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Loop-mediated isothermal amplification (LAMP) for the early diagnosis of invasive meningococcal disease in children.

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On behalf of Paediatric Emergency Research in the UK and Ireland (PERUKI)
Abstract

Background
Rapid molecular diagnostic testing has the potential to improve the early recognition of meningococcal disease (MD). The aim of this study was to report on the diagnostic test accuracy of point-of-care loop-mediated isothermal amplification (LAMP) in the diagnosis of MD.

Design
Data was collected prospectively from three UK emergency departments (ED) between November 2017 and June 2019. Consecutive children under 18 years of age attending the ED with features of MD were eligible for inclusion. The meningococcal LAMP test (index test) was performed on a dry swab of the child’s oropharynx. Reference standard testing was the confirmation of invasive meningococcal disease defined as positive *N. meningitidis* culture or PCR result from a sterile body site (blood or CSF).

Results
There were 260 children included in the final analysis. The median age was two years 11 months and 169 (65%) children were aged five years or younger. The LAMP test was negative in 246 children and positive in 14 children. Of the 14 children with positive LAMP tests there were five cases of invasive meningococcal disease. Of the 246 children with negative LAMP tests there were no cases of invasive meningococcal disease. The sensitivity of LAMP testing was 1.00 and the specificity was 0.97. The Negative and Positive predictive values were 1.00 and 0.36 respectively. The positive likelihood ratio was 28.3.

Discussion
Non-invasive LAMP testing using oropharyngeal swabs provided an accurate fast and minimally invasive mechanism for predicting invasive meningococcal disease in this study.

Registration
Introduction

Invasive meningococcal disease (MD) occurs when *Neisseria meningitidis* (*N. meningitidis*) crosses from the respiratory mucosa and invades the host (1). *N. meningitidis* is a gram-negative diplococcus that colonises the nasopharynx and oropharynx of humans (1,2). In most people carriage is asymptomatic but in a minority the bacteria cross the mucosa and enter the blood (1). Once *N. meningitidis* crosses from the naso/oropharynx to the blood it can multiply rapidly with resultant bacteraemia and an associated cytokine storm (1). This leads to increased host vascular permeability, organ dysfunction, and disseminated intravascular coagulation (1). *N. meningitidis* may also cross the blood-brain barrier resulting in meningitis. Even in resource rich settings invasive meningococcal disease carries an approximate 5-10% risk of mortality (1–5).

The early recognition of MD is challenging in children because during the prodrome phase MD often presents with symptoms and signs that are indistinguishable from self-limiting infections (5–7). When there is diagnostic uncertainty clinicians may perform tests such as a full blood count (FBC), C-reactive protein (CRP) and Procalcitonin (PCT) to identify those at highest risk (5,7), but these conventional tests lack the necessary sensitivity to rule out MD (5). This leads to many children receiving unnecessary parenteral antibiotics (just in case) whilst others are incorrectly reassured and discharged home (5,7).

Recent advances in molecular diagnostics have resulted in the development of Loop-mediated isothermal amplification (LAMP) technology (8,9). LAMP is a form of rapid nucleic acid amplification that utilises specific looped primers and strand displacing DNA polymerase (9). LAMP has several advantages over traditional molecular diagnostic techniques such as polymerase chain reaction (PCR) including rapidity, amount of equipment required, and tolerance of biological fluids (which facilitates direct testing of clinical material).

A commercially available CE-marked LAMP test has been developed for the rapid detection of the *ctrA* gene present within all serogroups of *N. meningitides*, and can be performed on a range of specimen types including blood, cerebrospinal fluid (CSF) and naso/oropharyngeal swabs (8,9). Data collected
during the development of this LAMP test suggested it has the potential to outperform traditional testing for MD identification in children (8,9), and its performance accuracy is equivalent on naso/oropharyngeal samples and blood testing (10). Naso/oropharyngeal swabs are easy to collect and require minimal DNA extraction (heating for five minutes) as opposed to blood which requires phlebotomy and a more complicated DNA extraction process (8,9). However nasal carriage of meningococci, rates of which vary across populations and age, may result in a positive test and unnecessary treatment (8,10–12). Such carriage is uncommon in infancy and early-childhood (<5%), but increases steadily to a peak in adolescence (approximately 25%) (11–14).

