Association of Procalcitonin With Acute Pyelonephritis and Renal Scars in Pediatric UTI

WHAT’S KNOWN ON THIS SUBJECT: Prompt, high-quality diagnosis of acute pyelonephritis and later identification of children with scarring are important to prevent future complications. Examination by dimercaptosuccinic acid scan is the current clinical gold standard but is not routinely performed.

WHAT THIS STUDY ADDS: Procalcitonin demonstrated a more robust predictive ability, compared with C-reactive protein or white blood cell count, to selectively identify both children who had acute pyelonephritis during the early stage of urinary tract infections, as well as those with late scarring.

abstract

BACKGROUND AND OBJECTIVE: Urinary tract infections (UTIs) are common childhood bacterial infections that may involve renal parenchymal infection (acute pyelonephritis [APN]) followed by late scarring. Prompt, high-quality diagnosis of APN and later identification of children with scarring are important for preventing future complications. Examination via dimercaptosuccinic acid scanning is the current clinical gold standard but is not routinely performed. A more accessible assay could therefore prove useful. Our goal was to study procalcitonin as a predictor for both APN and scarring in children with UTI.

METHODS: A systematic review and meta-analysis of individual patient data were performed; all data were gathered from children with UTIs who had undergone both procalcitonin measurement and dimercaptosuccinic acid scanning.

RESULTS: A total of 1011 patients (APN in 60.6%, late scarring in 25.7%) were included from 18 studies. Procalcitonin as a continuous, class, and binary variable was associated with APN and scarring (P < .001) and demonstrated a significantly higher (P < .05) area under the receiver operating characteristic curve than either C-reactive protein or white blood cell count for both pathologies. Procalcitonin ≥0.5 ng/mL yielded an adjusted odds ratio of 7.9 (95% confidence interval [CI]: 5.8–10.9) with 71% sensitivity (95% CI: 67–74) and 72% specificity (95% CI: 67–76) for APN. Procalcitonin ≥0.5 ng/mL was significantly associated with late scarring (adjusted odds ratio: 3.4 [95% CI: 2.1–5.7]) with 79% sensitivity (95% CI: 71–85) and 50% specificity (95% CI: 45–54).

CONCLUSIONS: Procalcitonin was a more robust predictor compared with C-reactive protein or white blood cell count for selectively identifying children who had APN during the early stages of UTI, as well as those with late scarring. Pediatrics 2013;131:870–879

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KEY WORDS
acute pyelonephritis, children, procalcitonin, renal scarring, urinary tract infection

ABBREVIATIONS
APN—acute pyelonephritis
AUC—area under the curve
CI—confidence interval
CRP—C-reactive protein
DCA—decision curve analysis
DMSA—dimercaptosuccinic acid
LR—likelihood ratio
OR—odds ratio
PCT—procalcitonin
ROC—receiver operating characteristic
UTI—urinary tract infection
VUR—vesicoureteral reflux
WBC—white blood cell

(Continued on last page)
Urinary tract infections (UTIs) are the most common invasive bacterial infections among young febrile children. UTIs can occur as simple bladder infections (lower UTI; bacteriuria only) but can also involve the kidneys (acute pyelonephritis [APN], in which bacteriuria is associated with infectious renal parenchymal involvement), leading to renal scarring. The belief that persisting APN effects followed by late renal scarring, sometimes with recurrences, may lead to future complications such as hypertension and/or end-stage renal failure has been the major driving force behind the aggressive investigation and treatment of first-occurrence UTIs. The prompt and high-quality diagnosis of APN and differentiation from lower UTI is therefore of key importance. A dimercaptosuccinic acid (DMSA) scan is considered the gold standard in imaging for both renal parenchymal involvement during acute infection and for late renal damage left by the infection. However, DMSA scans are not performed in most children with UTI due to the limited availability of nuclear medicine departments compared with the high number of children with UTIs. Thus, a more practical and accessible tool that could assist clinicians in determining the presence of renal parenchymal involvement and/or late renal damage would be of great clinical value.

