Cytokine 120 (2019) 258–263

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Serum soluble ST2 as a marker of renal scar in pediatric upper urinary tract infection

Naoki Ohta[a], Hiroki Yasudo[a,*], Makoto Mizutani[a], Takeshi Matsushige[a], Reiji Fukano[a], Setsuaki Kittaka[a], Kenji Maehara[a], Kiyoshi Ichihara[b], Shouichi Ohga[c], Shunji Hasegawa[a]

[a] Department of Pediatrics, Yamaguchi University Graduate School of Medicine, Ube, Japan
[b] Department of Clinical Laboratory Science, Faculty of Health Science, Yamaguchi University Graduate School of Medicine, Ube, Japan
[c] Department of Pediatrics, Kyushu University Graduate School of Medical Science, Fukuoka, Japan

ARTICLE INFO

Keywords:
Upper urinary tract infection
Acute pyelonephritis
Acute focal bacterial nephritis
Soluble ST2
Cytokine
Renal scarring

ABSTRACT

Background and objectives: Upper urinary tract infection is the most common serious bacterial infection in childhood. Patients with upper urinary tract infection have a risk for renal scarring with subsequent complications including hypertension, proteinuria, and progressive renal failure. However, the predictive biomarkers of renal scarring in children with upper urinary tract infection are still unknown. In this study, we evaluated whether soluble ST2 levels can be biomarkers of subsequent renal scarring in patients with upper urinary tract infection.

Design, setting, participants, and measurements: We retrospectively studied pediatric patients with upper urinary tract infection at a tertiary center. Twenty-eight children had an upper urinary tract infection with (n = 14) and without (n = 14) renal scarring and underwent 99mtechnetium dimercaptosuccinic acid imaging. In addition, 13 control subjects were enrolled. The clinical data and serum cytokine levels, including soluble ST2 levels, were compared between those with and without renal scars.

Results: Serum soluble ST2 levels were significantly higher in the scar group than in the non-scar group, whereas there was no difference in the levels of serum interferon-γ, interleukin-6, interleukin-10, soluble tumor necrosis factor receptor 1, and transforming growth factor-β between the scar and non-scar groups. The area under the curve for differentiating between the non-scar and scar groups on the basis of measurements of serum soluble ST2 was 0.79, with a sensitivity and specificity of 92.9% and 64.3%, respectively.

Conclusion: These results suggest that serum soluble ST2 levels on admission could be a useful biomarker of subsequent renal scarring in pediatric patients with upper urinary tract infection.

1. Introduction

Upper urinary tract infection (UTI) is one of the common serious bacterial infections that occur in early childhood [1]. Generally, UTI patients present characteristic symptoms, including dysuria, suprapubic discomfort, and flank pain. However, children with UTI may present with nonspecific symptoms, such as poor feeding, vomiting, irritability, jaundice, or fever alone, which require a broader approach to screening. Approximately 5% of fever of unknown origin in infants could be caused by UTI [2].

UTI is classified into three types: upper UTI, lower UTI, and asymptomatic bacteriuria [3]. Upper UTI is the most severe form of the disease and consists of acute pyelonephritis (APN), acute focal bacterial nephritis (AFBN), and renal abscess. Permanent renal damage characterized by scarring has been observed in 15–60% of pediatric patients with APN and 89% of pediatric patients with AFBN [1,3]. These damages could lead to hypertension, proteinuria, pregnancy-related complications, or even progressive renal failure as long-term sequelae [4].

It has been reported that risk factors for renal scar formation in

Abbreviations: UTI, upper urinary tract infection; sST2, soluble ST2; VUR, vesicoureteral reflux; TNF, tumor necrosis factor; IFN, interferon; IL, interleukin; JAID/JSC, Japanese Association for Infection Diseases/Japanese Society of Chemotherapy; 99mTc-DMSA, 99m-technetium dimercaptosuccinic acid; TGF-β, transforming growth factor-β; ELISA, enzyme-linked immunosorbent assay; ROC, receiver operating characteristics; AUC, area under the curve

* Corresponding author at: Department of Pediatrics, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan.
E-mail addresses: naoki@yamaguchi-u.ac.jp (N. Ohta), yasudo@yamaguchi-u.ac.jp (H. Yasudo), mizutani@yamaguchi-u.ac.jp (M. Mizutani), matsu@yamaguchi-u.ac.jp (T. Matsushige), fukano.r@yamaguchi-u.ac.jp (R. Fukano), maeharak@yamaguchi-u.ac.jp (K. Maehara), ichihara@yamaguchi-u.ac.jp (K. Ichihara), ohgas@pediatr.med.kyushu-u.ac.jp (S. Ohga), shunji@yamaguchi-u.ac.jp (S. Hasegawa).

