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Choosing a gold standard: support of Bayesian inference methods for diagnostic accuracy of new biomarkers in pediatric urinary tract infection

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Diagnostic accuracy of a test (1/2)

	D +	D –
T +	True Positive	False Positive
T –	False Negative	True Negative

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Sensitivity

Specificity

Diagnostic accuracy of a test (1/2)

	D +	D –
T +	True Positive	False Positive
T –	False Negative	True Negative

Sensitivity

Specificity

- Problem : Absence of a perfect gold standard

⇒ Two-latent class model

Diagnostic accuracy of a test (2/2)

	T_2+	T_2-	Total
T_1+	u	v	u + v
T_1-	w	x	w + x
Total	u + w	v + x	u + v + w + x

Diagnostic accuracy of a test (2/2)

	T_2+	T_2-	Total
T_1+	Y_1 / $u - Y_1$	Y_2 / $v - Y_2$	u + v
T_1-	Y_3 / $w - Y_3$	Y_4 / $x - Y_4$	w + x
Total	u + w	v + x	u + v + w + x

Se_1 and Sp_1 / Se_2 and Sp_2 / Disease prevalence

Diagnostic accuracy of a test (2/2)

	T_2+	T_2-	Total
T_1+	Y_1 / $u - Y_1$	Y_2 / $v - Y_2$	u + v
T_1-	Y_3 / $w - Y_3$	Y_4 / $x - Y_4$	w + x
Total	u + w	v + x	u + v + w + x

Se_1 and Sp_1 / Se_2 and Sp_2 / Disease prevalence

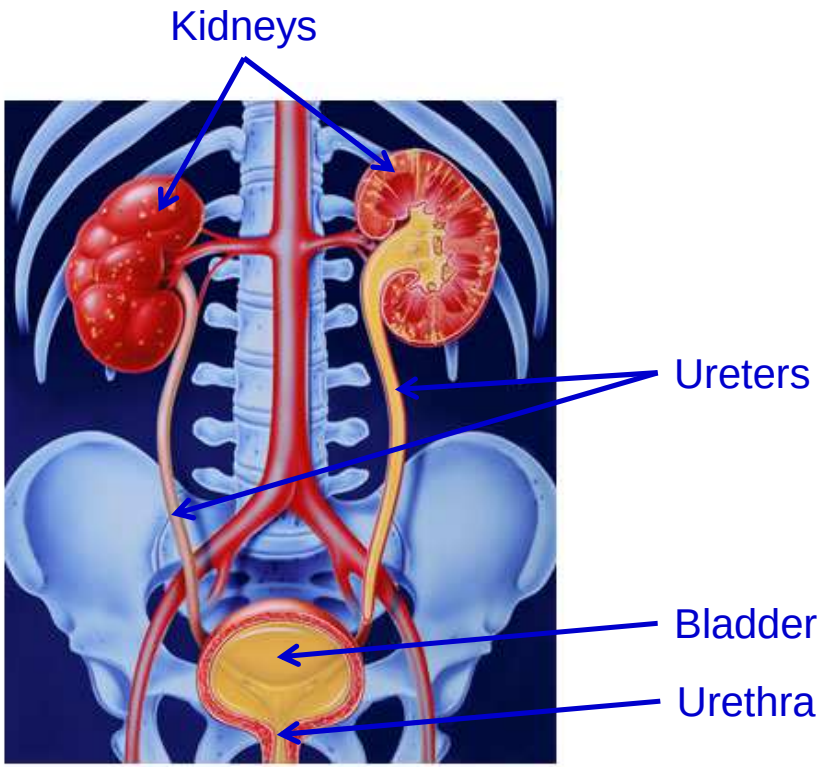
- Problem : Parameters > Degrees of freedom

