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C-Reactive Protein Monitoring Identifies Urinary Tract Infections in Ambulatory Kidney Transplant Recipients

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Abstract

Background: Urinary tract infections (UTI) are common in kidney transplant recipients (KTR). Although risk factors for UTI are well described, predicting symptomatic UTI with positive urine cultures in the first posttransplant year is challenging.
Objective: Our clinic routinely monitors serum highly sensitive C-reactive protein (CRP) as part of posttransplant care. We sought to define the role of CRP in identifying symptomatic UTI in KTR.
Design: Nested case control study
Setting: A large adult single-organ kidney transplant center in Toronto, Canada.
Patients: We identified a nested cohort of 78 KTR who experienced a symptomatic UTI with positive urine cultures (cases) and compared them to a cohort of 78 KTR controls matched by time elapsed posttransplant.
Measurements: Patient demographics, urine cultures, CRP, and kidney function during the first posttransplant year.
Methods: We identified a cohort of KTR transplanted between January 1, 2016, and December 31, 2019. A positive urine culture ordered only for clinical indication in the first posttransplant year identified KTR with a UTI defined $>10^5$ colony forming units/mL. UTI cases were matched 1:1 to non-UTI controls transplanted immediately preceding or succeeding the UTI case. Bivariate comparisons were performed by *t* test, Wilcoxon 2-sample test for continuous variables, chi-square, or Fisher's exact test as appropriate, with clinically significant variables entered into multivariable logistic regression models to determine associations.
Results: Older age, female sex, and the presence of a stent were each associated with a UTI. Immediately preceding UTI, eGFR ($P = .019$), serum albumin ($P < .0001$), and hemoglobin ($P = .002$) were lower, while serum CRP ($P < .0001$) and absolute neutrophils ($P = .03$) were higher in cases than controls. However, in several multivariable models, only absolute CRP ($P = .001$), change in CRP ($P = .005$), female sex ($P < .0001$), and ureteric stent ($P = .008$) consistently predicted a UTI. Each 5 mg/dL change between the 2 preceding CRP values predicted a 15% increased likelihood of UTI, while each 1 mg/dL in absolute CRP concentration was associated with a 5% risk.
Limitations: Retrospective case-control design, single-center, small sample size. Hospital inpatients and patients with other infections, acute inflammatory conditions, or rejection were excluded. Urine infections may more easily be detected when patients visit the clinic frequently.
Conclusions: Routine ambulatory CRP monitoring in the first year may help identify subsequent symptomatic UTI in KTR, allow for the initiation of earlier therapy, and reduce patient morbidity.
What was known before? UTI in KTR are common in the first posttransplant year. Antibiotic therapy is typically not initiated until the results of urine cultures become known.
What this adds: The routine use of appropriate biomarkers such as CRP as part of a posttransplant monitoring strategy may allow clinicians to order urine cultures, help identify UTI earlier, and start therapy sooner, promoting patient well-being.

Abrégé

Contexte: Les infections des voies urinaires (IVU) sont fréquentes chez les receveurs d'une greffe rénale (RGR). Bien que les facteurs de risque des IVU soient bien décrits, il reste difficile dans la première année post-transplantation, de prédire les IVU symptomatiques à partir de cultures d'urine positives.
Objectif: Notre clinique mesure régulièrement le taux sérique de protéine C-réactive (CRP) haute sensibilité dans le cadre des soins post-transplantation. Nous souhaitions définir le rôle de la CRP dans la détection des IU symptomatiques chez les RGR.