The primary objective of this study was to evaluate the diagnostic accuracy of LAMP testing of oropharyngeal swabs for identifying invasive MD in children and to compare LAMP testing with conventional tests such as CRP and white cell counts.

Methods

The data for this diagnostic accuracy study come from the Petechiae in Children (PiC) study (15), a mixed method prospective, multicentre cohort study. The full protocol is available as an open access publication (15). The PiC study was designed and reported in line with the Standards for Reporting Diagnostic accuracy studies (STARD) statement (16).

Participants

Consecutive children under 18 years of age attending Emergency Departments (ED) with a reported or recorded fever (≥38°C) and features of meningococcal sepsis/meningitis were eligible for inclusion. The case report form (Supplementary material) included 29 possible features of meningococcal sepsis/meningitis based on NICE guidance and based on a published review conducted by the research team (1,5). Children with pre-existing conditions predisposing to non-blanching rash including haematological malignancy, idiopathic thrombocytopenic purpura (ITP), coagulopathy, and active Henoch-Schonlein purpura (HSP) were excluded. Participants for this analysis were enrolled between the 9th of November 2017 and the 30th of June 2019 at three EDs in the UK.
Test methods

The index test employed in the study was the commercially available HG Direct Swab meningococcus LAMP test “HG-MENDS” (HiberGene Diagnostics Ltd, Ireland). This assay consists of reaction strips containing lyophilised reaction mix comprised of specific primers targeting a conserved region of the *N. meningitidis* *ctrA* gene, an exogenous bacteriophage sequence used as assay extraction control together with strand displacing polymerase enzyme, an intercalating dye and all other necessary reagents and buffer. Testing was performed on dry Nylon FLOQSwabs® product code 519C (Copan diagnostics, Italy) of the child’s oropharynx. Swabs were collected by ED clinical staff during the initial assessment of the child and placed in supplied HG elution buffer (HiberGene Diagnostics Ltd, Ireland) denatured at 95°C for 5 minutes with a 50μl aliquot analysed immediately as per the manufacturer’s instructions for use (http://www.hibergene.com/products/hg-meningococcus/). All reactions were performed in the ED using a supplied HG Swift LAMP instrument (HiberGene Diagnostics Ltd, Ireland) which interprets generated fluorescent signals in real time. The total run time for each sample was 40 minutes. At the end of each run HG swift reported one of three results - positive, negative or invalid.

The reference standard for invasive MD was positive culture or PCR for *N. meningitidis* from a sterile body site (blood or CSF). Reference standard testing was performed at accredited NHS hospital laboratories by individuals blinded to the results of the index test. In all instances LAMP testing was performed prior to the results of the reference standard testing being available.

Follow up

Researchers at each site checked attendance records at seven days to monitor for any unplanned re-attendances by study participants. Participating institutions also cross-referenced enrolled children with notifications of MD from their hospital laboratory to Public Health England or the Public Health Agency Northern Ireland. These processes ensured that all cases of MD were recorded, including any who had been discharged without treatment. In situations where the child was enrolled but discharged home without reference standard testing, they were assumed to not have MD provided they met the following criteria:

1) They were not subsequently diagnosed with MD within seven days of discharge
2) They did not have a MD notification to public health

**Analysis**

The study population was described in terms of demographic characteristics with median age and gender. Simple descriptive statistics (total number and proportion) were used to describe vaccination status, parenteral antibiotic use, admission to hospital, admission to intensive care units, and survival.

The diagnostic accuracy of LAMP testing was reported as sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and negative/positive likelihood ratios (LHR) with 95% confidence intervals (CI). In situations where the LAMP test provided an invalid result the test result was excluded from analysis.

**Sample size calculation**

As per the published protocol we calculated that we would need 203 LAMP negative patients to estimate an NPV of 95% or greater with CIs of +/- 3%. Disease prevalence was estimated at 15% or lower, based on preparatory work in our centre and other epidemiologic studies, and we anticipated a combined refusal of consent and dropout rate of 10%. Accounting for these factors we calculated that we would need to recruit 250 participants.

