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Procalcitonin for diagnosis of asymptomatic bacteriuria in kidney transplant recipients

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Implication for health policy/practice/research/medical education:

This study investigate the potential utility of serum procalcitonin concentrations, an early marker of infection, for asymptomatic bacteriuria diagnosis among kidney allograft recipients.

Abstract

Introduction: Asymptomatic bacteriuria (ASB) is a frequent finding in allograft kidney transplant recipients and may be associated with a higher incidence of urinary tract infections in this population.

Objectives: We aimed to investigate the potential utility of serum procalcitonin (PCT) concentrations, an early marker of infection, for ASB diagnosis. We also compared its diagnostic performance with white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and highly sensitive C-reactive protein (hsCRP).

Patients and Methods: In a single-center, cross-sectional study, 37 kidney transplant recipients with no clinical signs or symptoms of urinary tract infections were included. Asymptomatic bacteriuria was assessed by means of urine culture. Serum PCT concentrations were determined by the electrochemiluminescence immunoassay technique. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance of PCT and other classifiers.

Results: Seventeen patients (46%) had ASB. Serum PCT concentrations were significantly higher in ASB+ patients (0.14 versus 0.08 ng/ml, p=0.009). Serum procalcitonin concentration

significantly correlated with serum creatinine (r=0.408, p=0.012) and ESR (r=0.466, p=0.004). Of the four tested classifiers (PCT, WBC count, ESR, and hsCRP), only PCT was able to significantly distinguish between ASB^+ and ASB^- patients [area under the curve: 0.74, (95% CI: 0.57-0.91) p=0.012]. Adjustment of the ROC model for serum creatinine showed that the ability of PCT in classifying patients by ASB status is not affected by creatinine concentrations (crude versus adjusted area under the curve; 0.74 versus 0.72, test of AUC difference; p=0.891). A cut-point of 0.10 ng/ml of PCT correctly classified ASB^+ patients with a sensitivity and specificity of 64.7% and 80.0%, respectively.

Conclusion: Serum procalcitonin might be a useful surrogate marker for ASB diagnosis among kidney transplant recipients. Diagnostic performance of PCT is superior to that of WBC count, ESR, and hsCRP. Further, diagnostic ability of PCT appears to be independent of renal function.

Keyword: Urinary tract infections, Kidney transplant, Procalcitonin, Asymptomatic bacteriuria

Introduction

Urinary tract infections (UTIs) are the most frequently occurring types of infection among patients receiving allograft kidney transplants, in particular early after the procedure(1). The healthcare burden associated with UTIs in this patient population is astounding; a recent nation-wide study of kidney transplant patients in the United States found that UTIs increase the length of hospital stay by 74-87%, treatment costs by 22-28%, and transplant-related complications by 169-182%(2).

Given the deep level of immunosuppression required at the early phase of transplantation and the need for life-long immunosuppressive therapy, if left untreated, asymptomatic (ASB)may progress to symptomatic infections including cystitis, pyelonephritis and even life-threatening systemic bacteremia(3). Currently, the Infectious Disease Society of America (IDSA) guideline makes no recommendations with respect to diagnosis and treatment of ASB in solid organ transplant recipients(4). Yet, it should be noted that the advocated recommendations are based on inadequate level of evidence (strength of recommendation; C), and are principally based on expert opinion (Quality of evidence; III)(4). A number of studies published subsequently have proposed that ASB might be associated with detrimental complications, thus negatively impacting graft survival and increasing disease burden. In a 36-month follow-up study of 96 transplant recipients, Fiorante et al, demonstrated that patients with ASB are at an increased risk of cystitis and pyelonephritis(5). Further, it was shown that recurrent ASB episodes increase the