https://doi.org/10.1016/j.cyto.2019.05.006
Received 20 February 2019; Received in revised form 25 April 2019; Accepted 8 May 2019
Available online 29 May 2019

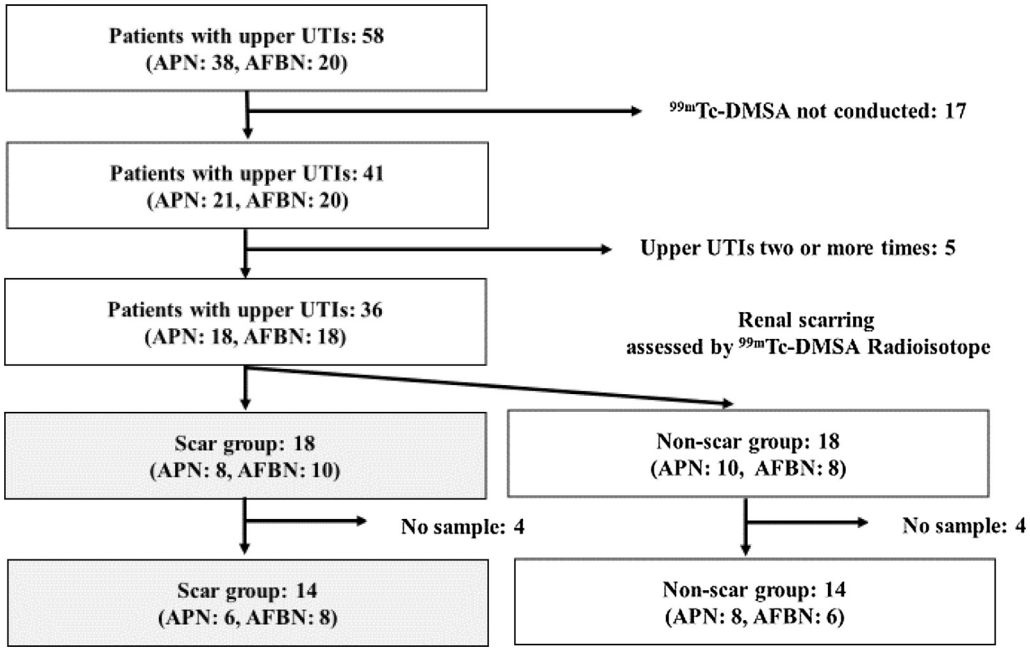

Fig. 1. Flowchart of the selection of patients in the scar group and non-scar group. AFBN, acute focal bacterial nephritis; APN, acute pyelonephritis; UTI, urinary tract infection.

children after febrile UTI are age at presentation, sex, recurrent infection peak fever, treatment delay, and presence of vesicoureteral reflux (VUR) [5]. However, there are few studies on risk factors for the development of renal scarring in upper UTI.

Cytokines are involved in the progression of renal fibrosis and tissue damage [6]. Proinflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, interferon [IFN]-γ, interleukin [IL]-1β, IL-6, IL-17, and IL-23) and anti-inflammatory cytokines (e.g., IL-4, IL-10, and transforming growth factor [TGF]-β) produced in resident and infiltrated immune cells are important mediators [7]. IL-33 is a member of the IL-1 cytokine family and promotes inflammation in parasitic infection and sepsis [8,9]. IL-33 is mainly present in the nucleus of epithelial cells and endothelial cells. When necrosis is induced by viral infection or physical stimulus in epithelial cells, IL-33 is released from the cell nucleus and acts on the cell surface expressing ST2, which is known as an IL-33 receptor, resulting in the activation of immune cells and the induction of inflammation [10–13]. Two major transcription variants of ST2, the full-length transmembrane form, ST2L, and the soluble form, sST2, have been identified [14]. It has been reported that sST2, which serves as a decoy receptor, could be a biomarker in various inflammatory diseases, leading to fibrosis [9,15]. Additionally, renal scarring is a characteristic feature and process of all forms of chronic kidney disease (CKD) and an elevated concentration of serum sST2 is found in CKD patients and correlates with disease severity [16,17]. These suggest that serum sST2 levels could be a useful biomarker of subsequent renal scar formation in patients with upper UTI. In this study, we focused on IL-33 and sST2 and investigated whether IL-33 and sST2 can serve as biomarkers of subsequent renal scarring in patients with upper UTI.

