

## **Supplementary data**

### **Evaluation of clinical examination and preoperative imaging in patients with right iliac fossa pain and a medium or high risk score for appendicitis**

#### **Appendices**

Appendix 1 – List of authors

Pages 1-15

Appendix 2 – Supplementary tables and materials

Pages 16-29

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## Appendix 2: Supplementary materials

Supplementary materials titles	Pages
Table S1: Diagnoses in patients who did not have appendectomy	17
Table S2: Validation of the Adult Appendicitis Score in women aged 16-45 years	18
Table S3: Validation of the Appendicitis Inflammatory Response Score in men aged 16-45 years	19
Table S4: Validation of the Adult Appendicitis Score in women aged $\geq 46$ years	20
Table S5: Validation of the Appendicitis Inflammatory Response Score in men aged $\geq 46$ years	21
Figure S1. Normal appendectomy rates stratified by risk scores	22
Table S6: Ultrasound scan findings other than appendicitis	23
Table S7: Diagnostic performance of ultrasound for diagnosis of appendicitis, in sub-group of patients with imaging findings other than appendicitis	24
Table S8: Computed tomography scan findings other than appendicitis	25
Table S9: Normal appendectomy rates by duration of pre-operative clinical observation	26
Table S10: Readmission rates	27
Table S11: Accuracy of intra-operative diagnosis	28

**Table S1: Diagnoses in patients who did not undergo appendicectomy**

	Age 16-45 years		Age ≥46 years	
	Men n=511	Women n=869	Men n=248	Women n=372
<b>Gastrointestinal</b>	<b>147</b>	<b>94</b>	<b>103</b>	<b>123</b>
Gastritis/ gastroenteritis	43	21	7	5
Duodenal ulcer disease	3	1	1	2
Mesenteric adenitis	10	14	1	1
Meckel's diverticulum	0	0	2	1
Intra-abdominal abscess	7	4	5	6
Colitis	41	27	20	20
Confirmed/ suspected colorectal cancer	4	2	11	10
Diverticulitis	15	10	38	44
Irritable bowel syndrome (IBS)	1	1	0	2
Constipation	10	7	4	10
Adhesional symptoms	2	0	1	2
Other gastrointestinal pathology	11	7	13	20
<b>Hepatobiliary</b>	<b>11</b>	<b>13</b>	<b>25</b>	<b>16</b>
Biliary colic	2	5	4	3
Cholecystitis	3	3	16	11
Pancreatitis	3	1	4	0
Other hepatobiliary pathology	3	4	1	2
<b>Gynaecological</b>	<b>-</b>	<b>268</b>	<b>-</b>	<b>49</b>
Benign ovarian cyst	-	146	-	21
Polycystic ovarian syndrome (PCOS)	-	5	-	0
Confirmed/ suspected ovarian cancer	-	5	-	5
Endometriosis	-	3	-	1
Fibroids	-	8	-	7
Menstrual pain	-	14	-	1
Pelvic inflammatory disease (PID)	-	59	-	9
Other gynaecological pathology	-	28	-	5
<b>Urological</b>	<b>45</b>	<b>84</b>	<b>27</b>	<b>29</b>
Urinary tract infection (UTI)	16	68	8	16
Renal stone	23	11	17	11
Testicular or epididymal pathology	4	0	0	0
Other urological pathology	2	5	2	2
<b>Other</b>	<b>308</b>	<b>410</b>	<b>93</b>	<b>155</b>
Non-specific abdominal pain*	267	383	67	113
Musculoskeletal pain	7	3	2	0
Hernia	8	1	4	9
Lower respiratory tract infection	1	2	0	3
Confirmed/suspected non-ovarian, non-colorectal cancer	1	3	6	12
Other miscellaneous pathology	10	11	7	12
Data missing	14	7	7	6

