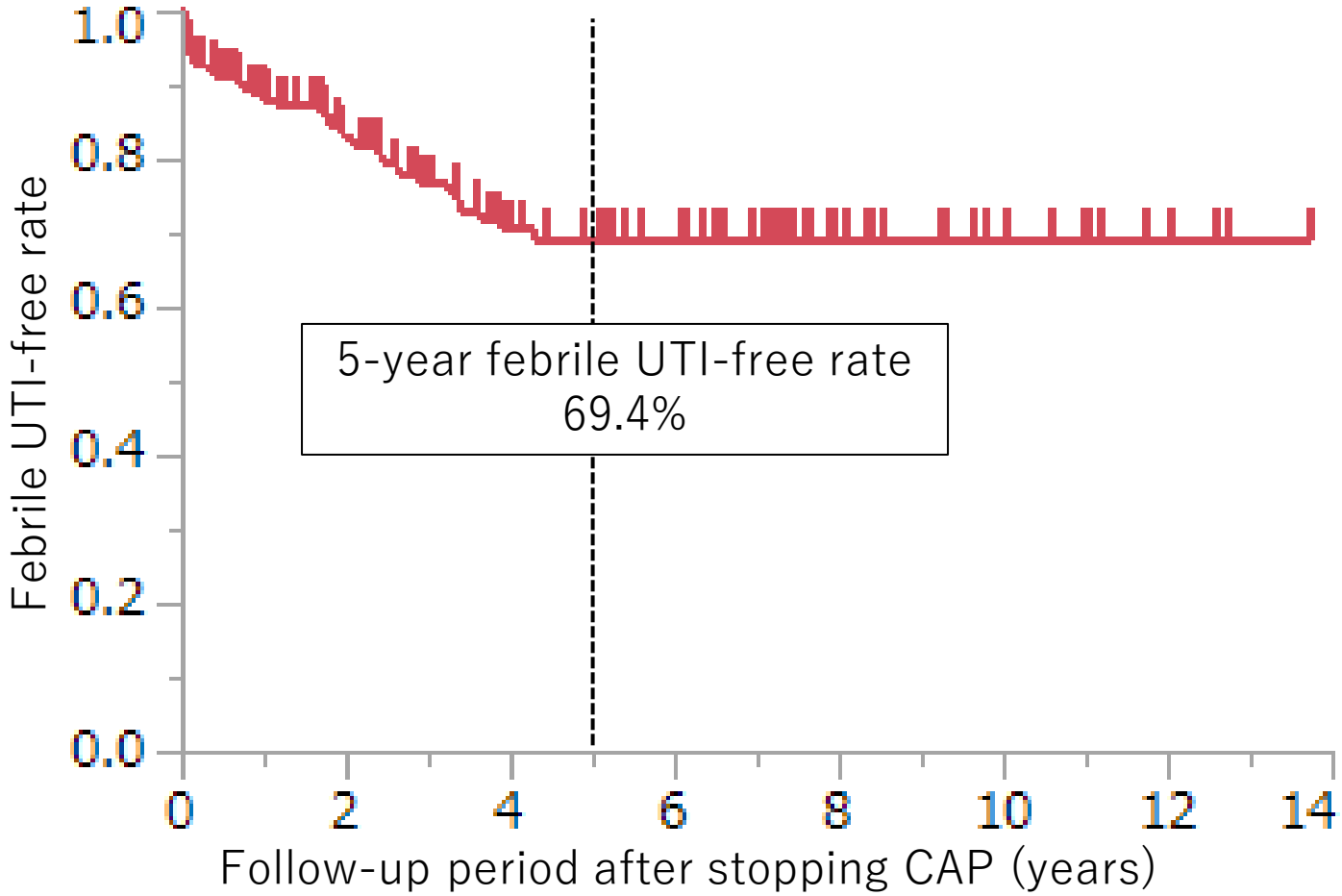


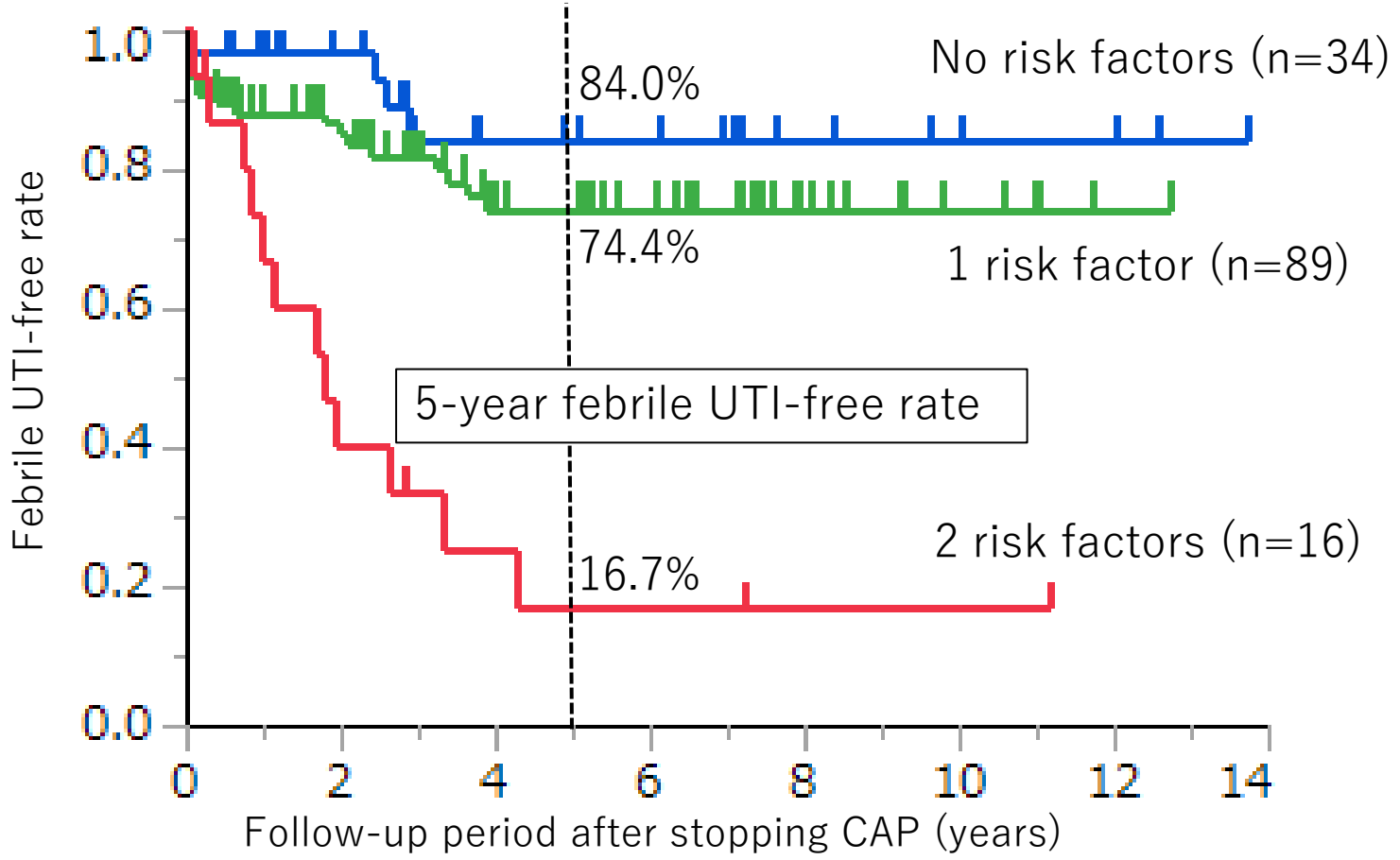
Figure 2: Febrile UTI free-rate after stopping CAP