Procalcitonin (PCT), a 116-amino acid propeptide of calcitonin without hormonal activity, is an early, sensitive, and specific marker of bacterial infection. PCT is almost undetectable under physiologic conditions or during viral infections but rises in response to bacterial endotoxins; the extent of this increase seems to be proportional to the severity of the infection. However, its exact role, if any, in the inflammatory response and in the cytokine cascade remains unknown. In febrile UTI, the predictive ability of high PCT concentrations for both APN and late renal scarring has been previously investigated by several teams. A review and a recent systematic review and meta-analysis showed that a serum PCT >0.5 ng/mL predicts early renal parenchymal involvement reasonably well (diagnostic odds ratio [OR]: 14.3 [95% confidence interval (CI): 4.7–43.2]); however, heterogeneity made these results inconclusive. Moreover, results concerning late renal scarring were controversial, with no pooled measurements provided. Most of this heterogeneity and these discrepancies may be due to threshold effects because the initial studies chose different PCT cutoff values due to population variation; unfortunately, any effects from the latter could not be fully explored with only pooled data from the studies. Under these circumstances, the only way to analyze PCT as a continuous biomarker without a priori threshold choice, simultaneously controlling for potential individual-level confounders, and then provide robust conclusions concerning PCT as a predictor of APN and/or scarring would be to obtain individual data unaltered by thresholds.

We thus aimed to perform an updated systematic review and meta-analysis on individual patient data to investigate PCT as a predictor for both APN and renal scarring in children with a febrile UTI. The most appropriate threshold values of PCT were simultaneously studied.

Methods

We performed a systematic review and meta-analysis on individual patient data, in accordance with international standards (Centre for Reviews and Dissemination guidelines, PRISMA, and and STARD). We electronically and manually searched for all cohort studies of children with UTI, a PCT measurement, and a renal DMSA scintigraphy published between January 1993 and September 2011. The search methods are detailed in Fig 1. Ethics committees from each participating center approved the protocol for each initial study from which data were collected. All cohort studies of consecutively included children with a febrile UTI, a PCT measurement, and an early (ie, within 14 days) and a late (ie, repeated at least

![Flow chart of the systematic review. The electronic search was conducted in Medline for all studies of UTI with a PCT measurement in children published from January 1993 (when PCT was first described in relation to bacterial infection) through November 2008, and updated in September 2011. The search strategy used medical subject heading terms and text words, including “procalcitonin” and “children.” The electronic search was enhanced by hand-searching reference lists of all included articles, obtaining any identified articles, and also supplemented by a manual review of abstracts from the European Society for Pediatric Infectious Diseases, the European Society for Pediatric Nephrology, the International Pediatric Nephrology Association, the American Academy of Pediatrics, and the American Society of Nephrology and by discussion with experts in the field. The electronic search was then validated, comparing the obtained list with the reference list of previous reviews on PCT and UTI to identify any potential systematic default. No language restriction was used. The search ended with 290 potentially eligible abstracts, among which 19 were considered for inclusion. One article was not included because of absence of DMSA scan data. Finally, 18 articles were included, representing 15 centers as follows: Afuwa (Israel), Ahvaz (Iran), Antalya (Turkey), Athens (Greece), Barcelona (Spain), Elazığ (Turkey), Geneva (Switzerland), Lille (France), Padova (Italy), Thrace (Greece), Toulouse (France), Udine (Italy), and Yvoir (Belgium).](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711718/fig1)
3 months later (if available) renal DMSA scintigraphy were included. Febrile UTI was defined as fever (≥38°C) with a positive result on bacterial urine culture (thresholds for collection techniques are given in Table 1). We asked the authors to send us their study datasets (duplicates were discarded if any), from which we extracted clinical (gender, age), laboratory (C-reactive protein [CRP], procalcitonin [PCT], white blood cell [WBC] count), and radiologic (DMSA scan results, vesicoureteral reflux [VUR] grade on cystography) data. Information concerning the standard operating procedures used for urine collection, PCT measurement, DMSA scanning (and timing), and cystography at each center was also collected. Methodologic study quality was assessed via a checklist (Supplemental Appendix).

We analyzed the relationships between APN/renal damage and PCT, CRP, and WBC count, respectively, using different, backward stepwise multilevel logistic regression models for each biomarker (center was a group-level variable), with fractional polynomial transformation for continuous variables if the model assumption of linearity was violated. The discriminative ability of each biomarker for APN and then late renal damage was evaluated by drawing receiver operating characteristic (ROC) curves, as well as by calculating sensitivity, specificity, predictive values, and likelihood ratios (LR) after dichotomization. In addition, we compared biomarker models by using decision curve analysis (DCA), a method for evaluating the clinical net benefit of prediction models in which the benefits (true-positives) are added and the harms (false-positives) are subtracted. 

