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Risk factors for imaging abnormalities after the first febrile urinary tract infection in infants ≤3 months old: a retrospective cohort study

Siew Lew Chong, Esther Huimin Leow, Celeste Jia Ying Yap, Sing Ming Chao, Indra Ganesan, Yong Hong Ng

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Paediatric Nephrology, KK Women's and Children's Hospital, Singapore

Correspondence to
Dr Esther Huimin Leow; Esther.Leow.H.M@singhealth.com.sg

ABSTRACT

Objectives To assess the association of clinical factors and investigation results (blood and urine) with imaging abnormalities (ultrasound of the kidneys, ureters and bladder; dimercaptosuccinic acid scan; and/or micturating cystourethrogram) and recurrent urinary tract infections (UTIs) in infants ≤3 months old presenting with their first febrile UTI.

Methods We conducted a retrospective cohort study of infants ≤3 months old with first febrile UTI admitted from 2010 to 2016. Multivariable logistic regression model was used to analyse the association of imaging abnormalities and recurrent UTI with covariates selected a priori: age at presentation, maximum temperature, duration of illness at presentation, interval between start of antibiotics and fever resolution, C-reactive protein, total white cell count on the full blood count, bacteraemia, white cell count on the urinalysis and non-*Escherichia coli* growth in the urine culture (non-*E. coli* UTI).

Results There were 190 infants but 12 did not undergo any imaging. Median age at presentation was 63 days (IQR 41–78). Twenty-four patients had imaging abnormalities. Non-*E. coli* UTI (adjusted OR (aOR) 5.01, 95% CI 1.65 to 15.24, p=0.004) was independently associated with imaging abnormalities, while bacteraemia (aOR 4.93, 95% CI 1.25 to 19.43, p=0.022) and non-*E. coli* UTI (aOR 5.06, 95% CI 1.90 to 13.48, p=0.001) were independently associated with recurrent UTI.

Conclusion Non-*E. coli* UTI at the first febrile UTI in infants ≤3 months old may be useful in predicting imaging abnormalities while bacteraemia and non-*E. coli* UTI may be useful to predict recurrent UTI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Imaging of the kidneys and urinary tracts after paediatric urinary tract infections (UTIs) varies between countries.

⇒ This study was performed to look at risk factors associated with imaging abnormalities and recurrent UTI in infants ≤3 months old.

WHAT THIS STUDY ADDS

⇒ Non-Escherichia coli growth in the urine culture (non-E. coli UTI) was independently associated with imaging abnormalities after the first febrile UTI in infants ≤3 months old.

⇒ Bacteraemia and non-E. coli UTI were independently associated with recurrent UTI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Risk factors associated with imaging abnormalities after the first febrile UTI in infants ≤3 months old identified in this study may aid future studies which aim to build a prediction model in risk-stratifying infants who would benefit from further imaging.

INTRODUCTION

Urinary tract infection (UTI) is common among infants ≤3 months old, with a prevalence of 7.2%.[1] The known risk factors of UTI in this group of young infants include the presence of congenital anomalies of the kidney and the urinary tract (eg, vesicoureteral reflux (VUR)),[2] uncircumcised infant boys[1] and incomplete or intermittent bladder emptying due to the infants' physiologic detrusor sphincter dyscoordination which usually improves with time.[3]

There are differences between guidelines regarding imaging after the first febrile UTI.[4–8] The indications of ultrasound of the kidneys, ureters and bladder (US KUB) are heterogeneous with some advocating for this to be a routine non-invasive test[6 7] while others have advised for this to be done for at-risk age groups or based on clinical indications.[4 5 8] Dimercaptosuccinic acid (DMSA) scan and micturating cystourethrogram (MCU) are generally not routine unless clinically indicated[4 5 7 8]—common indications include recurrent UTI or urinary tract dilatation on US KUB. Importantly, recommendations for some of the UTI guidelines do not apply to infants ≤2 months.[5–7]

UTIs can recur in up to 19% of children, even in the absence of urinary tract obstruction or VUR.[9] Risk factors for recurrent UTIs

include first UTI occurring at <6 months of age.[10] The most concerning complication of recurrent UTIs is the increased risk of kidney scarring with each episode of UTI recurrence.[11] With significant kidney scarring, there is a risk of developing hypertension,[12] proteinuria[13] and gradual loss of kidney function.[14]