Conception: étude rétrospective de cas-témoins nichée dans une cohort.
Cadre: Un grand center de transplantation rénale de Toronto (Canada).
Sujets: Nous avons identifié une cohorte nichée de 78 RGR ayant présenté une IVU symptomatique avec une culture urinaire positive (cas) et l'avons comparée à une cohorte de 78 RGR témoins appariés selon le temps écoulé depuis la transplantation.
Mesures: Données démographiques des patients, cultures urinaires, mesure de CRP et de la fonction rénale pendant la première année post-transplantation.
Méthodologie: Nous avons recensé une cohorte de RGR transplantés entre le 1er janvier 2016 et le 31 décembre 2019. Les RGR avec une IVU (définie par au moins 10^5 unités formant une colonie/ml) ont été identifiés par une culture d'urine positive demandée uniquement pour une indication clinique dans l'année post-transplantation. Ces cas ont été comparés (1:1) à des témoins sans IVU transplantés immédiatement avant ou après les cas d'IVU. Des comparaisons bivariées ont été réalisées à l'aide de tests t ou de tests de Wilcoxon sur deux échantillons pour les variables continues, de tests chi-deux ou de tests exacts de probabilité de Fisher selon le cas. Les associations ont été déterminées par la saisie des variables cliniquement significatives dans des modèles de régression logistique multivariés.
Résultats: Le sexe féminin, l'âge plus avancé et la présence d'une endoprothèse étaient tous associés à une IVU. Immédiatement avant l'IVU, le DFGe (p=0,019), l'albumine sérique ($p<0,0001$) et l'hémoglobine (p=0,002) étaient plus faibles, tandis que la CRP sérique ($p<0,0001$) et les neutrophiles absolus (p=0,03) étaient plus élevés chez les cas que chez les témoins. Cependant, dans plusieurs modèles multivariés, seuls la CRP absolue (p=0,001), une variation de la CRP (p=0,005), le sexe féminin ($p<0,0001$) et la présence d'une endoprothèse urétérale (p=0,008) étaient systématiquement prédictifs d'une IVU. Chaque variation de 5 mg/dl entre les deux valeurs précédentes de CRP était prédictive d'une augmentation de 15 % de la probabilité d'IVU. Ce risque était de 5 % pour une variation de 1 mg/dl en concentration absolue de CRP.
Limites: Conception rétrospective d'une étude cas-témoins, étude monocentrique, échantillon de petite taille. Étaient exclus les patients hospitalisés et les patients présentant d'autres types d'infections, une affection inflammatoire aiguë ou un rejet. Les IVU sont plus facilement détectées lorsque les patients se rendent fréquemment à la clinique.
Conclusion: Dans l'année suivant la transplantation, la mesure systématique de la CRP en ambulatoire peut aider à détecter les IVU symptomatiques chez les RGR, à devancer l'amorce du traitement et à réduire la morbidité pour les patients.
Connaissances actuelles: Les IVU sont fréquentes chez les RGR dans l'année suivant la transplantation. L'antibiothérapie n'est généralement pas initiée tant que les résultats des cultures d'urine ne sont pas connus.
Connaissances ajoutées: L'utilization systématique de biomarqueurs appropriés comme la CRP dans le cadre d'une stratégie de surveillance post-transplantation peut permettre aux cliniciens de demander des cultures urinaires, de détecter les IVU et de commencer le traitement plus tôt, favorisant ainsi le mieux-être des patients.

Keywords
bacteria, biomarkers, leukocytes, ureteric stent, urine cultures

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Introduction

Bacterial urinary tract infection (UTI) is a common, serious complication that kidney transplant recipients (KTR) experience.[1] The risk factors for postkidney transplant UTI are well described.[1,2] Despite the wide prevalence of UTI in KTR with their potential clinical implications, most centers do not routinely screen for bacteriuria since spontaneous clearance can occur without symptoms or other consequence.[3] Nonetheless, UTI can impact both short- and long-term kidney allograft function.[4,5]

Urinary frequency and visible pyuria or hematuria commonly indicate bacterial cystitis. Additional symptoms such as fever and pain over the allograft point toward acute graft pyelonephritis, but these symptoms and others such as chills, malaise, nausea, fatigue and diarrhea, while serious and demanding of treatment, defy formal validation as UTI

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predictor variables. Besides occurring in other clinical situations, these symptoms may also occur only after spread of a lower UTI to the allograft or bloodstream. Moreover, posttransplant immunosuppression may suppress the majority of symptoms related to an infection in its early stages. Alternate, preferably simple methods of monitoring for UTI occurrence are therefore required.

Although leukocytosis and elevations in C-reactive protein (CRP) are traditionally associated with upper rather than lower UTI,[6,7] these and other biomarkers may help predict any symptomatic UTI in KTR because of KT-specific risk factors.[1,2] Yet, the posttransplant inflammatory milieu itself may influence measured values for clinical biomarkers.[8] We therefore hypothesized that a change, rather than absolute value in commonly biomarker values may predict a subsequent clinically significant UTI in KTR. Predicting UTI in advance through biomarker monitoring may favorably influence posttransplant outcomes by allowing the clinician to call the patient if needed to ascertain the presence of symptoms, order urine cultures, initiate appropriate therapy earlier, and reduce the potential for avoidable or inappropriate antibiotic exposure.