Due to collinearity, no attempt was made to combine biomarkers. Statistical methods are detailed in the Appendix.

### TABLE 1 Population Characteristics According to Each Center

<table>
<thead>
<tr>
<th>Centera</th>
<th>Urine Collection Techniques (Threshold of the Positive Bacteriuria)b</th>
<th>Timing of Late DMSA Scan</th>
<th>No. Included for APN</th>
<th>APN, n (%)</th>
<th>No. Included for LRS</th>
<th>LRS, n (%)</th>
<th>Male, n (%)</th>
<th>Age (mo), Median (IQR)</th>
<th>All-Grade VUR, n (%)</th>
<th>Grade ≥3 VUR, n (%)</th>
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<tbody>
<tr>
<td>Centers using SA or UC</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Afula22</td>
<td>SA (any), UC (103)</td>
<td>—</td>
<td>64</td>
<td>23 (36)</td>
<td>0</td>
<td>—</td>
<td>22 (35)</td>
<td>14.0 (4.5–25.5)</td>
<td>17 (27)</td>
<td>9 (14)</td>
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<tr>
<td>Antalya22</td>
<td>UC (103), CVM (103)</td>
<td>3–6 mo</td>
<td>33</td>
<td>21 (64)</td>
<td>23</td>
<td>4 (17)</td>
<td>2 (8)</td>
<td>48.0 (24.0–72.0)</td>
<td>2 (33)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Athens27</td>
<td>SA (103), UC (103), CVM (103)</td>
<td>6 mo</td>
<td>61</td>
<td>25 (41)</td>
<td>59</td>
<td>10 (17)</td>
<td>27 (44)</td>
<td>0.6 (0.2–3.0)</td>
<td>9 (15)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Barcelona18,20</td>
<td>SA (103), UC (103), CVM (103)</td>
<td>6 mo</td>
<td>76</td>
<td>34 (45)</td>
<td>76</td>
<td>12 (16)</td>
<td>30.0 (10.5–72)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Elazig18,20</td>
<td>SA (103), UC (103), CVM (103)</td>
<td>6 mo</td>
<td>76</td>
<td>34 (45)</td>
<td>76</td>
<td>12 (16)</td>
<td>30.0 (10.5–72)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Geneve17,21,31</td>
<td>SA (103), UC (103), CVM (103)</td>
<td>6 mo</td>
<td>80</td>
<td>77 (96)</td>
<td>59</td>
<td>34 (58)</td>
<td>32 (42)</td>
<td>8.0 (2.4–21.5)</td>
<td>21 (28)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Thrace19,20</td>
<td>SA (any), UC (103), CVM (103)</td>
<td>6 mo</td>
<td>57</td>
<td>27 (47)</td>
<td>57</td>
<td>12 (21)</td>
<td>13 (23)</td>
<td>16.0 (7.0–40.0)</td>
<td>15 (29)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Udine23</td>
<td>UC (103), CVM (103)</td>
<td>6 mo</td>
<td>100</td>
<td>63 (63)</td>
<td>79</td>
<td>18 (23)</td>
<td>31 (31)</td>
<td>8.0 (4.0–17.9)</td>
<td>16 (18)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Yvoire24</td>
<td>SA (103), UC (103), CVM (103)</td>
<td>6 mo</td>
<td>61</td>
<td>48 (79)</td>
<td>52</td>
<td>18 (35)</td>
<td>37.2 (12.5–78.4)</td>
<td>13 (22)</td>
<td>6 (10)</td>
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<td>Centers using SB</td>
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<tr>
<td>Ahvaz22</td>
<td>SB (103), CVM (103)</td>
<td>—</td>
<td>100</td>
<td>62 (62)</td>
<td>0</td>
<td>—</td>
<td>19 (19)</td>
<td>8.0 (17.5–57.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lille25</td>
<td>SB (103)</td>
<td>6–12 mo</td>
<td>42</td>
<td>21 (50)</td>
<td>0</td>
<td>—</td>
<td>12 (29)</td>
<td>13.6 (6.0–48.0)</td>
<td>14 (36)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Padova18,22</td>
<td>SB (103)</td>
<td>12 mo</td>
<td>72</td>
<td>52 (72)</td>
<td>61</td>
<td>14 (23)</td>
<td>31 (43)</td>
<td>4.5 (1.1–9.8)</td>
<td>13 (18)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Toulouse16</td>
<td>SB (103), CVM (103)</td>
<td>6–24 mo</td>
<td>91</td>
<td>68 (75)</td>
<td>59</td>
<td>13 (22)</td>
<td>19 (21)</td>
<td>20.8 (8.9–64.9)</td>
<td>32 (36)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Between-center variability (P)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Total</td>
<td>1011</td>
<td>613 (61)</td>
<td>525</td>
<td>135 (26)</td>
<td>332 (33)</td>
<td>10.0 (4.0–30.0)</td>
<td>182 (23)</td>
<td>80 (10)</td>
<td></td>
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</tr>
</tbody>
</table>