2. Material and methods

2.1. Patients

The study was performed in accordance with the Declaration of Helsinki. All subjects were enrolled in Yamaguchi University Hospital between 2008 and 2016. Informed consent was obtained from all the subjects and/or their parents. The medical records were retrospectively reviewed to investigate the clinical and laboratory findings at the time of diagnosis and throughout the treatment course. All patients met the diagnostic criteria for upper UTI: fever (body temperature ≥38.0 °C), positive urine culture, low back pain, and the presence or absence of focal mass lesions in the kidney assessed by contrast abdominal computed tomography (n = 20) according to the Japanese Association for Infection Diseases/Japanese Society of Chemotherapy (JAID/JSC) guidelines [18]. Positivity of urine culture was defined as detection of a single organism at a density of $\geq 5 \times 10^4$ colony forming units/mL in urine samples obtained by transurethral catheterization or midstream urine [2]. APN and AFBN were diagnosed on the basis of imaging findings. We assessed the scarring on the basis of images obtained by ^{99m}technetium dimercaptosuccinic acid (^{99m}Tc-DMSA) 4 months after the onset of the UTI and categorized the severity of kidney scarring as group 1 and group 2 according to the classifications of the Reflux Nephropathy Forum Japan [19]. VUR grade was determined on the basis of radiological finding using the International Reflux Study Committee grading system [20]. All AFBN patients received intravenous antibiotics (cefmetazole, cefotaxime, piperacillin, or meropenem) for 2 weeks followed by oral cefaclor or sulfamethoxazole-trimethoprim for another 1 week. All APN patients were initially treated with intravenous antibiotics followed by oral antibiotics for 2 weeks [18]. This study was approved by the Institutional Review Board of Yamaguchi University Hospital (No. H30-160).

2.2. Study design

Fifty-eight patients aged < 15 years with upper UTI were enrolled. Control subjects (n = 13) were recruited from afebrile outpatients, including those with mental retardation, chromosome 8 abnormality, short stature, or inguinal hernia. Of the 58 non-control subjects, 38 subjects and 20 subjects were diagnosed with APN and AFBN, respectively. Seventeen patients were excluded because of a lack of ^{99m}Tc-DMSA test data, 5 patients were excluded because of repetitive UTI infections, and 8 patients were excluded because of a lack of blood samples. Ultimately, 14 patients with renal scarring (APN, n = 8; AFBN, n = 6) and 14 patients without renal scarring (APN, n = 6; AFBN, n = 8) were classified into the scar and non-scar groups, respectively (Fig. 1).

2.3. Sample preparation and analysis

Blood and urine samples were collected on admission at Yamaguchi University Hospital, and the serum samples were stored at −20 °C until the time of analysis.

The levels of serum IFN-γ, IL-2, IL-4, IL-6, IL-10, and TNF-α were measured using a BD™ Cytometric Bead Array Human Th1/Th2 Cytokine Kit (BD Biosciences, San Jose, CA, USA). The levels of serum soluble TNF-receptor 1 (sTNFR1), IL-33, and ST2 were measured using Human sTNFR1/TNFRSF1A, Human IL-33, and Human ST2/IL33R Quantikine enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA), respectively. The detection limits were as follows: IFN-γ, 7.1 pg/mL; IL-6, 3.0 pg/mL; IL-10 and TNF-α, 2.8 pg/mL; IL-2 and IL-4, 2.6 pg/mL; sTNFR1, 1.2 pg/mL; IL-33, 0.519 pg/mL; and sST2, 5.1 pg/mL.

2.4. Statistical analysis

The Mann-Whitney *U* test and Chi-square test were used to compare the groups. The associations between parameters were analyzed using Spearman's correlation. A significant difference was determined on the basis of p-values < 0.05. Receiver operating characteristics (ROC) analysis of sST2 was performed by logistic regression. All statistical analyses were performed using JMP® version 14 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical and laboratory findings

First, we compared the clinical and laboratory findings of control subjects and the scar and non-scar groups (Table 1). There were no differences in sex and age at the onset of UTI among the three groups. Fever at admission was higher in the scar group than in the non-scar group ($p = 0.04$). However, there was no significant difference in the other clinical factors between the two groups. Laboratory findings showed that the numbers of leukocytes and the levels of serum C-reactive protein were significantly increased in both the non-scar and scar groups compared with the controls, but there was no significant difference between the two UTI groups.