Methods

St. Michael's Hospital (SMH) is a tertiary care medical-surgical care center in Toronto, Ontario, Canada that performs approximately 130 adult single-organ kidney transplant procedures annually, while providing ongoing posttransplant care to approximately 1800 KTR. We performed a retrospective review of laboratory and clinical information collected in an electronic database extant since 2004. For this study, we identified a cohort of KTR who received their allograft at SMH between January 1, 2016, and December 31, 2019. A positive outpatient urine culture ordered only for clinical indication in the first posttransplant year identified KTR with a UTI. UTI was defined as a growth of 10^5 colony forming units (CFU)/mL, or any growth from a suprapubic specimen if applicable, with date of infection corresponding to the culture date. We excluded KTR who at the time of urine culture remained on dialysis posttransplant (ie, delayed graft function or primary nonfunction), were diagnosed with acute rejection requiring increased immunosuppression, had significant infections elsewhere (pneumonia, wound infections, cellulitis, and BK or cytomegalovirus viremia), were admitted as inpatients at the time of the UTI in cases or time of laboratory testing in both cases and controls, or transferred to SMH after having been transplanted at another center. Using a nested case-control design, all patients with a first posttransplant UTI cases were then compared to non-UTI controls by identifying the KTR closest in transplant date either before or after the date of transplant of the UTI patient case.

All KTR are regularly followed in the first posttransplant year through clinic visits and laboratory monitoring according to an established protocol. Clinic visits occur weekly to the end of the first month, biweekly to the end of the second month, then monthly to month 6, and every 3 months to the end of the first year. Laboratory testing is performed twice weekly to the end of month 3, then weekly to the end of month 6, biweekly to month 9, and then monthly to the end of the first year. Additional visits or tests may occur if clinically indicated. Demographic and anthropometric variables were extracted by chart review for both UTI cases and controls, in addition to clinical information such as relevant comorbidities and immunosuppression medication. Routine laboratory monitoring includes a complete blood count, serum creatinine concentration with estimated glomerular filtration rate derived by the CKD-Epi equation,[9] urine albumin-to-creatinine ratio, and highly-sensitive CRP (hs-CRP, or CRP for short). The last 2 clinical and laboratory values of each parameter preceding the UTI were collected for the cases to measure change (pretransplant value 2 minus pretransplant value 1), along with similar parameters immediately post-UTI treatment and 1 year posttransplant. Only information pertaining to the first UTI was collected. Data for the controls, chosen by being closest in transplant date to each case, were collected to correspond to the posttransplant time points anchored by when the UTI cases occurred, which included the next available measurement of kidney function, and kidney function selected to correspond in posttransplant time to 1 year post-UTI treatment of the corresponding case. Urine cultures were ordered and treatment initiated in all cases only after a specimen for culture was submitted.

Data are summarized as mean ± standard deviation (SD), median and interquartile range (IQR), and counts and percentages. Bivariate comparisons between cases and controls were performed using the *t* test or Wilcoxon 2-sample test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. Clinically significant variables were then entered into a series of multivariable logistic regression models to determine the association between UTI and change in CRP and other parameters, adjusting for demographic covariates. Odds ratios with 95% confidence intervals were estimated. Since this was a population-based review, all cases were identified, and a formal sample size was not calculated, nor individual patient consent obtained. Statistical significance was defined when *P* values were less than .05. All analyses were conducted using SAS version 9.4 (Cary, NC, USA). The study was conducted according to the World Medical Association Declaration of Helsinki. The study was approved by the Research Ethics Board at SMH (REB 19-230, October 11, 2019).

Results

There were a total of 78 identified confirmed cases of UTI over the study period, with a corresponding group of 78 non-infected controls identified who were closest in date of transplant to each identified case. Their baseline characteristics

Table 1. Demographic and Baseline Characteristics of Cases and Controls.