References for the articles corresponding to each center are presented in the Supplemental Appendix. CVM, clean-voided midstream; IQR, interquartile range; LRS, late renal scars; SA, suprapubic aspiration; SB, sterile bag; UC, urethral catheterization.

a Classified according to the urine collection technique in non-toilet-trained children.

b In colony-forming units per milliliter.

c Median of 9 months.
RESULTS

Study Characteristics

Following the aforementioned criteria, we retrieved 227 abstracts by electronic searching; 19 were potentially suitable (Fig 1). After full text review, 1 study was not included because of absence of DMSA scan data, leaving 18 articles to be included.\(^{16-35}\) The 13 corresponding study authors were contacted; all agreed to participate and send data. A total of 1011 (97.9%) patients fully met the inclusion criteria. All studies had a high methodologic quality (Supplemental Appendix Tables 1 and 2). Nine (69.2%) centers performed both early and late DMSA scans. All centers performed the early DMSA scan within 7 days; 5 of 9 centers performed the late scan at 6 months, and the other centers varied between 3 and 24 months (Table 1). Among the 9 centers performing late DMSA scans, late scanning was systematically conducted regardless of early-scan results in only 1 (11.1%) center (Elazig, Turkey). Nine (69.2%) centers collected urine samples following high-quality standard operating procedures (suprapubic aspiration, urethral catheterization for non–toilet-trained children, and clean-voided midstream for the other patients). All centers measured PCT by using the LUMItest PCT immunoluminometric assay or the BRAHMS PCT-Q semiquantitative rapid test (BRAHMS, Hennigsdorf, Germany). All centers included hospitalized children with UTI. No adverse events had been reported in performing PCT measurement, DMSA scanning, or cystography. Table 1 provides details on the characteristics of each center’s population.

Analysis of APN and late renal scars involved 1011 and 525 patients, respectively. APN by grade was analyzed in 357 patients. PCT as a continuous variable involved only 883 (87.3%) patients, as PCT was measured by the PCT-Q semiquantitative test for 128 patients. Analysis of CRP and WBC count involved 959 (94.9%) and 962 (95.2%) patients, respectively. VUR was examined in 772 (76.4%) patients.

Predicting APN

APN was demonstrated in 613 children (60.6%) of the 1011 patients included. The mean ± SD age of the children was 25.2 ± 32.8 months (median: 10.5; interquartile range: 4.3–32.3); 332 (32.8%) were boys. VUR was diagnosed in 182 (23.6%), and VUR ≥3 was found in 80 children (10.4%). PCT as a continuous, class, or binary variable was significantly associated with APN (Table 2, Fig 2). The strength of the association increased when the PCT category (when ordinal variable) increased (Table 2). PCT ≥0.5 ng/mL (current threshold used in the literature) yielded an adjusted OR of 7.9 (95% CI: 5.8–10.9). CRP and WBC count were also significantly related to APN, with similar OR values for CRP as previously described; however, lower OR values were obtained for WBC count (Table 2). PCT as a continuous variable offered an area under the ROC curve (AUC ROC) of 0.82 (95% CI: 0.79–0.84), after adjusting according to the chosen model. The AUC ROCs for CRP and WBC count were significantly lower (P < .0001): 0.72 (95% CI: 0.69–0.76) and 0.62 (95% CI: 0.57–0.65), respectively, once adjusted by using the model (Fig 3). The DCA demonstrated that PCT provided a more statistically robust test than CRP, WBC count, or extreme systematic strategies (ie, DMSA for all or no patients) for all threshold probabilities. A PCT threshold ≥0.3 ng/mL (median of nondiseased patient distribution) demonstrated 88% sensitivity (95% CI: 85–90), with 47% specificity (95% CI: 42–52) (Table 2); interestingly, PCT ≥0.5 ng/mL offered a higher specificity of 72% (95% CI: 67–76) with a 71% sensitivity (95% CI: 67–74) (Table 3). PCT remained strongly associated with APN when assessed by clinical grade, as did CRP and WBC count (Supplemental Appendix Table 3).