3.2. Cytokine profiles

To examine whether any serum cytokines were involved in renal scar formation in patients with UTI, we compared the serum levels of IFN-γ, IL-2, IL-4, IL-6, IL-10, TNF-α, sTNFR1, TGF-β, IL-33, and sST2 among the control subjects, non-scar group, and scar group. The serum levels of IL-6, IL-10, sTNFR1, and sST2 were significantly higher in the UTI groups than in the control group, whereas the serum levels of IFN-γ were not increased in the UTI groups compared with the control subjects (Table 2). The levels of serum TGF-β were lower in the scar group than in normal subjects; the non-scar and control group had similar serum TGF-β levels. There were no differences in the levels of serum IFN-γ, IL-6, IL-10, sTNFR1, and TGF-β between the non-scar and scar groups. As more than half the levels of IL-2, IL-4, and TNF-α were below the detection sensitivity in all groups, it was considered inappropriate to compare them statistically. The levels of IL-33 were also below the detection limit. However, the levels of serum sST2 were significantly higher in the scar group than in the non-scar group ($p = 0.01$) (Fig. 2). There were no correlations between serum sST2 levels and the levels of serum CRP, IL-6, or other cytokines (data not shown). Moreover, we evaluated the relationship between serum sST2 and the severity of renal scar (group 1 (n = 8), group2 (n = 6), group3 (n = 0)) using the classifications of the Reflux Nephropathy Forum Japan [19]. There was no difference in serum sST2 levels between the two groups (median 102 vs. 109, $p = 0.796$).

3.3. Receiver operating characteristics (ROC) analysis

We also evaluated the utility of serum sST2 level via the area under the curve (AUC) based on ROC analysis for differentiating between the non-scar and scar groups (Fig. 3). When the optimal cutoff was set to 38.7 ng/mL, AUC, sensitivity, and specificity were 0.79, 92.9%, and 64.3%, respectively.

4. Discussion

In our study, we evaluated the utility of serum sST2 levels as a predictive biomarker of subsequent renal scar formation in patients with upper UTI. Additionally, the levels were increased in upper UTI patients with subsequent renal scarring compared to that in those

Table 1
Clinical and laboratory profiles of patients with and without renal scar.

	Group A Control n = 13	Group B Non-scar group n = 14	Group C Scar group n = 14	p-value A vs. B	A vs. C	B vs. C
Sex, male:female	9:4	12:2	12:2	0.30	0.30	> 0.99
Age, months*	11 (3–63)	5 (1–67)	8 (2–175)	0.06	0.82	0.10
APN:AFBN		8:6	6:8			0.45
Clinical findings*						
Body temperature on admission, °C	< 38	38.7 (38.0–40.2)	39.5 (38.3–40.3)			0.04
Fever duration, hours	0	52 (11–110)	59 (26–164)			0.57
Laboratory findings*						
Leukocytes, $\times 10^9$/L	10.2 (5.6–15.8)	18.5 (10.0–25.0)	17.1 (7.6–25.1)	< 0.001	0.002	0.25
Hemoglobin, g/dL	12.1 (9.7–14.7)	10.6 (10–12.3)	11.7 (9.2–13.8)	0.05	0.79	0.19
Platelets, $\times 10^9$/L	411 (299–620)	425 (178–612)	337 (118–699)	0.85	0.11	0.12
C-reactive protein, mg/dL	0.01 (0.01–0.13)	4.41 (0.42–10.1)	7.34 (0.87–14.2)	< 0.001	< 0.001	0.07
Serum creatinine, mg/dL	0.22 (0.18–0.31)	0.21 (0.15–0.38)	0.23 (0.18–0.39)	0.68	0.31	0.09
Fibrinogen, mg/dL	no data	441 (206–613)	436 (247–899)			0.90
D-dimer, mg/L	no data	1.1 (0.7–1.5)	1.2 (0.7–2.2)			0.28
Imaging analysis						
VUR	no data	4 29%	6 43%			0.43
VUR Grade 1	no data	2	2			
VUR Grade 2	no data	0	1			
VUR Grade 3	no data	1	3			
VUR Grade 4	no data	1	0			

* Values are presented as median (range).

Table 2
Serum concentrations of cytokines on the admission in patients with and without renal scar.

	Group A Control n = 13	Group B Non-scar group n = 14	Group C Scar group n = 14	p-value		
				A vs. B	A vs. C	B vs. C
IFN-γ, pg/mL	27.6 (< 7.1–94.3)	29.7 (< 7.1–344.1)	92.7 (< 7.1–344.1)	0.45	0.25	0.81
IL-2, pg/mL	2.8 (< 2.6–4.3)	2.7 (< 2.6–4.2)	< 2.6 (< 2.6–3.8)	0.85	0.52	0.37
IL-4, pg/mL	3.0 (2.7–3.5)	3.0 (< 2.6–8.7)	< 2.6 (< 2.6–4.0)	0.64	< 0.001	< 0.01
IL-6, pg/mL	3.9 (7–94.3)	79.1 (15.2–591.0)	162.0 (26.8–353.4)	< 0.001	< 0.001	0.11
IL-10, pg/mL	3.4 (< 2.8–7.9)	10.7 (< 2.8–60.1)	9.9 (< 2.8–414.0)	0.029	0.095	0.73
TNF-α, pg/mL	< 2.8 (< 2.8–3.0)	< 2.8 (< 2.8–3.5)	< 2.8 (< 2.8–4.5)	0.13	0.48	0.31
sTNFR1, pg/mL	1113 (634–1981)	3092 (2329–9200)	3769 (1958–5549)	< 0.001	< 0.001	0.42
TGF-β, pg/mL	69,314 (50,572–82,718)	62,314 (41,823–82,462)	53,178 (27,992–90,743)	0.40	0.03	0.154
IL-33, pg/mL	< 6.25	< 6.25	< 6.25			