risk of acute graft rejection by 3.5 fold(5). In an assessment of renal graft recipients Dupont et al reported evidence of allograft tissue scarring detected by 2,3 dimercapto-succinic acid single-photon emission computed tomography among patients with recurrent UTIs(6). The authors suggested that the damaging process that leads to allograft scarring might be present in patients with ASB, even in the absence of vesicoureteral reflux(6). Pyelonephritis, which appears to be occurring more frequently among ASB^+ patients have been linked to impaired allograft function and might represent an independent risk factor for graft loss over the long-term(7-9).
At present, the accurate diagnosis of ASB is based on urine culture results, and alternative techniques such as reagent strip testing, or microscopic urinalysis had not been able to replace this diagnostic standard due to the unsatisfactory sensitivity and specificity rates(10). However, sampling and evaluation of urine culture is time-consuming, labor-intensive and the results may render uninterpretable due to contamination during collection, transformation, and evaluation in as many as 15% of the specimens(11). In such settings, surrogate biomarkers of infection that can be readily measured may have the potential to assist clinicians in screening and diagnosis of ASB. Numerous studies over the past decade have proposed that procalcitonin (PCT), a peptide precursor of calcitonin, might be a sensitive marker for diagnosis of a wide-array of clinical infections including those originating from the genitourinary tract(12, 13). More recently, the usefulness of PCT in the diagnosis of ASB in pregnancy has been demonstrated(14). However, whether its utility can be extended for use among kidney allograft recipient, another population group with a high rate of bacteriuria, remains to be elucidated.

Objectives

In the present cross-sectional study, we thus aimed to investigate the distinguishing ability of PCT for ASB diagnosis among a sample of kidney transplant recipients. We further sought to investigate whether PCT outperforms other common laboratory indices which tend to rise during infectious processes: white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and highly sensitive C-reactive protein (hsCRP).

Patients and Methods

Study design

In a cross-sectional setting between December 2013 to December 2014, consecutive kidney transplant patients visited in the transplant clinic of Imam Khomeini hospital (a teaching hospital affiliated with Tehran university of medical sciences) were assessed for eligibility. Patients were included if (1) they were 18 years or older; (2) had no complaints of lower urinary tract symptoms; (3) reported no history of genitourinary, respiratory, or gastrointestinal infections in the past month; (4) had no history of trauma or recent surgery (except for renal transplantation); and (5) had no clinical or laboratory findings suggestive of acute transplant rejection or graft loss. Acute rejection was suspected in the presence of rise in serum creatinine not attributable to competing diagnoses. In the initial phase of the study, a total of 46 patients were assessed among which 37 deemed eligible. Written informed consent was obtained from all patients prior to enrollment.

Assessment

A thorough medical history regarding the signs and symptoms of infection was taken by the principal investigator. Additional information regarding medical and transplant history were obtained from patients' case files and was recorded in pre-designed sheets. Patients were then referred to the hospital laboratory for urine and blood sampling. In the laboratory, patients were instructed to provide a voided mid-stream clean catch urine specimen directly into a sterile collection container cup. In women, bacteriuria was defined as the presence of $>10^5$ colony forming units of identical bacterial strains in two consecutive urine specimens. In men, the diagnosis was ascertained if the urine culture report indicated$>10^5$ colony forming units in a single clean-catch specimen. In cases where contamination of the specimen was suspected, a repeat sampling and culture was performed. Ten ml of venous blood was drawn from each patient. Complete blood count was analyzed using a hematology autoanalyzer. Erythrocyte sedimentation rate was measured by the Westergren technique. Serum concentrations of hsCRP were determined using available commercial kits (Diagnostics Biochem Canada Inc, Canada). Jaffe's kinetic method was used to determine serum concentrations of creatinine. Serum concentrations of PCT were measured by the electrochemiluminescence immunoassay technique using a Roche Elecsys autoanalyzer (Roche Diagnostics, Basel, Switzerland). The assay measures PCT concentrations in the range of 0.02-100 ng/ml.

Data analysis

All statistical analysis were conducted using Stata version 12 (Stata Corp., College Station, Texas). Continuous variables are presented as mean ± standard deviation with the exception of transplant duration which, given its non-normal distribution, is reported as median (interquartile range). Categorical variables are presented as proportions (percentages). Continuous variables between patients with and without ASB were compared using independent T-test or Mann-Whitney U test where appropriate. Chi square test (or Fisher's exact test where appropriate) was used to compare the distribution of categorical variables between patients with and without ASB. To evaluate the degree of association between PCT and clinical and laboratory variables, the Pearson's product moment correlation coefficient was calculated. The association between PCT and transplant duration was investigated using the Spearman's rank-order correlation test. Receiver operating characteristic (ROC) curve analysis was used to determine the predictive ability of PCT and other markers of infection in distinguishing patients with and without ASB. In ROC analysis, area under the curve (AUC) is a measure of diagnostic accuracy and can range from 0.0 to 1.0, with higher values indicating better discriminatory ability of the marker used. Optimal cut-point for PCT was determined using Youden's J statistic. Youden's method selects the optimum cut-point as the point of maximum sensitivity plus specificity. Given the strong correlation between PCT and serum creatinine, adjusted ROC curves were created using the parametric ROC-regression method accounting for the confounding effect of serum creatinine. In all tests, a p-value <0.05 was deemed necessary to reject the null hypothesis.