Predicting Late Renal Scars

Late scars were demonstrated in 135 (25.7%) of the 525 children included. The mean ± SD patient age was 26.6 ± 33.8 months (median: 11.0; interquartile range: 4–36); 162 (31%) were male. VUR was present in 107 (22.0%) of the 486 patients who underwent cystography; VUR ≥3 was diagnosed in 51 (10.5%) children. PCT as a continuous and binary variable was significantly associated with renal scars (Table 2, Fig 2). PCT ≥0.5 ng/mL yielded an adjusted OR of 3.4 (95% CI: 2.1–5.7). CRP and WBC count were also significantly related to renal scarring (Table 2, Fig 2). PCT as a continuous variable resulted in an AUC ROC of 0.75 (95% CI: 0.70–0.80) once adjusted according to the model built and was significantly higher (P = .02) than those values observed for CRP and WBC count (0.70 [95% CI: 0.65–0.76] and 0.66 [95% CI: 0.60–0.72], respectively) (Fig 3). According to DCA, PCT was better than CRP, WBC count, and both extreme systematic strategies (ie, DMSA for everyone or no one) (Fig 3). PCT ≥0.5 ng/mL had a 79% of sensitivity (95% CI: 71–85), with a 50% specificity (95% CI: 45–54) (Table 3).

DISCUSSION

We demonstrated that the measurement of serum PCT can provide considerable predictive value for the development of APN and renal scars, and that this predictive capacity is better than that provided by either CRP or WBC count regardless of considered thresholds. Because the related medical decision process is binary (to perform or not to perform a DMSA scan), our goal was to provide an alternative
Late renal scars formed in the same purpose as above into: ln(CRP/100) + 0.439036841.

3.33732173.

linear transformation); continuous PCT was transformed as follows to assess the model linearity assumption: ln(PCT/100) + 3.293186643.

The analysis included 478 patients. The final multivariate model was based on PCT and high-grade VUR; PCT was transformed in the same purpose as above into: ln(PCT/100) + 0.5.

The analysis included 883 patients for PCT as a continuous or class variable, 937 patients for PCT dichotomized according to the 0.5 ng/mL threshold (because some

The analysis included 962 patients. The final multivariate model was based on CRP and age (as a continuous variable, after linear transformation); CRP was transformed as follows to assess the model linearity assumption: ln(CRP/100) + 2.7.5 (2.3–3.3) < .0001

1.0 (1.0–1.0) < .0001

10000–15000 1.8 (1.2–3.1) .01 1.8 (1.1–3.0) .01

15000–20000 3.1 (1.9–5.1) < .0001 3.0 (1.8–5.0) < .0001

> 20000 4.9 (2.9–8.3) < .0001 4.9 (2.9–8.3) < .0001

WBC count, binary variable (≥15000) 2.4 (1.8–3.3) < .0001 2.4 (1.8–3.3) < .0001

Late renal scarring

PCT (ng/mL)Patients included were 8378. Together, they suggest a reasonably strong predictive value based on PCT levels; however, data from studies using pooled estimates lead to a more cautious interpretation due to the significant heterogeneity found within these study pools. We avoided these issues by working with individual data, adjusting for intercenter variability modeling with multilevel regressions, as well as accounting for all covariates of interest at the individual level. Moreover, the study design (a meta-analysis of individual patient data) allowed us to study the impact of different threshold levels, to perform DCA, and to draw conclusions without the usual threshold effect that often affects diagnostic accuracy assessed by meta-analysis, thus confounding results. Our approach was complementary to that of Zaffanello et al.7 who performed a nonsystematic review of the potential of PCT to predict late renal scarring, without computing pooled estimates, as they were confronted with different studies and cutoffs. With our systematic meta-analysis,