Values are presented as median (range).
IL, interleukin; IFN, interferon; sST2, soluble ST2; sTNFR1; soluble tumor necrosis factor receptor 1; TGF, transforming growth factor; TNF, tumor necrosis factor.

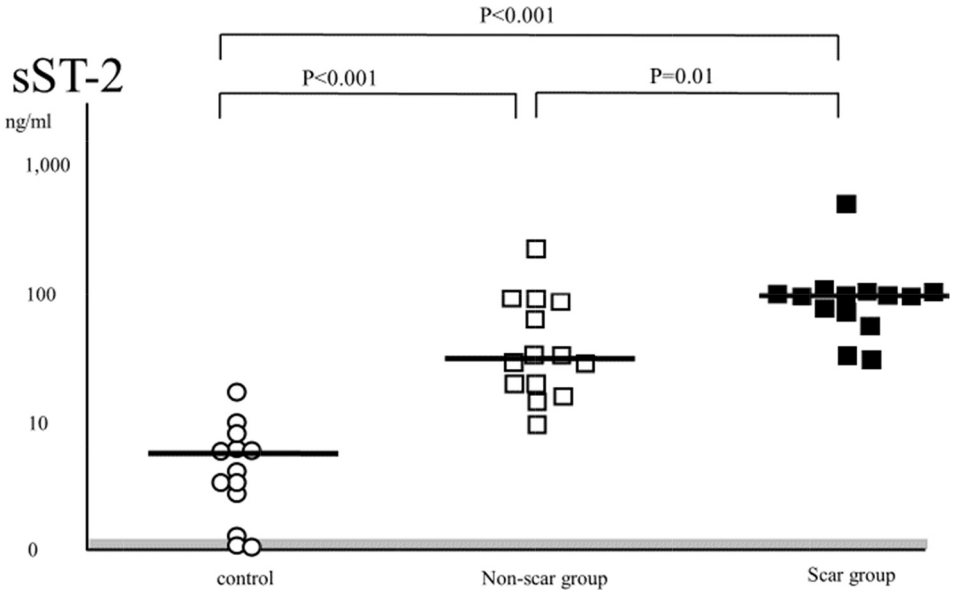

Fig. 2. Serum sST2 levels on admission in patients with Non-scar group and scar group. Each bar indicates the median value (Control subjects, Non-scar group, and Scar group; 5.9 ng/ml vs. 29.1 ng/ml vs. 105.3 ng/ml, respectively). The shaded area represents values below detectable ranges (sST2; < 5.1 ng/ml).

without subsequent renal scarring. Renal scarring is caused by the increase in α-smooth actin and collagen and results from activation of fibroblast because of tissue injury [21]. Acute inflammatory response, which is meant to eradicate invading bacteria, is also responsible for early renal parenchymal damage and subsequent scarring [22]. Because the elevation of serum sST2 levels in the acute phase of UTI is