With increasing awareness of the effects of recurrent UTIs on children, it would be important to identify risk factors for abnormal kidney imaging (US KUB, DMSA scan and/or MCU) and recurrent UTIs in very young infants who present with their first febrile UTI. To date, studies on paediatric UTIs have investigated association between a wide variety of risk factors in children or infants of varying ages with many different outcomes, such as kidney scarring, VUR and UTI recurrence.[15–17] We hypothesised that there is a set of risk factors in infants ≤3 months old who present with first febrile UTI which is associated with abnormal kidney imaging (US KUB, DMSA scan and/or MCU) and/or recurrent UTI. This is a pilot study from which results will be used to develop a prediction model or risk scoring system in a subsequent study with a larger group of patients.

MATERIALS AND METHODS

This was a retrospective cohort study of infants ≤3 months old with first febrile UTI admitted from May 2010 to April 2016 into KK Women's and Children's Hospital (KKH), an 800-bed tertiary institution in Singapore.

All infants ≤3 months old admitted for their first febrile UTI were included in this study. Fever was defined as an axillary temperature of ≥38°C. UTI was confirmed by positive urine culture(s): one urine specimen via transurethral catheterisation with bacteria growth of ≥10 000 cfu/mL or two clean catch midstream urine specimens both with the same bacteria with growth of ≥100 000 cfu/mL. Data collected during the hospital admission and at subsequent follow-up visits include baseline characteristics, antenatal and birth history, clinical course and investigation (blood, urine and imaging) results.

At KKH Children's Emergency, patients who are <6 months old with suspected febrile UTI are admitted for further management. Patients were all initially treated with intravenous gentamicin. Patients <1 month old received additional intravenous ampicillin to cover empirically for gram-positive bacteria. Gentamicin was converted to ceftriaxone if the serum creatinine (SCr) at admission was elevated. The antibiotics were subsequently adjusted based on urine culture sensitivity results. The total treatment course of antibiotics, both intravenous and oral, was 14 days. If there was bacteraemia, intravenous antibiotics were continued for a minimum 7 days. In general, US KUB was performed 4–6 weeks after a febrile UTI and DMSA scan was performed 4–6 months after a febrile UTI (figure 1). MCU was indicated if the febrile UTI was atypical or complicated (eg, a history of urinary tract abnormality, bacteraemia, sepsis, poor urine output, raised SCr, palpable abdominal mass/bladder or

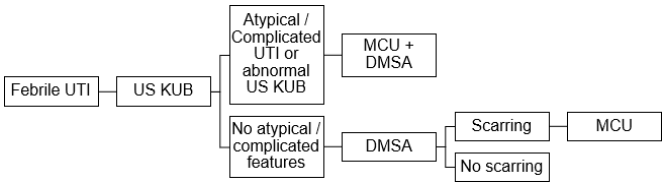

Figure 1 Imaging protocol in KKH. DMSA, dimercaptosuccinic acid scan; KKH, KK Women's and Children's Hospital; MCU, micturating cystourethrogram; US KUB, ultrasound of the kidneys, ureters and bladder; UTI, urinary tract infection.

persistent fever after 48 hours of appropriate antibiotic treatment), if there was recurrence of UTI and/or if US KUB or DMSA scans were abnormal. During the study period, antibiotic prophylaxis was given after the treatment of the first febrile UTI for infants <1 year old and stopped after a normal US KUB and DMSA scan.

The primary outcome was imaging abnormalities (US KUB, DMSA scan and/or MCU). The secondary outcome was recurrence of UTI (both febrile and afebrile).