Parameter	Cases (N = 78)	Controls (N = 78)	*P* value
Age (years)	59.1 ± 13	52.1 ± 13	.001
Sex, n (%)			<.0001
Male	36 (46)	67 (86)	
Female	42 (54)	11 (14)	
Ethnicity, n (%)			.796
White	29 (37)	35 (45)	
Black	8 (10)	7 (9)	
East Asian	17 (22)	16 (20)	
South Asian	24 (31)	20 (26)	
Cause of end-stage kidney disease, n (%)			
Diabetes	17 (22)	14 (18)	.527
Hypertension	10 (13)	7 (9)	
Glomerulonephritis	30 (38)	39 (50)	
Others	21 (27)	18 (23)	
Pre-transplant dialysis modality, n (%)			.518
Hemodialysis	44 (56)	46 (59)	
Peritoneal dialysis	30 (39)	25 (32)	
Preemptive	4 (5)	7 (9)	
Donor source, n (%)			.040
Living	19 (24)	31 (40)	
Deceased	59 (76)	47 (60)	
Side of allograft, n (%)			.144
Left	41 (53)	50 (64)	
Right	37 (47)	28 (36)	
Urinary tract stent, n (%)	52 (67)	35 (45)	.006
Prevalent diabetes	41 (53)	31 (40)	.108
Glycosylated hemoglobin	0.064 ± 0.01	0.059 ± 0.01	.044
Delayed graft function	32 (41)	22 (28)	.092
Acute rejection[a]	6 (8)	0 (0)	.028
Tacrolimus trough concentration (ng/mL)	7.0 ± 4	6.7 ± 2.5	.982

[a]Includes 5 cell-mediated and 1 antibody-mediated acute rejection.

are shown in Table 1. Reasons for exclusion are provided in Figure 1. Maintenance immunosuppression consisted of once-daily extended-release tacrolimus, mycophenolic acid, and prednisone in all KTR; in both groups 73 received intravenous basiliximab and 5 received anti-thymocyte globulin as induction therapy. All KTR received daily trimethoprim 80 mg-sulfamethoxazole 400 mg as prophylaxis against *Pneumocystis jirovecii* pneumonia for the first 12 months posttransplant. Bladder catheters typically dwelled for 5 days, and stents for 4 weeks posttransplant. Six UTI cases required subsequent hospitalization. Organisms identified on urine culture are shown in Table 2. As a response to infection, changes were made to extended-release tacrolimus in 26, mycophenolic acid in 19, and prednisone in 27 cases. Antibiotic median (IQR) duration was 10 days (range 7-12).

There was no difference in time posttransplant between the UTI cases and controls by design (median number of days (IQR) 40 (24-76) and 41 (23-77) respectively with almost all first infections occurring in the first 6 months. Urine leukocytes were noted in 73% of UTI cases immediately preceding the UTI, and 42% of controls. There were no differences in baseline systolic blood pressure (127.7 ± 17.6 vs 130.3 ± 16.5 mm Hg, $P = .352$), heart rate (78.6 ± 12.8 vs 81.0 ± 14.6 beats/min, $P = .278$), or body mass index (26.4 ± 5.4 vs 25.7 ± 4.3 kg/m^2, $P = .386$) between groups.

Among baseline characteristics, older age, female sex, higher glycosylated hemoglobin, prior acute rejection, deceased donor source, and the presence of a urinary tract stent were each associated with a UTI (Table 1). Table 3 provides the 2 values for each parameter preceding the UTI (premeasurements 1 and 2) with corresponding control values. Immediately preceding the UTI, eGFR, serum albumin, and hemoglobin were lower in the UTI cases, while serum CRP and absolute neutrophils were higher. However, when measured as a change in the 2 measurements leading to the UTI, only a lowering eGFR and rising CRP were associated with a UTI. Time from CRP measurement to positive urine culture was 3.0 ± 3.0 days, from CRP measurement to antibiotic initiation was 4.2 ± 10.7