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (cell/mm³)</td>
<td>1.0 (1.0–1.0)</td>
<td>&lt; .0001</td>
<td>1.0 (1.0–1.0)</td>
<td>&lt; .0001</td>
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<tr>
<td>WBC count as a continuous variable</td>
<td>&lt; 10</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10,000–15,000</td>
<td>1.8 (1.2–3.1)</td>
<td>.01</td>
<td>1.8 (1.1–3.0)</td>
<td>.01</td>
</tr>
<tr>
<td>15,000–20,000</td>
<td>3.1 (1.9–5.1)</td>
<td>&lt; .0001</td>
<td>3.0 (1.8–5.0)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>&gt; 20,000</td>
<td>4.9 (2.9–8.3)</td>
<td>&lt; .0001</td>
<td>4.9 (2.9–8.3)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
| Late renal scarring

PCT (ng/mL)Patients included were 8378. Together, they suggest a reasonably strong predictive value based on PCT levels; however, data from studies using pooled estimates lead to a more cautious interpretation due to the significant heterogeneity found within these study pools. We avoided these issues by working with individual data, adjusting for intercenter variability modeling with multilevel regressions, as well as accounting for all covariates of interest at the individual level. Moreover, the study design (a meta-analysis of individual patient data) allowed us to study the impact of different threshold levels, to perform DCA, and to draw conclusions without the usual threshold effect that often affects diagnostic accuracy assessed by meta-analysis, thus confounding results. Our approach was complementary to that of Zaffanello et al.7 who performed a nonsystematic review of the potential of PCT to predict late renal scarring, without computing pooled estimates, as they were confronted with different studies and cutoffs. With our systematic meta-analysis,
we offer further evidence to support their results, updating the review in a systematic manner and providing pooled estimates of the predictive ability of PCT, leading to a robust conclusion.

The use of imaging in this field has been largely debated in the last decade. However, the decision as to which tests, if any, should be routinely conducted in children with UTIs necessarily depends on many factors. The "top-down" approach uses early DMSA scanning as a screening test. Although children with a negative acute-phase DMSA scan are unlikely to develop scarring, DMSA scans are expensive, invasive, and expose children to radiation. However, the top-down strategy raises 2 concerns: first, it requires DMSA scan availability across countries and settings, which is not currently the case, and second, the identification of late renal scarring results in only a more careful follow-up of affected children. Therefore, PCT may occupy an intermediate position useful for identifying children at high risk for APN and renal scarring, and for whom a DMSA scan can be selectively proposed to confirm parenchymal involvement. The reported sensitivity and specificity values may not appear very convincing (~70%). However, PCT is not meant to replace DMSA scanning, which remains the gold standard for assessing parenchymal involvement (APN or scarring). PCT could be used as an intermediate strategy, based on a single biomarker, easier to set up than a nuclear imaging process, which can help discriminate between lower UTI and APN, even in settings in which DMSA scans are not available. Interestingly, PCT offered the best benefit/harm balance irrespective of the chosen threshold, compared with systematic strategies (DMSA for everyone or no one) for the selective identification of children who might benefit from a DMSA scan. Later in the imaging evaluation, a cystography could be proposed for children with a proven APN, to diagnose or rule out VUR, and treat it if necessary. Moreover, PCT may also be helpful when choosing between oral or intravenous antibiotic treatments during the early infectious phase, depending on the severity of the UTI (lower UTI or APN). PCT could find a place in the debated process of UTI imaging and treatment, as a key point test in the decisional flowchart.

There are several potential limitations to our study that should be addressed. First, despite the extensive electronic and hand searches performed, a publication bias is possible, especially because test accuracy studies are more

FIGURE 2
Distribution of PCT, CRP, and WBC count values according to the presence of APN or late renal scars. (A–C) Plots of PCT, CRP, and WBC count for APN. (D–F) Plots of PCT, CRP, and WBC count for late renal scars. In each graphic, the horizontal line is the proposed threshold for dichotomizing classification via the biomarker.
easily conducted and abandoned than randomized controlled trials, and are then particularly susceptible to publication bias. However, our current knowledge about the precise effects of publication bias on meta-analytic estimates, as well as how to assess the extents of these possible limitations, are limited. Therefore, due to the complexity of accurately assessing this issue, we can provide no estimates of the effect of a probable publication bias. Secondly, a participation bias related to the response and voluntary participation of the centers also might be possible but seems unlikely because all authors contacted responded positively to our study.