Statistical analysis

Continuous variables were summarised with medians and IQRs, and compared using the Mann-Whitney U test. Categorical variables were summarised in absolute counts and percentages, and compared using χ^2 or Fisher's exact tests. Multivariable logistic regression model was used to analyse the association of the primary outcome with covariates selected a priori: age at presentation, maximum temperature, duration of illness at presentation, interval between start of antibiotics and resolution of fever, C-reactive protein (CRP), total white cell count (TW) on the full blood count, bacteraemia, white cell count on the urinalysis and non-*Escherichia coli* growth in the urine culture (non-*E. coli* UTI). The area under the receiver operating characteristic curve (AUC-ROC) was measured for each continuous variable. The Youden Index (sensitivity+specificity−1) was determined for each continuous variable. The highest Youden Index for each continuous variable was used to select the cut-offs. The sensitivity, specificity, positive predictive value, negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−) of each variable were analysed. The same statistical analyses were applied for the secondary outcome, recurrent UTI. Sensitivity analysis was performed for patients with no imaging tests due to loss to follow-up—first, by assuming all of these patients had normal imaging results and, second, by assuming all of these patients had abnormal imaging results. All statistical analyses were performed using Stata V.15 (StataCorp, College Station, Texas) and two tailed, with $p<0.05$ taken as statistically significant.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures, design of this study or recruitment to and conduct of the study.

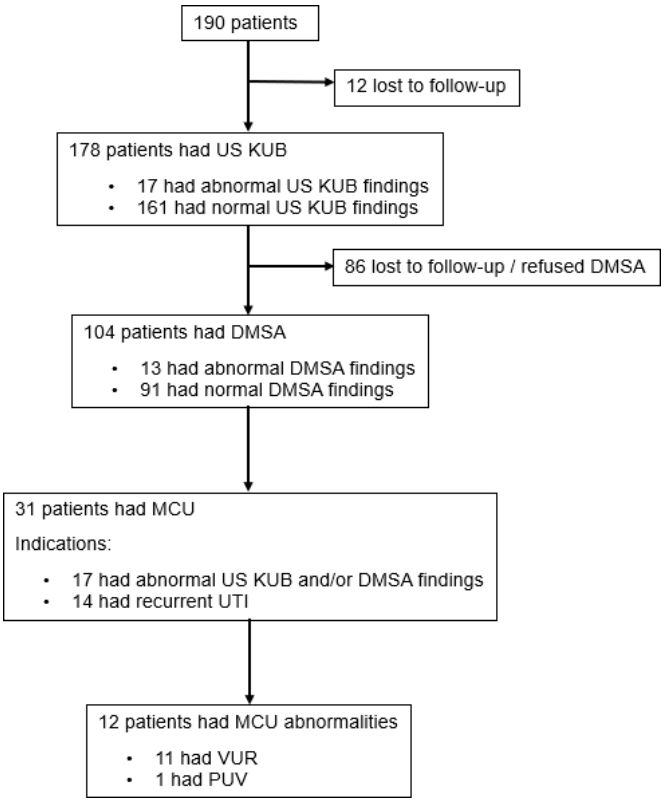

Figure 2 Study cohort. DMSA, dimercaptosuccinic acid scan; MCU, micturating cystourethrogram; PUV, posterior urethral value; US KUB, ultrasound of the kidneys, ureters and bladder; UTI, urinary tract infection; VUR, vesicoureteral reflux.

RESULTS

There were 190 infants 0–3 months old who were treated for first febrile UTI during the study period, of which 12 did not undergo any routine imaging due to loss to follow-up. MCU was performed for 31 patients (figure 2). The median age at presentation was 63 days (IQR 41–78) and 141 (74%) patients were male. Four patients had abnormalities of the urinary tract on antenatal US. Median maximum temperature of the patients was 38.9°C (IQR 38.4–39.4) and median days of illness or symptoms at presentation was 1 (IQR 1–2). Fever resolved at median 16 hours (IQR 4–30) after starting antibiotics. In terms of blood investigations, the median TW was 15.46×10^9/L (IQR 11.19–19.98) and median CRP was 28.6 mg/L (IQR 15.1–64.9). Urine specimens were collected via transurethral catheterisation in 148 (78%) patients. Median white cell count on urinalysis was 388/µL (IQR 26–1380) and 41 (22%) urine cultures grew bacteria which were non-*E. coli*. Median duration of follow-up was 7 months (IQR 4–11).