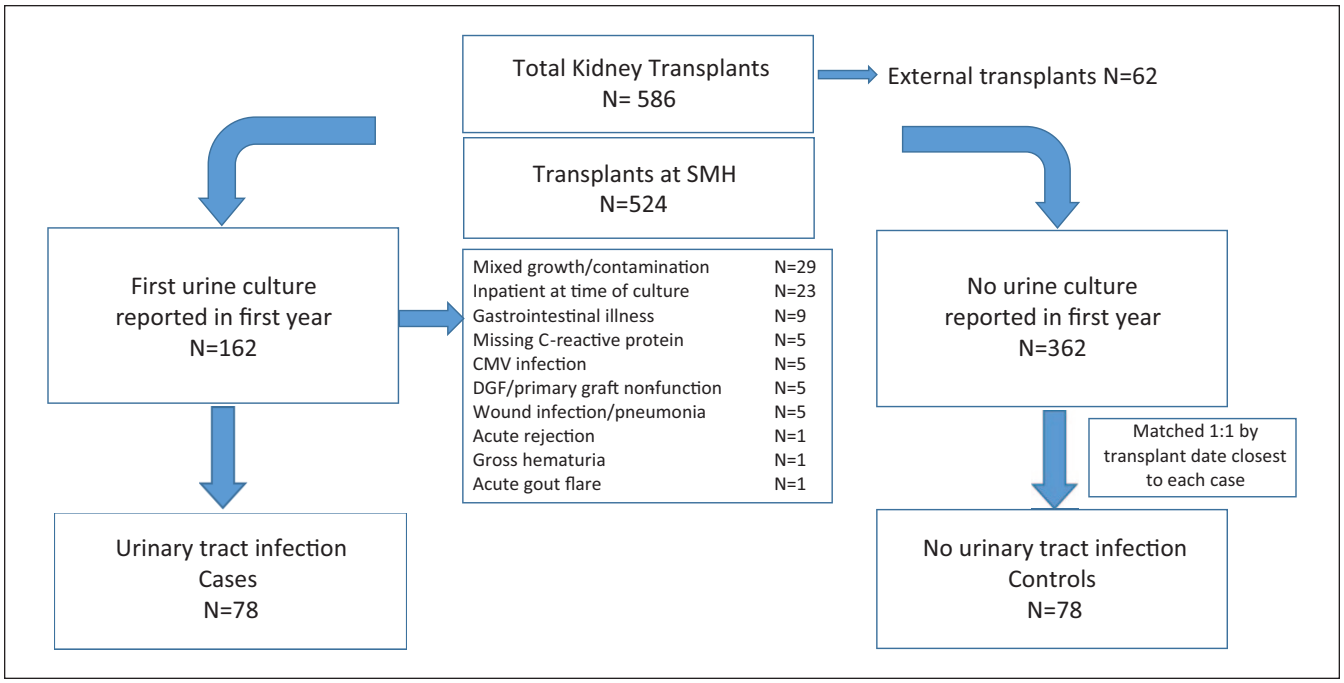

Figure 1. Selection process for the nested case-control study.
Abbreviations: SMH St. Michael's Hospital, CMV cytomegalovirus, DGF delayed graft function.

Table 2. Urinary Tract Organisms Identified by Culture in Cases (N = 78), by Gram Stain in Decreasing Order of Frequency.

	Organism	N
Gram positive (N = 7)	*Staphylococcus epidermidis*	3
	Coagulase-negative staphylococcus	3
	Staphylococcus hemolyticus	1
Gram negative (N = 71)	*Escherichia coli*	31
	Enterococcus faecalis	12
	Pseudomonas aeruginosa	11
	Klebsiella pneumonia	9
	Citrobacter freundii	2
	Morganella morganii	2
	Acinetobacter baumannii	1
	Enterobacter cloacae	1
	Klebsiella oxytoca	1
	Mixed *Escherichia coli-Enterococcus faecalis*	1

days, and from positive urine culture to antibiotic initiation was 1.2 ± 10 days. CRP after UTI treatment was 7.9 ± 11.2 mg/dL, with a corresponding CRP value of 4.6 ± 16.7 mg/dL in controls.

Graft survival and patient survival were each 100% to 1 year posttransplant in both groups. In the UTI group, eGFR was 50.5 ± 20 mL/min/1.73m^2 after antibiotic therapy, 49.7 ± 18 mL/min/1.73m^2 at 1 year posttransplant, and 48.8 ± 17 mL/min/1.73m^2 posttherapy; in the control group these values were 57.8 ± 19, 62.2 ± 18, and 61.8 ± 19 mL/min/1.73m^2, respectively. None of the controls developed a first UTI after the study, although 32 UTI cases developed a subsequent UTI within the first posttransplant year.

Tables 4A-F provide a series of multivariate models including possible predictors of posttransplant UTI. Leukocyte count in all its models (whether the total WBC or absolute neutrophil count), age, kidney function, donor source, and implantation side were not associated with UTI in any of the models. CRP (whether change in value or the absolute value) and female sex were consistent markers of a subsequently confirmed infection. However, despite an odds ratio greater than 2, presence of a stent was no

Table 3. Changes in Predictor Variables Prior to Urinary Tract Infection (UTI) Cases and Controls.