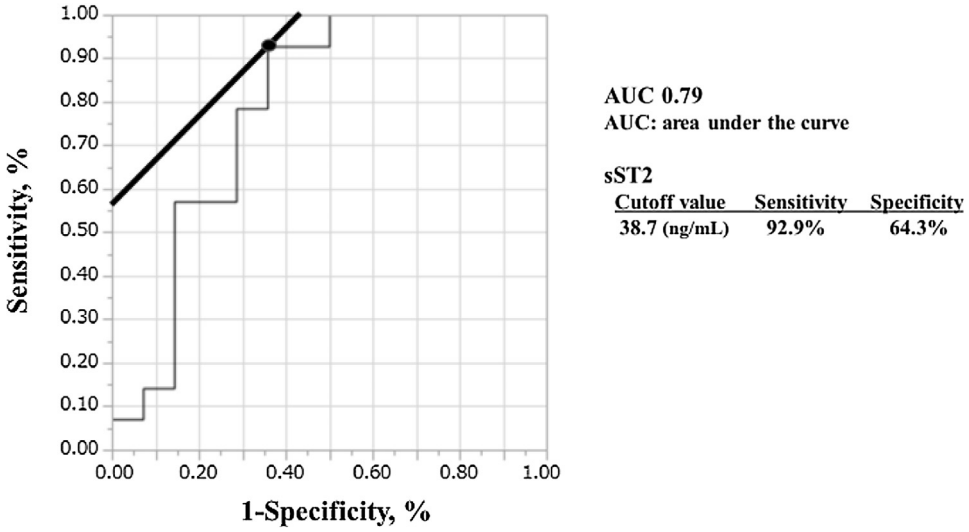

Fig. 3. Sensitivity and 1 – specificity of the receiver operating characteristic curve of serum sST2 level.

associated with the degree of tissue injury [23], sST2 could be secreted from endothelial cells and fibroblasts during the inflammatory response against bacterial infection in the upper UTI [24]. In upper UTI patients, the correlation between sST2 levels on admission and subsequent renal scar formation 4 months after onset is unclear.

Acute inflammatory lesions and the ischemic area of the kidney cortex associated with upper UTI exhibit the defects of DMSA imaging. Therefore, they cannot be distinguished from renal scarring, if defects are seen on a DMSA scan performed during the course of upper UTI [25]. Pohr et al. [26] showed that acute inflammation-related defects noted via renal DMSA persisted as renal scars in 36–52% of kidneys up to 8 months thereafter. Therefore, it is possible that renal scaring could have occurred in the earlier phase of upper UTI, although there have been no reports on this period or on mechanisms of renal scar formation in patients with a preceding episode of upper UTI. The levels of serum ST2 on admission might illustrate the extent of fibrosis in the early phase generated as a result of injury and/or inflammation after bacterial invasion. The elevation of serum ST2 levels in upper UTI patients on admission might reflect more extensive kidney injury and/or inflammation leading to irreversible renal scar formation.

We found that serum IL-33 levels were below detection limits in all samples. Plasma and serum sST2 levels increase in patients with dengue fever or chronic kidney disease without elevation of serum IL-33 levels, showing the disease specific occurrence and detection of these molecules [17,27]. This discrepancy may show that IL-33 is locally released in response to injury and/or inflammation in the kidneys, not reflecting elevation of serum IL-33 levels, whereas sST2 is systematically released, resulting in elevation of serum sST2 levels.

In this study serum IL-6 and sTNFR1 levels were also higher in patients with upper UTI than in control subjects. However, no significant differences were observed in the serum levels of other cytokines such as IL-6, IL-10, sTNFR1, and TGF-β between the upper UTI subjects with and without renal scarring, although these cytokines were at higher levels in UTI patients than in control subjects. The cytokine profile appeared to reflect systemic inflammation in upper UTI patients; however, this did not portend the fibrotic process leading to scar formation.

Some studies have demonstrated the AUC for differentiating scar formation from non-scar formation [28,29]. Rafiei et al. [28] showed that the urinary levels of neutrophil gelatinase-associated lipocalin were significantly higher in pediatric APN with scar than in pediatric APN without scar ($p = 0.037$) and that the AUC was 0.73 with a sensitivity of 81.3% and a specificity of 66% at the optimal cutoff. Lee et al. [29] reported the utility of urinary kidney injury molecule-1 as a predictive biomarker of renal scarring in pediatric patients with acute febrile UTI showing an AUC, sensitivity, and specificity of 0.71, 73.7%, and 76.7%, respectively. Compared with these results, the high AUC of serum sST2 (0.79) suggests that serum sST2 could be a good biomarker of subsequent renal scarring in the upper UTI.

There are several limitations to this study. The population was small, and a single-center retrospective design was utilized. Although serum samples were assessed, urine samples might be a better reflection of kidney injury leading to renal scar formation. It would be important to evaluate the utility of serum sST2 as a predictive marker of subsequent renal formation in upper UTI via a larger population or multicenter study, using not only serum sample but also plasma and urine samples.

In conclusion, our results suggest that serum sST2 levels on admission could be a useful biomarker of subsequent renal scarring in children with upper UTI.

Author contributions

NO and HY contributed equally to this work. NO, HY, MM, TM, SO, and SH were the principal investigators taking primary responsibility for the manuscript. RF, SK, KM performed the clinical management with helpful discussion for the completion of the study. TM and SK took responsibility for the diagnosis and data collection.

Declaration of Competing Interest

None.

Acknowledgments

We thank all of the staff members who helped treat patients at Yamaguchi University Hospital. This work was supported in part by a Grant-in-Aid for Scientific Research (grant no. 17K10142) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Morinaga Foundation for Health and Nutrition. This had no involvement in study design.