Primary and secondary outcomes

There were 24/178 (13.5%) patients who had imaging abnormalities (US KUB, DMSA scan and/or MCU), of which 17/178 (9.6%) had abnormalities on US KUB, 13/104 (12.5%) had kidney scarring on DMSA scan, 11 had VUR on MCU and 1 had posterior urethral valve on MCU. The highest VUR grades for the patients were grade I in one patient, grade III in two patients, grade IV in six patients and grade V in two patients. The US abnormalities were dilated distal right ureter with thickened bladder wall in one patient, hydronephrosis in seven patients, hydroureter in four patients, hydroureteronephrosis in three patients, unilateral small kidney in one patient and unilateral duplex kidney with ureterocoele in one patient. A higher proportion of patients with imaging abnormalities had non-*E. coli* UTIs (41.7% vs 18.8%, p=0.012) and recurrent UTIs (66.7 vs 10.4, p<0.001) (table 1). Patients who had imaging abnormalities had longer intervals between the start of antibiotics and complete resolution of fever (28 (IQR 17–39) vs 14 (4–29) hours, p=0.022).

Among the 32 patients with recurrent UTI, 16% (5/32) had bacteraemia during their first febrile UTI, whereas only 5% of patients with no UTI recurrence had bacteraemia during their first febrile UTI. Out of the 12 infants with bacteraemia, three (25%) had imaging abnormalities and five (41.7%) had recurrent UTI.

Using multivariable logistic regression models, CRP and non-*E. coli* UTI were independently associated with imaging abnormalities, while bacteraemia and non-*E. coli* UTI were independently associated with recurrent UTI (table 2).

Test characteristics

The 178 patients who had undergone any imaging were further analysed. The AUC-ROC, Youden Index and cut-offs for the continuous variables were first determined (online supplemental table 1), then test characteristics of categorical variables and variables with AUC-ROC >0.50 were calculated for the primary outcome (online supplemental figure 1). With regard to the primary outcome, bacteraemia had a specificity of 94% and an LR+ of 2.19. In addition, non-*E. coli* UTI has a specificity of 0.81 and LR+ of 2.21. The test characteristics for the secondary outcome and abnormalities of the individual scans (DMSA scan and MCU) were also determined (online supplemental table 2). For the secondary outcome, bacteraemia and non-*E. coli* UTI have specificities of 0.95 and 0.83, respectively, and LR+ 3.17 and 2.56, respectively. An interval of ≥27 hours between the start of antibiotics and resolution of fever may be useful in predicting abnormalities on MCU, with sensitivity 0.83, specificity 0.89, LR+ 7.92 and LR− 0.19. Even though not statistically significant in the multivariable logistic regression, longer interval between the start of antibiotics and complete resolution of fever may be associated with imaging abnormalities (online supplemental figure 1, table 1 and online supplemental tables 1 and 2).

Sensitivity analysis

Patients who were lost to follow-up and did not undergo scheduled imaging include 12 infants who did not undergo any imaging. Sensitivity analysis was performed for the 12 patients with no imaging—first, by assuming

Table 1 Clinical data of patients with and without abnormalities on DMSA scan, MCU and/or US KUB

	No abnormalities on US KUB, DMSA scan and/or MCU (n=154)	Abnormalities on US KUB, DMSA scan and/or MCU (n=24)	P value
Demographics			
Age at first UTI (days)	64.5 (46–78)	49 (33–79)	0.130
Male	114 (74.0%)	18 (75.0%)	0.919
Gestational age <37 weeks at birth	12 (7.8%)	2 (8.3%)	0.934
Birth weight (g)	3091 (2851–3308)	3363 (2965–3575)	0.015
Small for gestational age at birth	11 (7.2%)	0	0.365
Antenatal ultrasound abnormalities	1 (0.6%)	3 (12.5%)	<0.001
Clinical course at first UTI			
Maximum temperature (°C)	38.9 (38.4–39.4)	39.1 (38.4–39.6)	0.530
Duration of illness at presentation (days)	1 (1–2)	1 (1–2)	0.857
Interval between start of antibiotics and resolution of fever (hours)	14 (4–29)	28 (17–39)	0.022
Blood investigations			
CRP (mg/L)	28.3 (15.4–59.9)	30.0 (20.3–73.3)	0.217
Total white cell count (×10^9/L)	15.4 (11.0–19.9)	17.0 (14.1–22.3)	0.264
Positive blood culture	9 (5.4%)	3 (12.5%)	0.199
Urine investigations			
Interval between onset of illness and urine collection (days)	1 (1–2)	1 (1–2)	0.775
White cell count (per µL)	394 (22–1380)	259 (86–685)	0.817
Epithelial cell (per µL)	0 (0–8)	1 (0–5)	0.836
Bacteria seen on urinalysis	100 (64.9%)	15 (62.5%)	0.817
Nitrites positive	28 (18.2%)	7 (29.2%)	0.208
Non-*Escherichia coli*	29 (18.8%)	10 (41.7%)	0.012
Post-UTI treatment and follow-up			
Antibiotic prophylaxis			0.121
Nil	3 (1.9%)	0	
Cephalexin	136 (88.3%)	19 (79.2%)	
Trimethoprim-sulfamethoxazole	9 (5.8%)	5 (20.8%)	
Nitrofurantoin	2 (1.3%)	0	
Recurrent UTI	16 (10.4%)	16 (66.7%)	<0.001