	Pre-Measurement 1			Pre-Measurement 2			Difference (2-1)		
Parameter	UTI cases	Controls	*P* value	UTI cases	Controls	*P* value	UTI cases	Controls	*P* value
Serum creatinine (μmol/L)	159.5 ± 114.4	163.8 ± 130.4	.845	161.9 ± 99.1	153.5 ± 105.5	.506	2.4 ± 42.3	−10.2 ± 33	.002
eGFR (mL/min/1.73m^2)	49.7 ± 25.3	56.1 ± 24.7	.112	47.2 ± 24.6	56.1 ± 22.6	.019	−2.5 ± 8.5	0 ± 7.2	.022
C-reactive protein (CRP) (mg/L)	19.8 ± 29.9	5.6 ± 14.5	.0001	40.4 ± 55.5	4.3 ± 7.9	<.0001	21.5 ± 53.8	−1.3 ± 8	.017
Albumin (g/L)	36.9 ± 5.2	40.1 ± 5.0	.0002	36.6 ± 5.1	40.6 ± 4.7	<.0001	−0.2 ± 3.0	−0.5 ± 2.0	.130
Hemoglobin (g/L)	100.4 ± 15.3	111.1 ± 21.2	.0004	100.8 ± 15.9	111.7 ± 21.8	.002	0.4 ± 6.9	0.6 ± 5	.488
Platelets (thousands per mm^3)	243.1 ± 88.9	231.6 ± 68.3	.469	247.0 ± 92.5	234.4 ± 71.6	.684	3.9 ± 51.7	3 ± 29	.468
Total leukocytes (thousands per mm^3)	9.5 ± 4.8	8.3 ± 2.7	.384	9.8 ± 5.0	8.4 ± 3.3	.191	0.3 ± 3.2	0.1 ± 2	.317
Neutrophils (thousands per mm^3)	7.7 ± 4.3	6.3 ± 2.6	.101	7.9 ± 4.6	6.3 ± 3.1	.034	0.2 ± 2.8	0.0 ± 2	.362
Urine albumin-to-creatinine ratio (uACR) (mg/mmol)	25.7 ± 76.4	9.1 ± 12.8	.001	31.5 ± 96.6	11.0 ± 23.2	.0002	6.7 ± 101.6	0.9 ± 19	.065

Table 4. Odds Ratios and 95% Confidence Intervals (CI) From Multivariate Logistic Regression Models for Immediately Preceding Laboratory Parameters in Predicting a Urinary Tract Infection.

Model 4A: Includes Change in CRP, Change in WBC, and Change in eGFR.

Effect	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
CRP change (per 5mg/dL)	1.15	1.04	1.27	.006
WBC change (per 1000/mm^3)	0.97	0.80	1.17	.738
eGFR change (per mL/min/1.73m^2)	1.03	0.97	1.10	.303
Age at transplant	1.03	1.00	1.07	.092
Female sex (vs male)	11.78	4.10	33.90	<.0001
White ethnicity (vs non-white)	0.47	0.19	1.16	.101
Deceased donor (vs living)	1.96	0.57	6.71	.285
Right side implantation (vs left)	1.06	0.35	3.15	.923
Presence of stent (vs no stent)	3.21	1.34	7.66	.008

Model 4B: Includes Change in CRP, Change in Neutrophils, and Change in eGFR.

Effect	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
CRP change (per 5mg/dL)	1.15	1.04	1.28	.006
Neutrophils change (per 1000/mm^3)	0.96	0.79	1.16	.650
eGFR change (per mL/min/1.73m^2)	1.03	0.97	1.10	.305
Age at transplant	1.03	1.00	1.07	.090
Female sex (vs male)	11.75	4.09	33.76	<.0001
White ethnicity (vs non-white)	0.47	0.19	1.16	.100
Deceased donor (vs living)	1.96	0.58	6.66	.281
Right side implantation (vs left)	1.06	0.36	3.14	.920
Presence of stent (vs no stent)	3.26	1.36	7.82	.008

Model 4C: Includes Immediately Preceding Absolute CRP, WBC, and eGFR.

Effect	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
CRP (per 1mg/dL)	1.06	1.02	1.09	.001
WBC (per 1000/mm^3)	0.94	0.83	1.06	.309
eGFR (per mL/min/1.73m^2)	0.99	0.97	1.01	.463
Age at transplant	1.03	0.99	1.07	.138
Female sex (vs male)	9.33	3.33	26.11	<.0001
White ethnicity (vs non-white)	0.36	0.13	0.96	.041
Deceased donor (vs living)	1.26	0.33	4.87	.738
Right side implantation (vs left)	1.12	0.38	3.31	.832
Presence of stent (vs no stent)	2.78	1.09	7.08	.032

Model 4D: Includes Immediately Preceding Absolute CRP, Neutrophils, and eGFR.