References

[1] S.A. Saadeh, T.K. Mattoo, Managing urinary tract infections, Pediatr. Nephrol. 26 (2011) 1967–1976, https://doi.org/10.1007/s00467-011-1801-5.
[2] American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection, Practice parameter, the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children, American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection, Pediatrics 103 (1999) 843–852. < https://www.ncbi.nlm.nih.gov/pubmed/10103321 > .
[3] A. Hoberman, M. Charron, R.W. Hickey, M. Baskin, D.H. Kearney, E.R. Wald, Imaging studies after a first febrile urinary tract infection in young children, N. Engl. J. Med. 348 (2003) 195–202, https://doi.org/10.1056/NEJMoa021698.
[4] T.K. Mattoo, Vesicoureteral reflux and reflux nephropathy, Adv. Chronic Kidney Dis. 18 (2003) 348–354, https://doi.org/10.1053/j.ackd.2011.07.006.
[5] M. Hiraoka, G. Hashimoto, S. Tsuchida, H. Tsukahara, Y. Ohshima, M. Mayumi, Early treatment of urinary infection prevents renal damage on cortical scintigraphy, Pediatr. Nephrol. 18 (2003) 115–118, https://doi.org/10.1007/s00467-002-1023-y.
[6] X.M. Meng, D.J. Nikolic-Paterson, H.Y. Lan, Inflammatory process in renal fibrosis, Nat. Rev. Nephrol. 10 (2004) 493–503, https://doi.org/10.1038/nrneph.2014.114.
[7] C. Kurts, U. Panzer, H.J. Anders, A.J. Rees, The immune system and kidney disease: basic concepts and clinical implications, Nat. Rev. Immunol. 13 (2013) 738–753, https://doi.org/10.1038/nri3523.
[8] C. Cayrol, J.P. Girard, IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy, Curr. Opin. Immunol. 31 (2014) 31–37, https://doi.org/10.1016/j.coi.2014.09.004.
[9] R. Kakkar, R.T. Lee, The IL-33/ST-2 pathway: therapeutic target and novel biomarker, Nat. Rev. Drug. Discov. 7 (2008) 827–840, https://doi.org/10.1038/nrd2660.
[10] J. Schmitz, A. Owyang, E. Oldham, Y. Song, E. Murphy, T.K. McClanahan, G. Zurawski, M. Moshrefi, J. Qin, X. Li, D.M. Gorman, J.F. Bazan, R.A. Kastelein, IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines, Immunity 23 (2005) 479–490, https://doi.org/10.1016/j.immuni.2005.09.015.
[11] K. Yasuda, T. Muto, T. Kawagoe, M. Matsumoto, Y. Sasaki, K. Matsushita, Y. Taki, S. Futatsugi-Yumikura, H. Tsutsui, K.J. Ishi, T. Yoshimoto, S. Akira, K. Nakanishi, Contribution of IL-33-activated type II innate lymphoid cells to pulmonary eosinophilia in intestinal nematode-infected mice, Proc. Natl. Acad. Sci. USA 109 (2012) 3451–3456, https://doi.org/10.1073/pnas.1201042109.
[12] D.R. Nagarkar, V. Ramirez-Carrozzi, D.F. Choy, K. Lee, R. Soriano, G. Jia, A.R. Abbas, Z. Modrusan, R. Pappu, J.R. Arron, IL-13 mediates IL-33-dependent mast cell and type 2 innate lymphoid cell effects on bronchial epithelial cells, J. Allergy. Clin. Immunol. 136 (2015) 202–205, https://doi.org/10.1016/j.jaci.2015.01.036.
[13] H.Y. Kim, Y.J. Chang, S. Subramanian, H.H. Lee, L.A. Albacker, P. Matangkasombut, P.B. Savage, A.N. McKenzie, D.E. Smith, J.B. Rottman, R.H. DeKruyff, D.T. Umetsu, Innate lymphoid cells responding to IL-33 mediate airway hyperreactivity independently of adaptive immunity, J. Allergy Clin. Immunol. 129 (2012) 216–227, https://doi.org/10.1016/j.jaci.2011.10.036.
[14] R. Kakkar, H. Hei, S. Dobner, R.T. Lee, Interleukin 33 as a mechanically responsive cytokine secreted by living cells, J. Biol. Chem. 287 (2012) 6941–6948, https://doi.org/10.1074/jbc.M111.298703.
[15] M. De la Fuente, T.T. MacDonald, M.A. Hermoso, The IL-33/ST2 axis: role in health and disease, Cytokine Growth Factor Rev. 26 (2015) 615–623, https://doi.org/10.1016/j.cytogfr.2015.07.017.
[16] J.S. Duffield, Cellular and molecular mechanisms in kidney fibrosis, J. Clin. Invest. 124 (2014) 2299–2306, https://doi.org/10.1172/JCI72267.
[17] Y.S. Bao, S.P. Na, P. Zhang, X.B. Jia, R.C. Liu, C.Y. Yu, S.H. Mu, R.J. Xie, Characterization of interleukin-33 and soluble ST2 in serum and their association with disease severity in patients with chronic kidney disease, J. Clin. Immunol. 32 (2012) 587–594, https://doi.org/10.1007/s10875-011-9622-7.
[18] S. Yamamoto, K. Ishikawa, H. Hayami, T. Nakamura, I. Miyairi, T. Hoshino, M. Hasui, K. Tanaka, H. Kiyota, S. Arakawa, The JAID/JSC guidelines to clinical