Continuous variables were summarised with medians and IQRs and compared using the Mann-Whitney U test. Categorical variables were summarised in absolute counts and percentages, and compared using χ^2 or Fisher's exact tests.
CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; MCU, micturating cystourethrogram; US KUB, ultrasound of the kidneys, ureters and bladder; UTI, urinary tract infection.

all of these patients had normal imaging results and, second, by assuming all of these patients had abnormal imaging results. The results are similar (online supplemental table 3).

DISCUSSION

In infants ≤3 months old who presented with their first febrile UTI, elevated CRP and non-*E. coli* UTI were independently associated with imaging (US KUB, DMSA scan and/or MCU) abnormalities, while bacteraemia and non-*E. coli* UTI were independently associated with recurrent UTI.

In our study, non-*E. coli* UTI was an independent risk factor associated with imaging abnormalities and also with recurrent UTI. This finding in our Asian cohort is similar to other international studies. Data from the Finnish nationwide surveillance system among paediatric hospitals showed that obstruction in the urinary tract or VUR occurred more frequently among children with non-*E. coli* bacteraemic UTI than those with *E. coli* bacteraemic

Table 2 Logistic regression models predicting primary and secondary outcomes

	Abnormalities on US KUB, DMSA scan and/or MCU		Recurrent UTI	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age at first UTI	0.99 (0.97 to 1.01)	0.355	1.00 (0.98 to 1.02)	0.738
Maximum temperature	0.92 (0.43 to 1.97)	0.829	0.99 (0.51 to 1.91)	0.981
Duration of illness at presentation	0.84 (0.49 to 1.46)	0.539	0.73 (0.43 to 1.22)	0.233
Interval between start of antibiotics and resolution of fever	1.02 (1.00 to 1.04)	0.101	1.01 (0.99 to 1.03)	0.335
CRP	1.01 (1.00 to 1.03)	0.016	1.01 (1.00 to 1.02)	0.081
TW on FBC	1.04 (0.96 to 1.12)	0.354	1.02 (0.95 to 1.09)	0.623
Bacteraemia	2.93 (0.58 to 14.78)	0.193	4.93 (1.25 to 19.43)	0.022
White cell count on urinalysis	1.00 (1.00 to 1.00)	0.722	1.00 (1.00 to 1.00)	0.695
Non-*Escherichia coli*	5.01 (1.65 to 15.24)	0.004	5.06 (1.90 to 13.48)	0.001

CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; FBC, full blood count; MCU, micturating cystourethrogram; TW, total white cell count; US KUB, ultrasound of the kidneys, ureters and bladder; UTI, urinary tract infection.

UTI (89% vs 46%, p<0.01).[18] In a review of the medical records of 139 children, 14/18 (77%) with urinary tract anomalies had non-*E. coli* UTI.[19] Larger studies involving 607[20] and 414 children[21] further confirmed that non-*E. coli* UTI is associated with higher grades of VUR.