Effect	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
CRP (per 1mg/dL)	1.05	1.02	1.09	.002
Neutrophils (per 1000/mm^3)	0.98	0.86	1.12	.779
eGFR (per mL/min/1.73m^2)	0.99	0.97	1.01	.484
Age at transplant	1.03	0.99	1.08	.113
Female sex (vs male)	9.32	3.34	26.03	<.0001
White ethnicity (vs non-white)	0.37	0.14	0.98	.044
Deceased donor (vs living)	1.27	0.33	4.90	.733
Right side implantation (vs left)	1.14	0.39	3.37	.808
Presence of stent (vs no stent)	2.60	1.03	6.57	.044

(continued)

Table 4. (continued)

Model 4E: Includes Immediately Preceding Absolute CRP, WBC, eGFR, and Urine ACR.				
Effect	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
CRP (per 1mg/dL)	1.06	1.02	1.10	.001
WBC (per 1000/mm^3)	0.94	0.83	1.07	.330
eGFR (per mL/min/1.73m^2)	1.00	0.97	1.02	.743
Urine ACR (per 1 mg/mmol)	1.02	1.00	1.03	.078
Age at transplant	1.04	1.00	1.09	.064
Female sex (vs male)	10.60	3.62	31.04	<.0001
White ethnicity (vs non-white)	0.35	0.13	0.97	.043
Deceased donor (vs living)	1.24	0.31	4.93	.756
Right side implantation (vs left)	0.99	0.32	3.00	.980
Presence of stent (vs no stent)	2.40	0.92	6.27	.074
Model 4F: Includes Immediately Preceding Absolute CRP, Neutrophils, eGFR, and Urine ACR.				
	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
CRP (per 1mg/dL)	1.06	1.02	1.09	.002
Neutrophils (per 1000/mm^3)	0.98	0.86	1.13	.819
eGFR (per mL/min/1.73m^2)	1.00	0.97	1.02	.762
Urine ACR (per 1 mg/mmol)	1.02	1.00	1.04	.078
Age at transplant	1.04	1.00	1.09	.050
Female sex (vs male)	10.61	3.63	30.98	<.0001
White ethnicity (vs non-white)	0.37	0.14	0.99	.048
Deceased donor (vs living)	1.24	0.31	4.94	.756
Right side implantation (vs left)	1.01	0.33	3.07	.986
Presence of stent (vs no stent)	2.24	0.87	5.82	.097

*ACR = albumin-to-creatinine ratio, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, WBC = white blood cells.

longer statistically significant when models were adjusted for urine ACR.

Discussion

This study demonstrates that CRP as a biomarker strongly predicts the presence of a UTI. Change in CRP, identified through regular monitoring, can be a useful tool to identify patients with a true UTI associated with a positive urine culture ordered for cause in the first posttransplant year. By regularly monitoring CRP, antibiotics may even be prescribed by kidney transplant programs without waiting for the urine culture report to return in the presence of symptoms, since clinical suspicion greatly heightens when the CRP is elevated, or has significantly changed. Each 5mg/dL change in CRP value suggests a 15% increased likelihood of UTI, and each 1 mg/dL in CRP associates with a 5% risk. Since CRP often rises to 50 mg/dL or higher, its predictive value increases quite remarkably. Predicting UTI accurately in the outpatient clinic, without waiting for a culture report to return 48 or 72 hours later, decreases time to action and can potentially reduce morbidity in symptomatic patients. Both absolute CRP and change in CRP can be useful biomarkers, especially when the baseline CRP may be elevated for other reasons.

Among solid organ transplant recipients, UTI are most prevalent in kidney recipients, and *Escherichia coli* is the most common organism.[2] UTI cases uniformly distribute across the first 6 months posttransplant with age and female gender being important predictors.[10] Earlier studies indicated that ureteric stents increase the risk for UTI,[11] but more recent analyses have introduced controversy.[12] Choice of immunosuppression is unlikely to play a significant role with the possible exception of anti-thymocyte globulin.[13] Transplant programs encourage early removal of urine catheters[14] and stents[15] to reduce infections despite some analytic uncertainty, but most patients are discharged without a urine catheter. Patients will however typically have a ureteric stent indwelling during their early outpatient visits. This study focused on laboratory predictors such as WBC and CRP, collected routinely as part of posttransplant monitoring, since these tests may enable immediate decision making without the need for an in-person clinician–patient interaction. It is highly unlikely that clinically significant UTI were missed in this study due to the patients' intense posttransplant monitoring schedule.