Results

Complete clinical and laboratory data were available for 37 kidney transplant patients of which 48.6% were female. Age of the patients ranged from 18 to 68 years. The median time elapsed from transplantation was 3.0 years (interquartile range; 1.5-6.0 years). Among patients with positive urine cultures, *Escherichia coli* was the predominant strain isolated from 14 (82.4%) patients. In the three remaining patients the organisms responsible for bacteriuria were *Staphylococcus epidermidis*, *Acinetobacter*, and *Klebsiella pneumoniae*.

Baseline characteristics of enrolled patients by ASB status are presented in Table 1. Age, gender, duration of transplantation, and source of the donated kidney were comparable between the two groups ($p>0.05$ in all tests). Hemoglobin concentrations were on average 1.1 g/dl higher in ASB- patients and the difference reached near significance ($p=0.052$). On the other hand, platelet count and hsCRP concentrations were comparable between ASB^+ and ASB^- patients. ASB^+ patients

had higher serum creatinine concentrations, WBC count, and ESR levels, albeit the difference not reaching statistical significance (Table 1). Finally, serum PCT concentrations were significantly higher in ASB^+ patients (p=0.009).

Findings from correlation analysis between PCT and clinical/laboratory variables are summarized in Table 2. PCT concentrations were significantly and positively correlated with serum creatinine (r=0.408, p=0.012) and ESR (r=0.466, p=0.004), but not with age, transplantation duration, WBC count, or hsCRP concentrations (p>0.05).

To test the discriminatory ability of PCT as well as other markers which typically rise during infectious and inflammatory processes (i.e. WBC count, hsCRP, and ESR) ROC curve analysis was conducted and the findings are depicted in Table 3 and Figure 1. Among the four tested variables, only PCT was able to significantly distinguish between ASB^+ and ASB^- patients with a corresponding AUC of 0.74 (95% CI: 0.57-0.91). The confidence limits of AUC of WBC count, hsCRP, and ESR all contained 0.50 (the reference line) and thus failed to reach statistical significance (Table 3). Based on the point of maximum sensitivity plus specificity, an optimum cut-point of 0.10 ng/ml for PCT concentrations was chosen. This cut-point correctly classified ASB+ patients with a sensitivity and specificity of 64.7% and 80.0%, respectively (Table 4).

Given the strong correlation between PCT and serum creatinine concentrations, and also since serum creatinine concentrations are higher among ASB+ patients, we postulated that serum creatinine might be a confounding variable in the PCT-ASB relationship. To test this hypothesis, we used ROC-regression models that allow for adjustment for the effects of confounding variables similar to that of binary logistic regression. In the adjusted ROC model, serum creatinine was not flagged as a significant confounding variable (p=0.244). Comparison of AUC in crude versus adjusted ROC models also showed that the ability of PCT in classifying patients by ASB status is not affected by creatinine concentrations (crude versus adjusted AUC: 0.74 versus 0.72, test of AUC difference: p=0.891) further corroborating the conjecture that the association between PCT and ASB in not dependent upon creatinine concentrations.

Discussion

In the present study, the predictive ability of PCT for distinguishing between patients with and without ASB was investigated. We showed here that PCT can reliably be used to diagnose ASB among allograft kidney transplant recipients. A cut-point of 0.10 ng/ml correctly classified ASB^+ patients with acceptable sensitivity and specificity. Our analysis revealed that asymptomatic

patients with serum PCT concentrations higher than this cut-point have a 75.3% risk of having bacteriuria.

Since the first report by Assicot et al describing an association between elevated serum PCT concentrations and infectious processes of bacterial and viral origin (15), numerous studies have delved into the possible utility of this marker for timely and accurate diagnosis of infections (16). In healthy individuals, PCT, a 116 amino acid precursor of calcitonin is primarily produced by thyroid C-cells and remains undetectable in the sera(17). However, in response to infectious processes, large quantities of PCT are produced and released by the monocyte-macrophage system and the liver, making it not merely a pre-hormone, but an acute phase reactant (18), since calcitonin concentrations remain largely unaffected by PCT concentrations up to 1000 ng/ml (19).