CRP was independently associated with imaging abnormalities in this study, however with only an adjusted OR of 1.01 (95% CI 1.00 to 1.03, p=0.016). With regard to using CRP to diagnose pyelonephritis, a Cochrane meta-analysis showed that the sensitivity and specificity estimates for a CRP level of 20 mg/L were 0.93 (95% CI 0.86 to 0.96) and 0.37 (95% CI 0.24 to 0.53), respectively.[22] This suggests that if a child has a CRP <20 mg/L, the probability of this child having pyelonephritis is low. In relation to predicting VUR, a combination of US KUB abnormalities and CRP level of ≥80 mg/L had a sensitivity and specificity of 47.8% and 87.8%, respectively.[23] In addition, specific CRP cut-off values were studied: 23.5 mg/L for predicting presence of any VUR (sensitivity 61.9%, specificity 62.8%) and 50 mg/L for predicting high-grade VUR (sensitivity 91%, specificity 71%).[24] The cut-off of 23.5 mg/L is similar to our study of 20 mg/L (online supplemental table 1) for predicting MCU abnormalities (sensitivity 92%, specificity 29%) (online supplemental table 2). In another study recruiting 48 children after their first pyelonephritis and diagnosed with unilateral VUR, patients who developed kidney scar on DMSA scan had a higher CRP level on admission (12.9 mg/L±10.9 vs 6.9 mg/L±7.4, p<0.05) compared with those who did not.[25] In our study, however, the cut-off of 68.7 mg/L chosen in this study based on the Youden Index did not perform well to predict the primary outcome (sensitivity 30%, specificity 83%). This might be because the primary outcome was a combination of abnormalities of the US KUB, DMSA scan and/or MCU and that different cut-offs for each individual imaging modality might be more relevant. However, the number of patients was too small to perform subgroup analysis based on each imaging result.

Bacteraemia was independently associated with recurrent UTI in the logistic regression model. While VUR has been shown to occur more frequently in children with bacteraemic UTI compared with those who did not have bacteraemia,[26] there seems to be no correlation between bacteraemia and kidney scarring.[27] In a retrospective cohort study of 257 infants of less than <3 months of age with bacteraemic UTI, 98.8% underwent US KUB and 87.2% underwent MCU, of which 55.1% had US KUB abnormalities and 33.5% had MCU abnormalities.[28] In our study, of the 12 infants who had bacteraemia, three (25%) had both abnormal US KUB and MCU and one out of these three had scarring on DMSA scan. This lower percentage of imaging abnormalities might be due to patients defaulting the planned follow-up imaging (12 infants did not undergo any imaging) and MCU was not routinely performed (indications for MCU described in the Materials and methods section).

Among infants with antenatal US abnormalities, about 1%–6% develop UTI postnatally.[29–31] Even though a higher proportion of patients with the primary outcome had antenatal US abnormalities in our study, the presence of antenatal US abnormalities was not included in the logistic regression model because of the low numbers—2.1% (4/190) had documented antenatal US abnormalities. Similarly, a prospective observational study of 250 children with first UTI also reported that 1.4% of their patients had antenatal US abnormalities.[32]

There are several limitations to our study. First, due to small number of patients, the primary outcome was a composite one, combining abnormalities of US KUB, DMSA scan and MCU. Therefore, clinical risk factors associated with abnormalities of the individual scans were not demonstrated in our current study. In addition, as this was a retrospective cohort study, there were significant missing data because there were patients who defaulted routine follow-up. Lastly, the test characteristics of the

variables were not externally validated with a separate group of patients.

In conclusion, this is a pilot study in our institution to identify clinical and laboratory risk factors associated with imaging abnormalities after the first febrile UTI in infants ≤3 months old. Non-*E. coli* UTI was independently associated with imaging abnormalities, while bacteraemia and non-*E. coli* UTI were independently associated with recurrent UTI. Future studies are required to build a robust prediction model to aid physicians in risk stratifying infants after the first episode of pyelonephritis and therefore avoiding unnecessary investigations and follow-up.

Contributors SLC conceptualised and designed the study, designed the data collection instruments and collected the data. EHL carried out the data analyses, drafted the initial manuscript and reviewed and revised the manuscript. EHL is responsible for the overall content as the guarantor, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. CJYY, SMC, IG and YHN were involved in reviewing the results of the data analysis and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by SingHealth Centralised Institutional Review Board (reference number: 2017/2175) with a waiver of informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified individual participant data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to the corresponding author.

ORCID iD

Esther Huimin Leow http://orcid.org/0000-0002-3504-7656

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