Clinical prediction rules for assisting diagnosis

Submitted in total fulfilment of the requirements of the degree of

Doctor of Philosophy

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Thesis summary

Background: Diagnostic prediction rules are tools to assist clinical decision making and aim to either improve patients’ health or provide other benefits without adversely affecting patients. However their uptake in clinical practice has been limited. Possible explanations include uncertainty about their performance compared to and in combination with clinicians’ clinical judgment and complexity for use at the bedside.

Objectives: My four aims in this thesis were to:

1. compare the diagnostic performance of diagnostic prediction rules and clinical judgment versus a reference standard;
2. determine the effect of care provided with and without diagnostic prediction rules on patient and process outcomes;
3. derive and validate a prediction rule for the identification of children with serious bacterial infection in primary care, and to determine the accuracy, independent and added value of an inflammatory biomarker, C-reactive protein (CRP). An existing dataset was to be used for the derivation study and study of the added value of CRP;
4. investigate how simplifying a prediction rule affected performance.

Methods: To address aim 1, I completed a systematic review comparing the diagnostic performance of diagnostic prediction rules and clinical judgment against a reference standard. To address aim 2, I completed a systematic review comparing the effect of care provided with and without a diagnostic prediction rule on patient health and process outcomes. To address aim 3, I completed a systematic review of the diagnostic accuracy and independent value of CRP for detecting serious bacterial infection in non-hospitalised children. However, due to the volume of missing data in the dataset sourced to derive the prediction rule, a valid prediction rule could not be derived. To address aim 4, I conducted a study in which an existing prediction rule was simplified using several methods, and the effect on performance assessed.

Results: Existing diagnostic prediction rules were not clearly superior to clinical judgment in terms of diagnostic performance. In some situations prediction rules moved the threshold for diagnosing disease such that fewer patients with disease were missed, but this was at the cost of further investigations in a larger proportion of patients, or vice versa. The findings are limited by the small number and potential biases of the included studies. Diagnostic prediction rules improved symptoms and reduced antibiotic prescribing for sore throat, improved early
discharge and hospitalisations for possible cardiac chest pain and reduced time to therapeutic operations in suspected appendicitis, but did not improve process outcomes in studies of children with fever. Few studies evaluated patient health outcomes and details of study interventions and implementation were infrequently reported. CRP provides moderate diagnostic information for ruling in and ruling out serious bacterial infection in non-hospitalised children and diagnostic information independent of other clinical features. Simplifying a diagnostic prediction rule did not affect overall accuracy, but reduced the proportion of patients classified as low risk and resulted in worse classification.

**Summary:** In terms of diagnostic performance, existing diagnostic prediction rules do not clearly outperform the judgment of clinicians. However, they may improve patient health and process outcomes in some clinical conditions. C-reactive protein provides useful diagnostic information for children with suspected bacterial infection. Simplification reduced the performance of one diagnostic prediction rule with acceptability of this context dependent.
Declaration and Addendum

This thesis is submitted to Bond University in fulfilment of the requirements of the degree of Doctor of Philosophy. This thesis represents my own original work towards this research degree and contains no material which has been previously submitted for a degree or diploma at this University or any other institution, except where due acknowledgement is made.

Sharon Lea Sanders is the sole author of the Introduction and Discussion chapters, Chapter 4 and lead author on all other chapters which are substantially unchanged multi-author papers. The original research work underpinning Chapters 2, 3, 5 and 6 was driven primarily by Sharon Lea Sanders, who managed all aspects of the collaborative research projects and also produced initial, subsequent and final drafts of each manuscript. None of the work submitted in this thesis was carried out before the PhD candidature.

As per university rules, where a substantially unchanged multi-author paper is included in the thesis, a statement appears at the end of the chapter outlining the contributions of all involved, and these statements have been signed by all authors.
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It has been a privilege to have been able to undertake this interesting and challenging program of research.

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Finally, I am very grateful for the opportunity to submit this thesis and sincerely appreciate the time and effort that will go into the examination procedure.
Peer reviewed journal articles arising from this thesis


Manuscripts submitted and under review


Peer reviewed journal articles published that relate to, but did not arise from this thesis


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Abbreviations and Acronyms

AUROC \hspace{1em} \text{Area under the Receiver Operating Characteristic curve}

AVDSf \hspace{1em} \text{Alveolar dead-space fraction}

CI \hspace{1em} \text{Confidence interval}

CONSORT \hspace{1em} \text{Consolidated Standards of Reporting Trials}

COPD \hspace{1em} \text{Chronic obstructive pulmonary disease}

CPR \hspace{1em} \text{Clinical prediction rule}

CRP \hspace{1em} \text{C-reactive protein}

CT \hspace{1em} \text{Computed tomography}

DVT \hspace{1em} \text{Deep vein thrombosis}

ECG \hspace{1em} \text{Electrocardiogram}

ED \hspace{1em} \text{Emergency department}

EDACs \hspace{1em} \text{Emergency Department Assessment of Chest Pain Score}

ES \hspace{1em} \text{Emergency services}

FN \hspace{1em} \text{False negative}

FP \hspace{1em} \text{False positive}

F/U \hspace{1em} \text{Follow-up}

HR \hspace{1em} \text{Hazard ratio}

HTA \hspace{1em} \text{Health Technology Assessment program}

IP \hspace{1em} \text{Inpatient clinic}

LR \hspace{1em} \text{Likelihood ratio}

MD \hspace{1em} \text{Mean difference}

MACE \hspace{1em} \text{Major adverse cardiac event}

NMD \hspace{1em} \text{Nuclear medicine department}

NRI \hspace{1em} \text{Net reclassification improvement}

OAR \hspace{1em} \text{Ottawa Ankle Rules}

OPC \hspace{1em} \text{Outpatient clinic}

OR \hspace{1em} \text{Odds ratio}

PC \hspace{1em} \text{Primary care}
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
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<tr>
<td>QUADAS</td>
<td>Quality Assessment of Diagnostic Accuracy Studies</td>
</tr>
<tr>
<td>RADT</td>
<td>Rapid antigen detection test</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>RR</td>
<td>Risk ratio</td>
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<tr>
<td>SBI</td>
<td>Serious bacterial infection</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDC</td>
<td>Structured data collection</td>
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<tr>
<td>STARD</td>
<td>Standards for the Reporting of Diagnostic accuracy studies</td>
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<tr>
<td>SU</td>
<td>Surgical unit</td>
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<tr>
<td>TP</td>
<td>True positive</td>
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<tr>
<td>US</td>
<td>Ultrasound</td>
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<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
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<tr>
<td>VQ</td>
<td>Ventilation perfusion scan</td>
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<tr>
<td>VL</td>
<td>Vascular laboratory</td>
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<tr>
<td>wNRI</td>
<td>Weighted net reclassification improvement</td>
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