Patients at risk

	1 year	2 years	3 years	5 years
patients at risk	106	90	68	48

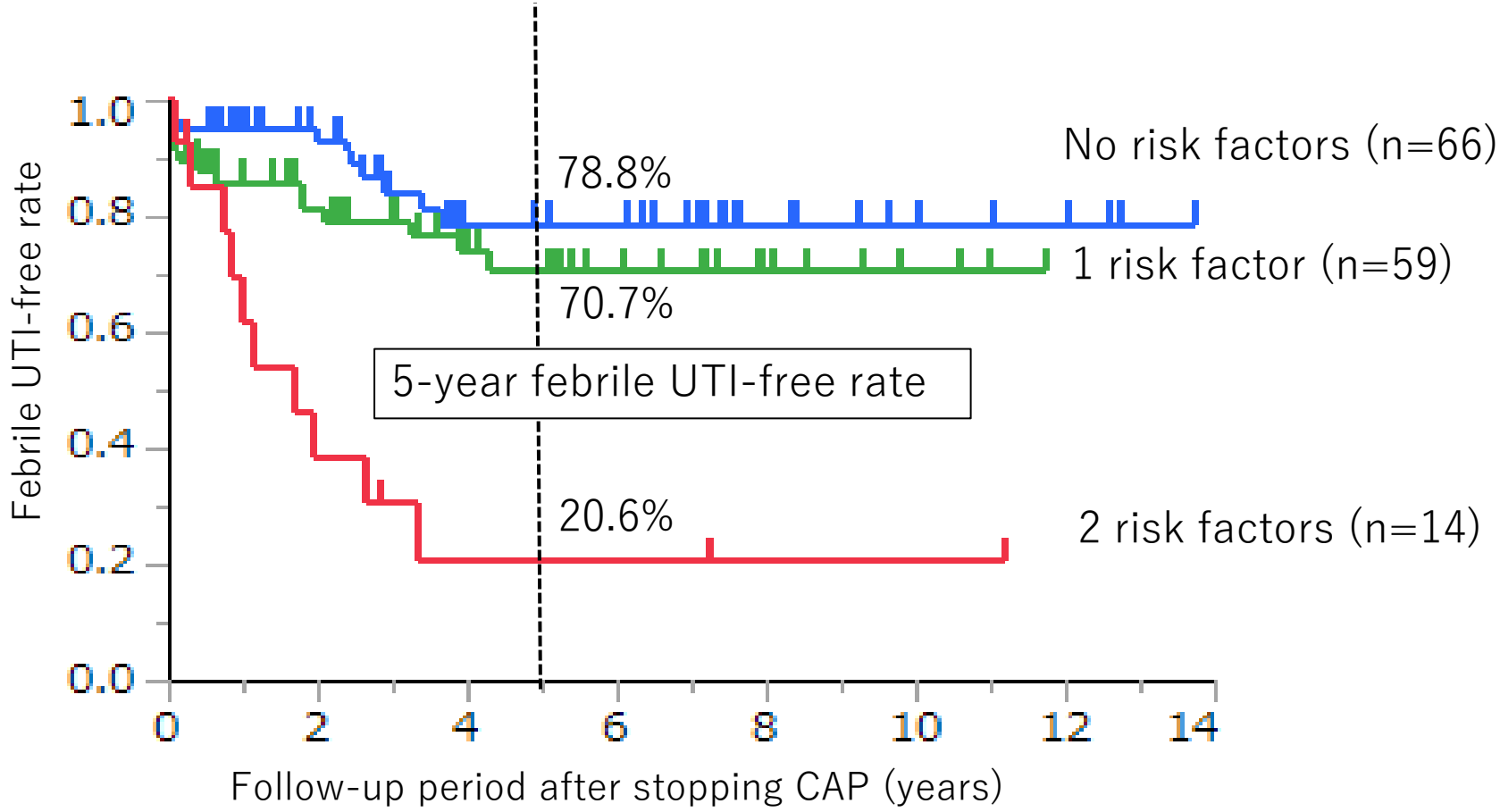
Figure 3: Febrile UTI free-rate after stopping CAP based on risk factors (girl and abnormality on DMSA scan)



Patients at risk

	1 year	2 years	3 years	5 years
no risk factors	30	26	17	13
1 risk factor	63	57	47	34
2 risk factors	11	7	5	3

Figure 4: Febrile UTI free-rate after stopping CAP based on risk factors (girl and focal defect on DMSA scan)



Patients at risk

	1 year	2 years	3 years	5 years
no risk factors	52	46	32	24
1 risk factor	43	38	33	23
2 risk factors	9	6	4	3