In a sample of 82 patients including 56 patients undergoing dialysis and 28 kidney transplant recipients, Dumea et al measured PCT concentrations(20). Based on their findings, patients with a strong suspicion of clinical infection of any source had significantly higher PCT levels compared to those without infection (20). Moreover, the authors suggested that a cut-point of 0.5 ng/ml will correctly differentiate between patients with and without infection with a sensitivity and specificity of 93.1% and 78.6%, respectively (20). Similar findings have been corroborated in other studies of solid organ transplant recipients. In a meta-analysis of seven studies comprising 1226 episodes of suspected infections among kidney, heart, lung, or liver transplant recipients, PCT correctly identified episodes of infection with a pooled sensitivity and specificity of 90% (95% CI, 75%-97%) and 85% (95% CI, 77%-91%), respectively(21). Despite established evidence citing a role for PCT in diagnosis of infection among kidney transplant recipients, its potential for diagnosis of ASB has not been investigated so far. To the best of our knowledge only one study has assessed the association between PCT concentrations and ASB. In a case-control study of 69 pregnant women (30 patients with ASB and 39 healthy controls) by Bilir et al (2013) serum concentrations of PCT were determined(14). For PCT measurement, a semi-quantitative method was incorporated in which PCT concentrations <0.05 ng/ml were considered negative(14). Thirty percent of the ASB^{+} patients had PCT levels above the diagnostic threshold, whereas PCT levels were undetectable in all control subjects, thus amounting to a sensitivity and specificity of 30% and 100%, respectively(14). In the present study, we used a more accurate method for PCT quantification which was able to report serum concentrations as low as 0.02

ng/ml. In fact, the entire range for PCT concentrations in our sample was 0.02-0.28 ng/ml and if a determination method similar to the Bilir et al study was used, it would have resulted in negative results for all the participants. It appears that although PCT concentrations rise in response to ASB, their increase is less conspicuous compared with manifest clinical infections and hence, sensitive techniques able to flag even slight increments in PCT concentrations are required.

In an assessment of children with acute lymphoid leukemia undergoing chemotherapy, Hatzistilianou et al compared several markers of inflammation including but not limited to PCT, CRP, interleukin 8, and tumor necrosis factor α to predict bacterial infections(22). Based on their findings, PCT consistently outperformed other cytokines and surrogate markers of inflammation especially early in the disease process and was also a better indicator of infection severity(22). Along the same lines, in our sample of kidney transplant recipients undergoing maintenance immunosuppression therapy, the diagnostic performance of PCT was better than other measured markers of infection and inflammation including WBC count, ESR, and hsCRP. Therefore, it can be conjectured that although indices such as hsCRP, an acute phase reactant, rapidly rise in response to various bacterial stimuli, their response in immunosuppressed patients are relatively hampered and use of a more sensitive marker such as PCT in these settings yields better diagnostic precision.

In the present study, among ASB^+ patients, serum creatinine concentrations were on average 0.3 mg/dl higher, albeit the between group difference not reaching statistical significance ($p=0.117$). Moreover, PCT concentrations were significantly and positive correlated with creatinine concentrations ($r=0.408$, $p=0.0.012$). It might be argued perhaps that higher concentrations of PCT among ASB^+ patients are the result of slower elimination rate in patients with renal dysfunction and not due to the underlying infectious process. From this vantage-point PCT may be regarded as an intermediary variable merely reflecting the status of more impaired renal function in ASB^+ patients. To delve into this issue, we created an adjusted ROC curve model and included serum creatinine into the model as a covariate. Adjusted ROC analysis, using the same principle as to that of multivariate logistic regression model, tests the hypothesis of whether covariate(s) improve or worsen the discriminatory ability of the classifier under testing. Here, we showed that not only serum creatinine is not a significant covariate in the ROC-regression model, but also it bears only minimal impact on the function of PCT as a classifier. Indeed, it has

been shown that the major route for PCT elimination is protein degradation with renal filtration having a negligible influence on the plasma concentrations of the peptide. In a comparative assessment of subjects with normal and impaired renal function, Meisner et al revealed that although PCT elimination rate is markedly prolonged among subjects with reduced glomerular filtration rate, it does not change PCT concentrations significant enough to render the marker unreliable for clinical and laboratory diagnoses(23). Hence, it could be concluded that PCT can reliably distinguish between patients with and without ASB, irrespective of the patient's renal function.