**Consent Model**

Due to the potentially life-threatening nature of MD we used research without prior consent (RWPC) (17), described in detail elsewhere (15,18). All participants were invited to provide consent at the earliest appropriate opportunity once the clinical condition had stabilised (typically within 24 hours of enrolment).

**Data Management**

Study data were collected and managed using REDCap (Research Electronic Data Capture). The initial REDCap case report form (CRF1) was used to contemporaneously record data regarding the initial clinical assessment and results of LAMP testing. The second CRF was completed seven days after discharge and was used to record laboratory results, length of stay, and other aspects of care not susceptible to recall bias (Copies of the CRFs are available in supplementary material).
Public and patient involvement (PPI)

There has been public and patient involvement with the PiC study from outset. The PPI group assisted in the design of the PiC study including the protocol, study information, and RWPC methodology. The lead of the PPI group sat on the trial oversight committee and received regular updates regarding progress, and was a co-author of the published PiC protocol (15). PPI group members have promoted the study locally and nationally through appearances on local and national radio and television.

Office for Research Ethics Committees (OREC) and local Research Governance

The study was approved by both the Northern Ireland OREC (Project ID 224660, OREC ID 17/NI/0169) and by the Belfast Health and Social Care Trust Research Governance.

Study Registration

The PiC study was registered at https://www.clinicaltrials.gov (trial registration: NCT03378258) on the 19th of December 2017.

Findings

A total of 304 consecutive children were screened for inclusion in the study across the three sites, of which 24 were ineligible; 18 of these were screened after hospital admission and laboratory testing, four did not meet inclusion criteria, two could not provide consent due to unavailability of translators, and one declined consent. Of the 280 participants, 17 did not have LAMP testing performed due to a lack of time and/or trained staff, and three had invalid results, leaving 260 patients for inclusion in the final analysis. The three invalid results occurred in children without MD (Figure 1). Of the analysis population of 260, 245 were enrolled in the lead study site, 12 from the second site, and three from the third site. Reference standard testing was performed in 253 participants; none of the seven children without reference standard testing received parenteral antibiotics, all were diagnosed with "viral illness" by the discharging clinician, and none re-presented within seven days of discharge.

142 participants (54.6%) were male, and the median age was two years, 11 months (range 1 month - 13 years, 11 months), with 169 (65%) aged five years or younger. A total of 253 (97.3%) were
appropriately vaccinated for age according to the UK vaccination schedule; 150 (57.7%) had received meningococcal B vaccination, and 179 (68.8%) meningococcal C vaccination. Parenteral antibiotics were given to 120 (46.2%), and 142 (54.6%) were admitted; four were admitted to a paediatric intensive care unit (PICU) and one died. There were five (1.9%) confirmed cases of invasive MD (Tables 1 and 2), all of which had positive blood PCR for *N. meningitidis*. One case was confirmed by both culture and PCR for *N. meningitidis* in blood (Table 2).

The LAMP testing of oropharyngeal swabs was positive in 14 children, of whom five had invasive MD (Table 2). All five cases of invasive MD were recruited from the Royal Belfast Hospital for Sick Children. Of the 246 with negative LAMP tests there were no cases of invasive MD. The sensitivity of LAMP testing was 1.00 (95% CI 0.46-1.00) and the specificity was 0.97 (95% CI 0.93-0.98). The NPV and PPV were 1.00 (95% CI 0.98-1.00) and 0.36 (95% CI 0.14-0.64) respectively. The positive likelihood ratio was 28.3 (95% CI 14.9-53.8); the negative likelihood ratio was incalculable due to there being no false negatives in this cohort (Table 3). In all instances the LAMP test result was available within 40 minutes. The oropharyngeal swabs used to perform LAMP testing underwent additional laboratory testing for meningococcal *ctrA* gene using PCR. Of the 260 analysed oropharyngeal specimens, seven (2.7%) tested positive for *N. meningitidis* and 253 tested negative. The seven positive test results included all of the cases of invasive MD.