$\Rightarrow$ Bayesian inference methods using prior information

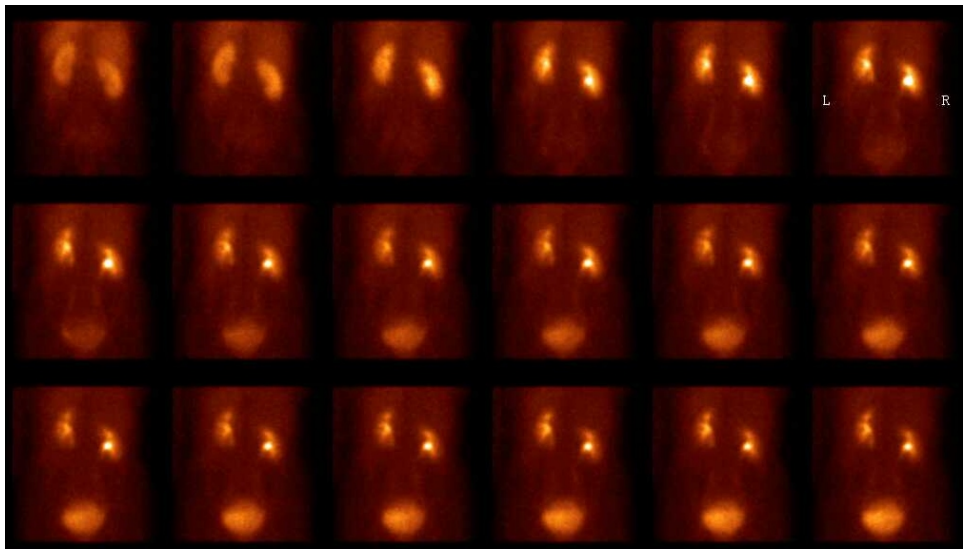
$$f(\theta|y) \propto f(y|\theta) \times f(\theta)$$

$$\textit{Posterior} \propto \text{Likelihood} \times \textit{Prior}$$

Pediatric urinary tract infection



DMSA Scan



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Introduction

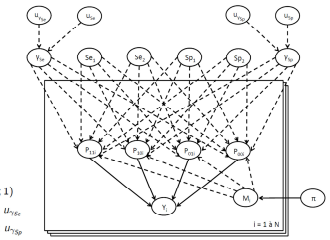
Acute pyelonephritis (APN) is a bacterial urinary tract infection that affects the kidney, which is common in pediatrics. A biomarkers-based strategy using procalcitonin (PCT) aimed at quickly diagnosing APN. It was compared to DMSA (dimercaptosuccinic acid) scan, considered as gold standard even if it raises concerns. We used for the first time Bayesian methods, which allows simultaneous inferences about the population prevalence (π) and the sensitivity (Se) and specificity (Sp) of each test, to estimate the diagnostic accuracy both of PCT and DMSA.

Data

Data were obtained from a published meta-analysis of individual patient data [1]. 1011 patients were included (boys 33%, median age 10.0 (IQR: 4.0 – 30.0)), 61% APN were diagnosed with DMSA.

Methods

Model: Bayesian fixed effects model with conditional dependence between tests [2]



$$M_i \sim \mathcal{B}(\pi\ ;1)$$
$$\gamma_{Se} = u_{Se} \times u_{\gamma_{Se}}$$
$$\gamma_{Sp} = u_{Sp} \times u_{\gamma_{Sp}}$$

$$P_{11} = M_i \times \left(Se_1 \times Se_2 + \gamma_{Se}\right) + (1 - M_i) \times \left((1 - Sp_1) \times (1 - Sp_2) + \gamma_{Sp}\right)$$
$$P_{10} = M_i \times \left(Se_1 \times (1 - Se_2) + \gamma_{Se}\right) + (1 - M_i) \times \left((1 - Sp_1) \times Sp_2 + \gamma_{Sp}\right)$$
$$P_{01} = M_i \times \left((1 - Se_1) \times Se_2 + \gamma_{Se}\right) + (1 - M_i) \times \left(Sp_1 \times (1 - Sp_2) + \gamma_{Sp}\right)$$
$$P_{00} = M_i \times \left((1 - Se_1) \times (1 - Se_2) + \gamma_{Se}\right) + (1 - M_i) \times \left(Sp_1 \times Sp_2 + \gamma_{Sp}\right)$$

$$Y_i \sim \mathcal{M}(P_{11}, P_{10}, P_{01}, P_{00}\ ;1)$$

Prior distributions:
Beta distributions based on two levels of information:

- Informative (meta-analysis data and pediatrician beliefs)
- Few information called "Uninformative"

A priori range (%)	Uninformative prior distributions	Informative prior distributions
Prevalence	[0.4 – 1]	[0.50 – 0.64]
PCT sensitivity	[0.5 – 1]	[0.70 – 0.78]
PCT specificity	[0.5 – 1]	[0.66 – 0.76]
DMSA sensitivity	[0.5 – 1]	[0.80 – 1.00]
DMSA specificity	[0.5 – 1]	[0.80 – 1.00]
Sensitivity covariance	Generalized Beta(α=1, β=1)	
Specificity covariance	Generalized Beta(α=1, β=1)	

Model checking: Posterior predictive checking to compare the predictive effective cross tabs with the observed data.

Sensitivity analysis: Use of the power prior to assess the impact of the information quantity contained in the prior distributions.

R computational tasks

Estimation: numeric simulation by MCMC using a Gibbs sampler (Software: OpenBUGS)

R Packages: Brugs, R2OpenBugs and Coda

Code:

```
fixed.sim <- bugs(data,inits,parameters,model.file="fixed.txt",n.chains=3,n.iter=40000,n.burnin=5000,n.thin=20,debug=FALSE)
model <- as.mcmc.list(fixed.sim)
```

MCMC convergence:

- Trace and density estimate

```
plot(model)
```

- Autocorrelation function

```
autocorr.plot(model,auto.layout=F)
```

- Gelman criterion

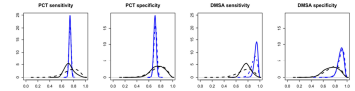
```
gelman.plot(model)
gelman.diag(model)
```

- Geweke criterion

```
geweke.plot(model)
geweke.diag(model)
```

Results

Diagnostic accuracy (Prior vs posterior distributions)



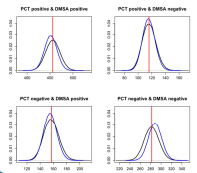
72% [59 – 90] 74% [71 – 77]
75% [53 – 94] 70% [66 – 74]
77% [64 – 92] 94% [87 – 98]
74% [50 – 94] 90% [80 – 97]

Uninformative prior
Informative prior

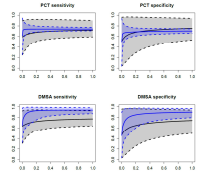
PCT \ DMSA	Positive	Negative
Positive*	456	116
Negative	157	282

(* PCT > 0.5 ng/mL)

Posterior predictive checking



Sensitivity analysis



Discussion

Bayesian methods are nowadays easier to implement using R and a Gibbs sampler (OpenBUGS or rjags).
Based on the two prior distribution cases, PCT accuracy was valuable and DMSA did not appear as a perfect gold standard even if the estimations were different. Given the important amount of the additional information contained in prior samples, the uninformative prior seemed more judicious.

Conclusion

A Bayesian approach showed DMSA, the gold standard test for diagnosing APN, was not perfect despite clinical beliefs. Support of Bayesian inference methods for diagnostic accuracy of new biomarkers, such as PCT, should be fostered.

[1] Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervaix A, Gurgoze M K, Bressan S, Smolkin V, Tuerlinckx D, Stefanidis CJ, Vaos G, Leblond P, Gungor F, Gendrel D, Chalumeau M. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. Pediatrics 2013;131:870-879.
[2] Dendukuri N, Joseph L. Bayesian Approaches to Modeling the Conditional Dependence Between Multiple Diagnostic Tests. Biometrics 2001;57(1):158-167.