Conclusion

We report preliminary evidence that PCT concentrations are significantly elevated in ASB and therefore it might be a useful surrogate marker for diagnosis of ASB among kidney allograft recipients. PCT outperforms WBC count, ESR, and hsCRP in this regard and its predictive ability appears to be independent of serum creatinine concentrations.

Limitations of the study

This study also has several limitations. First, there is not a gold standard for diagnosis of UTI. Second, this is a highly selected sample from a single center. Third, sample size is small. So we recommended to further study with large sample size and multicenter.

Authors' contribution

FA designed the study. FA, ML and ER edited the draft.TZ gathered the data, wrote the primary manuscript and performed analysis and interpretation of data. All authors read, revised, and approved the final manuscript.

Ethical issues

The research followed the tents of the Declaration of Helsinki. This study was approved by The Ethics Committee of Tehran University of Medical Sciences. The institutional ethical committee at Tehran University of Medical Sciences approved all study protocols (1049)Accordingly, written informed consent taken from all participants before any intervention. This study was extracted from nephrology fellowship thesis of Tahere Zarouk at this university (Thesis#1852)Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

Conflicts of interest

None

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This research did not receive any specific grant from agencies in the public, commercial, or not for profit sectors.

Abbreviations

PCT, procalcitonin; WBC, white blood cell; hsCRP, highly sensitive C-reactive protein; ESR, erythrocyte sedimentation rate.

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Table 1. Baseline characteristics of kidney transplant patients with and without asymptomatic bacteriuria

	ASB+ (n=17)	ASB- (n=20)	P-value
Age, years	42.5 ± 14.7	41.9 ± 13.4	0.892
Gender (n %) Female Male	 8 (47%) 9 (53%)	 10 (50%) 10 (50%)	1.000
Transplantation duration, years[1]	4.0 (1.0-10.5)	3.0 (2.0-5.0)	0.619
Donated kidney source, n (%)			0.101

Living Cadaver	9 (53%) 8 (47%)	5 (25%) 15 (75%)	
Serum creatinine, mg/dl	1.5 ± 0.6	1.2 ± 0.3	0.117
Hemoglobin, g/dl	11.8 ± 1.4	12.9 ± 1.7	0.052
Platelet count, /μl	$236 \times 10^3 \pm 56 \times 10^3$	$252 \times 10^3 \pm 46 \times 10^3$	0.343
WBC count, /μl	7229 ± 2111	6125 ± 1648	0.083
hsCRP, mg/l	8.59 ± 1.70	8.50 ± 2.25	0.976
ESR, mm/h	24.9 ± 5.1	14.8 ± 2.5	0.072
Procalcitonin, ng/ml	0.14 ± 0.07	0.08 ± 0.04	0.009

Abbreviations: ASB, asymptomatic bacteriuria; WBC, white blood cell; hsCRP, highly sensitive C-reactive protein; ESR, erythrocyte sedimentation rate.
[1] reported as median (interquartile range)

Table 2. Correlation of procalcitonin with clinical and laboratory parameters in kidney transplant patients

	Correlation coefficient	P-value
Age, years	0.022	0.898
Transplantation duration, months	0.222	0.187
Serum creatinine, mg/dl	0.408	0.012
WBC count, /μl	0.052	0.760
hsCRP, mg/l	0.059	0.730
ESR, mm/h	0.466	0.004

Abbreviations: WBC, white blood cell; hsCRP, highly sensitive C-reactive protein; ESR, erythrocyte sedimentation rate.
[1] correlation coefficient reported from Spearman's rank test

Table 3. Area under the curve of markers of inflammation for predicting asymptomatic bacteriuria in kidney transplant patients

Abbreviations: AUC, area under the curve; WBC, white blood cell;
hsCRP, highly sensitiveC-reactive protein; ESR, erythrocyte sedimentation rate.