![ROC curve and DCA for PCT, CRP, and WBC count.](image)

**FIGURE 3**

ROC curve and DCA for PCT, CRP, and WBC count. (A) ROC curves of PCT, CRP, and WBC count for APN. (B) ROC curves of PCT, CRP, and WBC count for late renal scars. (C) The DCA of PCT, CRP, and WBC count for APN. One line represents 1 biomarker (PCT, CRP, and WBC count); the line “all” represents the benefit/harm curve if everyone is investigated with a DMSA scan, whereas the line “none” represents the corresponding curve if no one undergoes examination. (D) The DCA of PCT, CRP, and WBC count for late renal scars. One line represents 1 biomarker (PCT, CRP, and WBC count); the line “all” represents the benefit/harm curve if everyone is investigated with a DMSA scan, whereas the line “none” represents the corresponding curve if no one undergoes examination.

**TABLE 3** Diagnostic Accuracy of PCT, CRP, and WBC Count for APN and Late Renal Scars

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For APN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT ≥ 0.3 ng/mL</td>
<td>88 (85–90)</td>
<td>47 (42–52)</td>
<td>74 (71–77)</td>
<td>68 (63–74)</td>
<td>1.6 (1.5–1.8)</td>
<td>0.3 (0.2–0.3)</td>
</tr>
<tr>
<td>PCT ≥ 0.5 ng/mL</td>
<td>71 (67–74)</td>
<td>72 (67–76)</td>
<td>79 (76–83)</td>
<td>61 (57–68)</td>
<td>2.5 (2.1–3.0)</td>
<td>0.4 (0.4–0.5)</td>
</tr>
<tr>
<td>PCT ≥ 1 ng/mL</td>
<td>65 (61–69)</td>
<td>87 (83–90)</td>
<td>90 (86–92)</td>
<td>60 (55–64)</td>
<td>4.9 (3.7–6.3)</td>
<td>0.4 (0.4–0.5)</td>
</tr>
<tr>
<td>CRP ≥ 20 mg/L</td>
<td>87 (84–89)</td>
<td>41 (37–47)</td>
<td>70 (67–74)</td>
<td>66 (59–71)</td>
<td>1.5 (1.3–1.6)</td>
<td>0.3 (0.3–0.4)</td>
</tr>
<tr>
<td>CRP ≥ 30 mg/L</td>
<td>74 (70–77)</td>
<td>54 (49–59)</td>
<td>72 (69–76)</td>
<td>56 (51–61)</td>
<td>1.6 (1.4–1.8)</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>WBC count ≥ 15,000/mm³</td>
<td>65 (59–67)</td>
<td>53 (50–58)</td>
<td>71 (67–74)</td>
<td>46 (42–51)</td>
<td>1.4 (1.2–1.6)</td>
<td>0.7 (0.6–0.8)</td>
</tr>
<tr>
<td><strong>For late renal scars</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCT ≥ 0.3 ng/mL</td>
<td>91 (85–95)</td>
<td>30 (26–35)</td>
<td>31 (27–36)</td>
<td>91 (84–95)</td>
<td>1.3 (1.2–1.4)</td>
<td>0.3 (0.2–0.5)</td>
</tr>
<tr>
<td>PCT ≥ 0.5 ng/mL</td>
<td>88 (83–91)</td>
<td>50 (45–54)</td>
<td>51 (46–56)</td>
<td>87 (82–91)</td>
<td>1.6 (1.4–1.8)</td>
<td>0.4 (0.3–0.6)</td>
</tr>
<tr>
<td>PCT ≥ 1.0 ng/mL</td>
<td>74 (66–81)</td>
<td>67 (62–71)</td>
<td>45 (37–50)</td>
<td>88 (84–92)</td>
<td>2.3 (1.9–2.6)</td>
<td>0.4 (0.3–0.5)</td>
</tr>
<tr>
<td>CRP ≥ 20 mg/L</td>
<td>85 (78–90)</td>
<td>36 (32–41)</td>
<td>32 (27–37)</td>
<td>87 (81–92)</td>
<td>1.3 (1.2–1.5)</td>
<td>0.4 (0.3–0.6)</td>
</tr>
<tr>
<td>CRP ≥ 30 mg/L</td>
<td>78 (71–85)</td>
<td>47 (41–52)</td>
<td>34 (29–39)</td>
<td>86 (81–90)</td>
<td>1.5 (1.3–1.7)</td>
<td>0.5 (0.3–0.7)</td>
</tr>
<tr>
<td>WBC count ≥ 15,000/mm³</td>
<td>68 (60–75)</td>
<td>51 (46–56)</td>
<td>33 (27–38)</td>
<td>82 (77–86)</td>
<td>1.4 (1.2–1.6)</td>
<td>0.6 (0.5–0.8)</td>
</tr>
</tbody>
</table>