All of the 260 children included in the final analysis had data relating to their measured C-reactive protein levels (CRP), total white cell counts (WCC) and neutrophil counts recorded. The diagnostic accuracy of these tests are shown in Table 4. The LAMP test performed better than CRP, WCC or neutrophil counts in this population with a significantly higher specificity (*p*<0.0001) for all.

**Interpretation**

This study found the LAMP test can be performed using oropharyngeal swabs in the ED, as a point-of-care test, with results available within the hour. The invalid rate was low (n=3; 1.1%) and the LAMP test was highly sensitive and specific for identification of invasive MD. The LAMP test performed favourably when compared to conventional tests such as CRP, WCC and neutrophil count in this cohort.
Although vaccination programmes have made MD uncommon in the UK, a small but significant number of children develop invasive MD each year (19, 20). Differentiating children with MD from those with a self-limiting viral infection is increasingly difficult on clinical grounds alone. Existing biomarkers such as CRP, WCC, and neutrophil counts, are of little additional help to clinicians given their inaccuracy for predicting MD (5, 21). The findings of the parent study from which the data in this analysis are drawn (the PiC study) further support this, demonstrating that an abnormal WCC, neutrophil count or elevated CRP were all poorly specific for MD (0.67, 0.29 and 0.73) respectively (22). These specificities were significantly lower than that of the LAMP test (specificity 0.97, p<0.0001).

In summary the LAMP test was as sensitive as CRP at a cut-off of 6mg/l and more specific than an abnormal WCC or an elevated neutrophil count for the detection of MD. The LAMP test conferred additional benefits for patients, including a quicker time to result than conventional microbiology testing and it would be entirely plausible for a child to have their throat swabbed at triage and results available within the hour.

Further research to fully ascertain the best use of LAMP testing within the diagnostic pathway is required but potential uses include as an adjuvant to blood culture and PCR techniques to rapidly identify those children with likely MD and tailor antimicrobial therapy.

**Limitations**

This study has some limitations. Firstly, the majority of participants were under five years of age, a group which has low carriage rates of *N. meningitidis* in the naso/oropharynx. This will have over-inflated the specificity of the LAMP test due to fewer false positive results than would be seen with higher carriage rates. Our findings should therefore be applied with caution to populations with higher carriage rates, such as adolescents and young adults, and its performance accuracy is worthy of further study in this age group.

There were seven recorded false positive results (positive on LAMP testing but negative by PCR using the same swab) it is unclear if the difference in results was due to issues with handling samples (i.e. genuine false positives) within the ED or due to a greater sensitivity of LAMP testing compared to
conventional PCR. Previous studies have suggested that molecular amplification techniques utilising LAMP technology may offer a greater sensitivity than conventional PCR techniques (10). Further research to determine if LAMP testing in the ED results in a greater number of false positives than LAMP testing in a laboratory setting could help to determine the ideal location and service model for LAMP testing. One potential solution could be co-located laboratories within the ED able to perform rapid tests including some molecular diagnostic tests.

The presented data is based on very few cases (N=5) of confirmed invasive MD, resulting in wide 95% confidence intervals for sensitivity. This was despite the selection of eligibility criteria designed to include only participants with symptoms or signs suggestive of MD. Further study in a high prevalence setting would therefore be helpful to further illuminate the performance accuracy of LAMP as a rule out test in isolation. Based on this study alone, with only five cases of MD, the LAMP test could not be used as a rule out-test.

Finally the majority of the LAMP testing occurred in a single large tertiary children’s hospital. While it is likely that this centre is similar to other large city secondary and tertiary care centres, the dominance of one centre increases the inherent risk of bias within the study and makes the results more difficult to generalise. A prospective multicentre study involving a range of site types, and a greater number of older children and adolescents, is required to fully understand the clinical utility of the LAMP test.

**What is known about this topic?**

Invasive meningococcal disease occurs when *Neisseria meningitidis* crosses from the respiratory mucosa and invades the host. Even in resource rich settings invasive meningococcal disease carries an approximate 5-10% risk of mortality.