CRP measurement has been used to monitor for bacteruria[16] and bacteremia[17] in patients requiring admission to intensive care units; in neonates;[18] as well as in children,[19] and older adults[20] in the ambulatory clinical setting. CRP is also used to predict urosepsis in acute renal colic[21] and after lithotripsy,[22] and associates with acute kidney injury in COVID-19 infection.[23] CRP elevation may also help differentiate upper from lower UTIs.[7] This study extends the promise of routine CRP monitoring to the ambulatory posttransplant clinics as a screening tool for UTI, and perhaps posttransplant infections more generally when symptoms and biomarkers such as WBC and neutrophils are altered by immunosuppressive medication, making them less useful. Even kidney function as estimated by the eGFR was unsuitable as a biomarker, possibly because most UTI were limited to the lower urinary tract. Mild chronic elevation in CRP is common in KTRs,[8] as well as in conditions such as chronic kidney disease and acute kidney injury, but the present study demonstrates that both the absolute CRP concentration and its elevation when routinely monitored associate with a subsequently confirmed symptomatic UTI. Dysuria is common in KTR, for reasons such as distension of a bladder severely contracted from years of anuria, thereby misleading the clinician. This study design does not permit a claim that CRP should be measured whenever a UTI is suspected, but rather that a preceding CRP elevation from routine monitoring should heighten clinical suspicion for UTI.

This study has some limitations. Since the study was retrospective, we could not reliably assess the contribution of UTI-related symptoms such as fever, dysuria, or pain over the allograft to a UTI diagnosis to contextualize CRP changes. Urine infections may more easily be detected when patients visit the clinic frequently. Time intervals between CRP tests was variable over the course of the first year. Cases were identified on the basis of a positive urine culture, but this culture was ordered based on symptoms called in via telephone by patients or the clinic calling patients when the CRP was high, and so we could not exclude the presence of similar symptoms in controls. Ultrasound scans of the kidney allograft were not routinely obtained. Most patients adhered to the prescribed laboratory monitoring schedule, but the time interval between CRP tests may still have varied. Virtual clinic visits are challenged by the amount of information available, including symptoms.[24] Cases may also have been asked to provide urine specimens between clinic visits, and so recording of symptoms in the absence of an in-person visit may be incomplete. Adequate posttransplant care depends on patients reporting symptoms, and so additional tools are needed in clinical decision making. Diabetes, acute rejection, and delayed graft function may be other important clinical variables to consider in deciding to order a urine culture in a symptomatic patient in the clinic. We did not match cases and controls by sex and stent since they are established powerful predictors of UTI, and our study aim was only to discern the role of routine CRP monitoring as a policy for all outpatients. Inter- and intraobserver variability in CRP measurement within and between laboratories complicates interpretation and comparison across studies. We did not have a sufficient number of cases to stratify analyses by severity of CRP elevation. Larger sample sizes will permit inclusion of these important clinical variables in models to assess their importance when considering therapy for symptomatic early posttransplant patients. CRP is a nonspecific biomarker for infections and other inflammatory conditions. Future clinical studies of posttransplant outcomes should also study only hs-CRP as a potentially more sensitive biomarker, for both UTI and other infectious complications. Measuring CRP is inexpensive, but urine cultures must still be ordered to avoid inappropriate antibiotic prescription. Such urine cultures can be ordered earlier, even if symptoms are absent. A prospective cost effect analysis will help answer whether routine CRP monitoring improves UTI detection, and at what cost.

In summary, routine highly sensitive CRP monitoring in the ambulatory clinic for early post-KTRs, when performed in the first year, may help identify subsequent symptomatic UTI and assist in initiating earlier therapy, with the goal of reducing patient morbidity.

Declaration of Conflicting Interests

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Ethics Approval

The study was approved by the Research Ethics Board at SMH (REB 19-230, October 11, 2019).

Consent to Participate

Since this was a population-based review, all cases were identified and individual patient consent was not obtained.

Consent for Publication

All authors reviewed the final manuscript and provided consent for publication.

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Availability of Data and Materials

Please send any requests for data sharing to the Corresponding Author.

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