Data are presented as % (95% CI).
requests for patient data sets. Thirdly, the possibility of a classification bias seems unlikely because PCT was measured by using validated techniques (immunoluminometric assay or semi-quantitative PCT-Q assay), while blinded to the outcome. Fourthly, we assumed that patients who had a normal DMSA had no late lesions even if late DMSA was not performed. However, this assumption is commonplace in the literature, and we verified this assumption in the only center (Elazığ, Turkey) in which all patients systematically underwent both late and early DMSA: none of the negative early DMSA cases were followed by a positive late DMSA. This outcome gives an indication on the robustness of our assumption. Fifth, we addressed heterogeneity issues due to data pooling from different centers (including different time frames for the late DMSA scan) by analyzing them as hierarchical data and using multilevel modeling. We chose to analyze the data set as a meta-analysis of individual patient data because this method provides the least biased and most reliable means of addressing the questions at hand. Sixth, technical concerns, such as the collection of urine from non-toilet-trained children in sterile bags at 4 of the selected centers (not a recommended method) could have led to selection bias. This procedure could have increased the number of false-positive results for UTI but without consequences to the relationship between APN or late scarring and PCT or other biomarkers.

In addition, the inclusion of only hospitalized children by the centers might have led to another selection bias, due to the inclusion of only the sickest children. However, all children with febrile UTI were systematically hospitalized in the included centers. Seventh, the absence of previous negative DMSA scintigraphy results might also have introduced a selection bias. Even if all the centers confirmed having included exclusively or mostly children with a first febrile UTI, it could not guarantee that previous UTI with persistent scarring had not occurred in the included patients, as correct diagnosis depends on the clinical evaluation performed during previous febrile episodes. Moreover, not all UTIs in children are accompanied by fever, which is the main clinical reason for obtaining urine cultures in infants; therefore, previous UTIs unaccompanied by fever may not have been clearly identified. Lastly, the delay between the first indications of infection and PCT level measures was not taken into account, and this might have introduced a bias in the results but only by underestimating the relationship between APN or late scarring and PCT, because this marker increases as early as 6 hours after infection and also decreases just as quickly at the end of infection.

CONCLUSIONS

We demonstrated that PCT has a robust predictive ability to selectively identify children who had APN in the early stages of UTI and those that developed later renal scarring. The use of serum PCT measurements has the potential to aid the clinical decision-making process regarding the appropriate acute management of children with UTI. In particular, due to limited resources and technical availability, it may be helpful to use such an assay to selectively identify children who may benefit from a DMSA scan at the early and late stages of infection. The impact of PCT measurements on the currently debated practice of UTI examinations needs to be evaluated by a well-designed impact study and may lead to possible refinement of the decisional process.

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REFERENCES


Dr Leroy designed the study, helped in collecting the data, analyzed the data, interpreted results, drafted the manuscript, and approved the article version to be published; Drs Fernandez-Lopez, Nikfar, Romanello, Bouissou, Gurgoze, Bressan, Smolkin, Leblond, Mr Vaos, and Mr Gervaix contributed to the study design, acquired all the data in their individual centers, revised the paper for important intellectual content, and approved the article version to be published; Drs Tuerlinckx and Gungor contributed to the study design, acquired all the data in their centers, and revised the paper for important intellectual content; Mr Stefanidis had great input in the conception of the study, realized the data collection in his center, performed in-depth revision of the manuscript, and approved the article version to be published; and Ms Gendrel and Mr Chalumeau contributed to the study design and interpretation of results, critically revised the manuscript, and approved the article version to be published.

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