Recent advances in molecular diagnostics have resulted in the development of Loop-mediated isothermal amplification (LAMP) technology. LAMP is a form of rapid nucleic acid amplification that has several advantages over traditional molecular diagnostic techniques such as polymerase chain reaction
(PCR) including rapidity, amount of equipment required, and tolerance of biological fluids (which facilitates direct testing of clinical material).

What this study adds

A meningococcus LAMP test can be performed using oropharyngeal swabs with results available within one hour. The test was highly sensitive and specific for identification of invasive meningococcal disease. The LAMP test performed favourably when compared to conventional tests such as CRP, WCC and neutrophil count.

Declarations

- **Ethics approval** The Northern Ireland Research Ethics Committee (REC Reference - 17/NI/0169) and the Belfast Health & Social Care Trust Research Governance (Reference 16201MS-SW) approved the protocol.

- **Declaration of interests**: Dr McKenna Holds share options in HiberGene Diagnostics Ltd.

- **Funding** This study was primarily funded by the Public Health Agency of Northern Ireland (EAT/5313/16). The Royal College of Emergency Medicine provided some additional funding. The funder had no involvement in the design or conduct of the study.

- **Authors contributions** Dr Waterfield, Dr Lyttle, Dr Roland, Dr Maney, Dr Fairley, Dr Mckenna and Professor Shields conceived and designed the study. Dr Waterfield co-ordinated the running of the study including data management and site training. Dr Corr and Ms Patenall were involved with the conduct of the study including data collection. Dr Woolfall provided study design expertise and designed the approach to consent.

- **Acknowledgements** We would like to thank all of the children and their families who participated in this study. We would also like to thank all of the people involved with screening and recruiting patients to the PiC study.

- **Data Sharing** All of the individual participant data collected during this study will be available (including data dictionaries) on the Queen’s University Belfast data repository. The full study protocol is available as an open access publication.
References


5. NICE. Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management | Guidance and guidelines | NICE. 2015 [cited 2017 Oct 10]; Available from: https://www.nice.org.uk/guidance/cg102


Figure 1: Flow of patients through the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months; median (range))</td>
<td>35 (1 - 156)</td>
</tr>
<tr>
<td>Male sex</td>
<td>142 (54.6)</td>
</tr>
<tr>
<td>Vaccination status</td>
<td></td>
</tr>
<tr>
<td>Vaccinations up-to-date</td>
<td>253 (97.3)</td>
</tr>
<tr>
<td>Meningococcal B vaccinated</td>
<td>150 (57.7)</td>
</tr>
<tr>
<td>Meningococcal C vaccinated</td>
<td>179 (68.8)</td>
</tr>
<tr>
<td>Index Tests</td>
<td></td>
</tr>
<tr>
<td>LAMP</td>
<td>260 (100)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>260 (100)</td>
</tr>
<tr>
<td>White cell counts</td>
<td>260 (100)</td>
</tr>
<tr>
<td>Reference Standard</td>
<td></td>
</tr>
<tr>
<td>Culture/PCR</td>
<td>253 (97.3)</td>
</tr>
<tr>
<td>Presumed negative</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Received parenteral antibiotics at first presentation</td>
<td>120 (46.2)</td>
</tr>
<tr>
<td>Admitted to hospital</td>
<td>142 (54.6)</td>
</tr>
<tr>
<td>Admitted to PICU</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Confirmed meningococcal disease</td>
<td>5 (1.9)</td>
</tr>
</tbody>
</table>
Table 2: Summary of children with confirmed meningococcal disease

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>BLOOD CULTURE</th>
<th>BLOOD PCR</th>
<th>AGE</th>
<th>RECEIVED MENINGOCOCCAL B VACCINE</th>
<th>RECEIVED MENINGOCOCCAL C VACCINE</th>
<th>ADMITTED TO INTENSIVE CARE</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. MENINGITIDIS B</td>
<td>Negative</td>
<td>N. meningitidis B</td>
<td>4 years 10 months</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>N. MENINGITIDIS B</td>
<td>Negative</td>
<td>N. meningitidis B</td>
<td>4 years 10 months</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>N. MENINGITIDIS B</td>
<td>Negative</td>
<td>N. meningitidis B</td>
<td>4 years 7 months</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>N. MENINGITIDIS B</td>
<td>N. meningitidis B</td>
<td>N. meningitidis B</td>
<td>3 months</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>N. MENINGITIDIS B</td>
<td>Negative</td>
<td>N. meningitidis B</td>
<td>3 years 1 month</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 3: Diagnostic accuracy of LAMP testing on oropharyngeal swabs for predicting meningococcal disease.