management of infections diseases (Urinary tract infections and Male genital infections), Kansenshogaku Zasshi 90 (2016) 1–30, https://doi.org/10.1016/j.jiac.2017.02.002.
[19] H. Nakai, H. Kakizaki, R. Konda, Y. Hayashi, S. Hosokawa, S. Kawaguchi, H. Matsuoka, K. Nonomura, K. Shimada, T. Kawamura, Prospective Study Committee of Reflux Nephropathy Forum, Japan, Clinical characteristics of primary vesicoureteral reflux in infants: multicenter retrospective study in Japan. Prospective Study Committee of Reflux Nephropathy Forum, Japan, J. Urol. 169 (2003) 309–312, https://doi.org/10.1097/01.ju.0000042766.09295.72.
[20] R.L. Lebowitz, H. Olbing, K.V. Parkkulainen, J.M. Smellie, T.E. Tamminen-Möbius, International system of radiographic grading of vesicoureteric reflux, Pediatr Radiol 15 (2) (1985) 105–109, https://doi.org/10.1007/BF02388714.
[21] A. Kuma, M. Tamura, Y. Otsuji, Mechanism of and therapy for kidney fibrosis, J. UOEH 38 (2016) 25–34, https://doi.org/10.7888/juoeh.38.25.
[22] J.A. Roberts, Etiology and pathophysiology of pyelonephritis, Am. J. Kidney Dis. 17 (1991) 1–9, https://doi.org/10.1016/S0272-6386(12)80242-3.
[23] J.J. Hoogerwerf, M.W. Tanck, M.A. van Zoelen, X. Wittebole, P.F. Laterre, T. van der Poll, Soluble ST2 plasma concentrations predict mortality in severe sepsis, Intensive Care. Med. 36 (2010) 630–637, https://doi.org/10.1007/s00134-010-1773-0.
[24] S. Demyanets, C. Kaun, R. Pentz, K.A. Krychtiuk, S. Rauscher, S. Pfaffenberger, A. Zuckermann, A. Aliabadi, M. Gröger, G. Maurer, K. Huber, J. Wojta, Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature, J. Mol. Cell. Cardiol. 60 (2013) 16–26, https://doi.org/10.1016/j.yjmcc.2013.03.020.
[25] N.P. Goldraich, I. Goldraich, Update on dimercaptosuccinic acid renal scanning in children with urinary tract infection, Pediatr. Nephrol. 9 (1995) 221–226.
[26] H.G. Pohl, A.B. Belman, The “top-down” approach to the evaluation of children with febrile urinary tract infection, Adv. Urol. 10 (2009) 1155, https://doi.org/10.1155/2009/783409.
[27] C.D. Guerrero, A.F. Arrieta, N.D. Ramirez, L.S. Rodríguez, R. Vega, J.A. Bosch, J.A. Rodríguez, C.F. Narváez, D.M. Salgado, High plasma levels of soluble ST2 but not its ligand IL-33 is associated with severe forms of pediatric dengue, Cytokine 61 (2013) 766–771, https://doi.org/10.1016/j.cyto.2012.12.024.
[28] A. Rafiei, H. Mohammadjafari, S. Bazi, A.M. Mirabi, Urinary neutrophil gelatinase-associated lipocalin (NGAL) might be an independent marker for anticipating scar formation in children with acute pyelonephritis, J. Renal Inj. Prev. 4 (2015) 39–44, https://doi.org/10.12861/jrip.2015.09.
[29] H.E. Lee, D.K. Kim, H.K. Kang, K. Park, The diagnosis of febrile urinary tract infection in children may be facilitated by urinary biomarker, Pediatr. Nephrol. 30 (2015) 123–130, https://doi.org/10.1007/s00467-014-2905-5.