	AUC (95% CI)	P-value
WBC count	0.67 (0.49-0.85)	0.085
HsCRP	0.60 (0.41-0.79)	0.300
ESR	0.66 (0.48-0.84)	0.100
Procalcitonin	0.74 (0.57-0.91)	0.012

Table 4. Optimal cut-off values of procalcitonin for diagnosis of asymptomatic bacteriuria in kidney transplant patients

Cut-off, ng/ml	0.10
Sensitivity	64.7%
Specificity	80.0%
PPV	75.3%
NPV	81.5%

Abbreviations: PPV, positive predictive value; NPV, negative predictive value

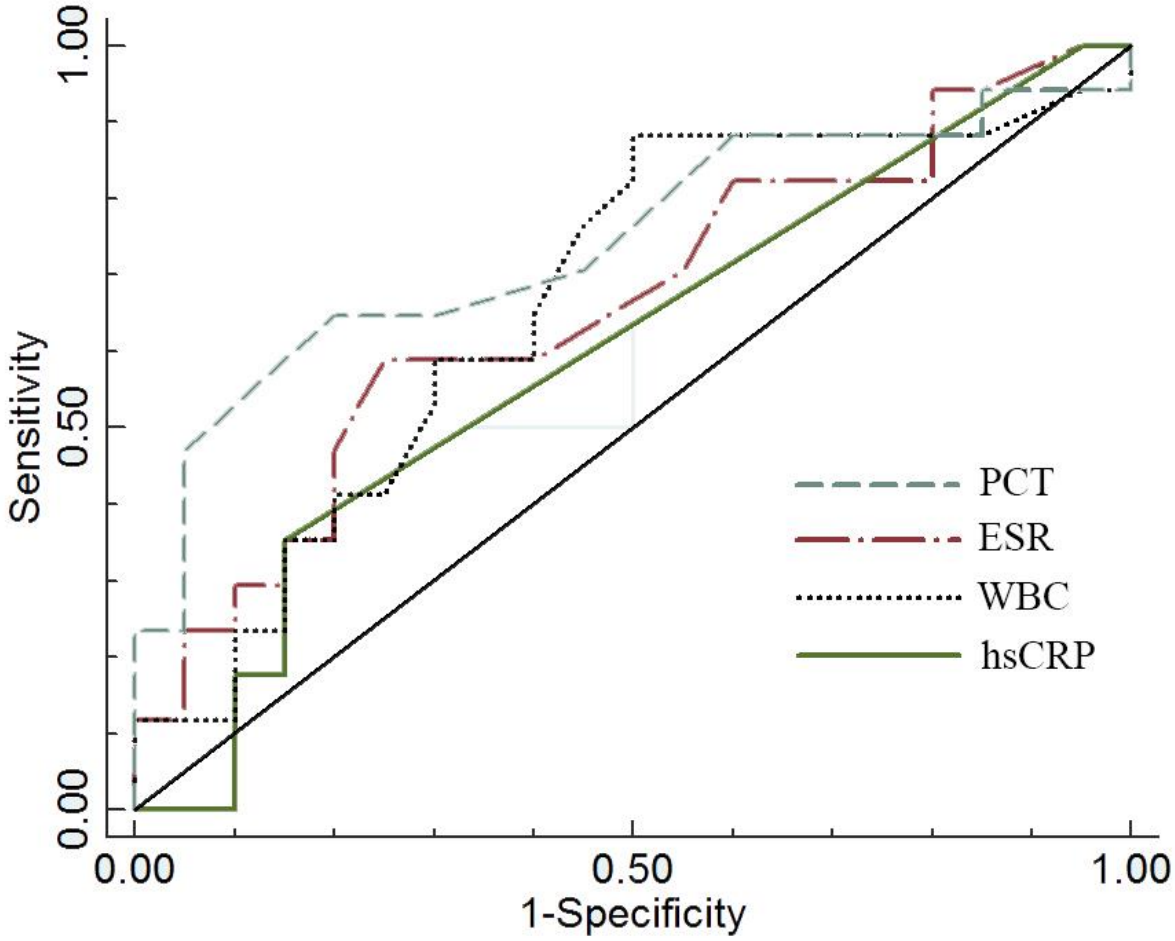

Figure 1. Receiver operating characteristic (ROC) curve analysis of markers of inflammation for predicting asymptomatic bacteriuria in kidney transplant patients
Among the four tested predictors (procalcitonin, hsCRP, WBC, and ESR), only procalcitonin was able to significantly distinguish between patients with and without ASB, p=0.012 (also see Table 3).