<table>
<thead>
<tr>
<th>Index Test</th>
<th>Meningococcal Disease</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value (95% CI)</th>
<th>Negative Predictive Value (95% CI)</th>
<th>Positive Likelihood Ratio (95% CI)</th>
<th>Negative Likelihood Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>LAMP Positive</td>
<td>5</td>
<td>9</td>
<td>1.00(0.46 to 1.00)</td>
<td>0.97(0.93 to 0.98)</td>
<td>0.36(0.14 to 0.64)</td>
<td>1.00(0.98 to 1.00)</td>
<td>28.3(14.9 to 53.8)</td>
</tr>
<tr>
<td>LAMP Negative</td>
<td>0</td>
<td>246</td>
<td>1.00(0.46 to 1.00)</td>
<td>0.97(0.93 to 0.98)</td>
<td>0.36(0.14 to 0.64)</td>
<td>1.00(0.98 to 1.00)</td>
<td>28.3(14.9 to 53.8)</td>
</tr>
</tbody>
</table>
Table 4: Diagnostic accuracy of CRP, abnormal white cell count (<5,000/ul or >15,000/ul) and elevated neutrophil count (>10,000/ul) at predicting meningococcal disease.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Positive LHR (95% CI)</th>
<th>Negative LHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein &gt; 6mg/l</td>
<td>1.00(0.46 to 1.0)</td>
<td>0.29(0.23 to 0.35)</td>
<td>0.03(0.01 to 0.06)</td>
<td>1.00(0.94 to 1.00)</td>
<td>1.4(1.3 to 1.5)</td>
<td>NA</td>
</tr>
<tr>
<td>C-reactive protein ≥ 10mg/l</td>
<td>1.00(0.46 to 1.0)</td>
<td>0.39(0.33 to 0.45)</td>
<td>0.03(0.01 to 0.07)</td>
<td>1.00 (0.95 to 1.00)</td>
<td>1.6(1.5 to 1.8)</td>
<td>NA</td>
</tr>
<tr>
<td>C-reactive protein ≥ 20mg/l</td>
<td>1.00(0.46 to 1.0)</td>
<td>0.54(0.47 to 0.60)</td>
<td>0.04(0.01 to 0.10)</td>
<td>1.00(0.96 to 1.00)</td>
<td>2.2(1.9 to 2.5)</td>
<td>NA</td>
</tr>
<tr>
<td>C-reactive protein ≥ 50mg/l</td>
<td>0.60(0.17 to 0.93)</td>
<td>0.78(0.73 to 0.83)</td>
<td>0.05(0.01 to 0.15)</td>
<td>0.99(0.96 to 0.99)</td>
<td>2.8(1.3 to 6.0)</td>
<td>0.5(0.2 to 1.5)</td>
</tr>
<tr>
<td>Abnormal white cell count</td>
<td>0.60(0.17 to 0.93)</td>
<td>0.67(0.61 to 0.73)</td>
<td>0.03(0.01 to 0.11)</td>
<td>0.99(0.95 to 1.00)</td>
<td>1.8(0.9 to 3.9)</td>
<td>0.6(0.2 to 1.7)</td>
</tr>
<tr>
<td>Elevated neutrophil count</td>
<td>0.40(0.07 to 0.83)</td>
<td>0.73(0.67 to 0.78)</td>
<td>0.03(0.00 to 0.11)</td>
<td>0.98(0.95 to 1.00)</td>
<td>1.5(0.5 to 4.4)</td>
<td>0.8(0.4 to 1.7)</td>
</tr>
</tbody>
</table>