\*Includes patients for whom no formal diagnosis was made

**Table S2: Validation of the Adult Appendicitis Score in women aged 16-45 years**

AAS cut-off for high-risk group*	Sensitivity	Specificity	PPV	NPV
>8	88.5% (85.7-91.0)	63.1% (61.3-64.9)	34.0% (31.6-36.4)	96.3% (95.3-97.1)
>9	80.7% (77.3-83.8)	71.7% (70.0-73.4)	38.0% (35.3-40.7)	94.6% (93.5-95.5)
>10	71.6% (67.8-75.2)	79.6% (78.0-81.8)	42.9% (39.8-46.1)	92.9% (91.8-93.9)
>11	59.6% (55.6-63.6)	86.4% (85.1-87.6)	48.4% (44.8-52.1)	90.9% (89.7-92.0)
>12	45.0% (41.0-49.1)	91.0% (89.8-92.0)	51.6% (47.3-56.0)	88.5% (87.3-89.7)
>13	32.2% (28.5-36.1)	94.5% (93.6-95.3)	55.6% (50.2-60.9)	86.7% (85.4-87.9)
>14	22.1% (18.8-25.6)	96.7% (96.0-97.3)	59.1% (52.4-65.6)	85.3% (84.0-86.5)
>15	13.6% (11.0-16.6)	98.6% (98.1-99.0)	68.3% (59.2-76.5)	84.2% (82.9-85.4)
>16	7.6% (5.7-10.1)	99.4% (99.0-99.6)	71.9% (59.2-82.4)	83.4% (82.1-84.6)
>17	3.5% (2.2-5.3)	99.9% (99.7-100.0)	91.3% (72.0-98.9)	82.5% (81.5-84.1)
>18	1.7% (0.8-3.0)	100.0% (99.8-100.0)	90.9% (58.7-99.8)	82.6% (81.3-83.8)
>19	0.7% (0.2-1.7)	100.0% (99.9-100.0)	100.0% (39.8-100.0)	82.4% (81.1-83.7)
>20	0.5% (0.1-1.5)	100.0% (99.9-100.0)	100.0% (29.2-100.0)	82.4% (81.1-83.7)
>21	0.5% (0.1-1.5)	100.0% (99.9-100.0)	100.0% (29.2-100.0)	82.4% (81.1-83.7)

AAS: Adult Appendicitis Score; NPV: Negative predictive value; PPV: Positive predictive value. 95% confidence intervals given in parentheses.

\*AAS cut-off  $\leq 8$  has previously been identified as the optimum cut-off for identifying women aged 16-45 years at low-risk of appendicitis. The maximum AAS score is 24 points, however, as only 3 patients score over 21 points, the validation terminated at the >21 cut-off.

*Outcome: The pre-determined value to recommend the use of the risk prediction model to identify patients with appendicitis were a PPV of  $\geq 95\%$  coupled with a sensitivity of  $\geq 30\%$ . In women aged 16-45 years, the AAS risk prediction model did not achieve a PPV of  $\geq 95\%$  coupled with a sensitivity of  $\geq 30\%$  at any cut-off. Therefore, the use of the risk prediction model cannot be recommended to identify women aged 16-45 years with appendicitis.*

**Table S3: Validation of the Appendicitis Inflammatory Response Score in men aged 16-45 years**

AIRS cut-off for high-risk group*	Sensitivity	Specificity	PPV	NPV
>2	99.4% (98.5-99.8)	24.7% (21.8-27.8)	56.0% (53.4-58.6)	91.6% (94.5-99.2)
>3	93.5% (91.6-95.1)	45.3% (41.9-48.8)	62.3% (59.5-65.1)	87.8% (84.3-90.8)
>4	84.5% (81.8-86.9)	62.8% (59.4-66.1)	68.7% (65.7-71.6)	80.7% (77.4-83.7)
>5	67.5% (64.1-70.7)	76.4% (73.4-79.3)	73.4% (70.1-76.6)	70.9% (67.7-73.8)
>6	46.6% (43.1-50.1)	85.6% (83.0-87.9)	75.8% (71.7-79.5)	62.4% (59.5-65.2)
>7	26.0% (23.0-29.2)	93.3% (91.4-95)	79.1%(73.7-83.8)	56.6% (54.0-59.3)
>8	11.9% (9.7-14.3)	97.3% (96.0-98.3)	81.2% (72.9-87.8)	53.3% (50.8-55.9)
>9	3.5% (2.3-5.0)	99.3% (98.4-99.7)	82.4% (65.5-93.2)	51.6% (49.1-54.1)

AIRS: Appendicitis Inflammatory Response Score; NPV: Negative predictive value; PPV: Positive predictive value. 95% confidence intervals given in parentheses.

\*AIRS cut-off  $\leq 2$  has previously been identified as the optimum cut-off for identifying men aged 16-45 years at low-risk of appendicitis. The maximum AIRS score is 10 points.

*Outcome: The pre-determined value to recommend the use of the risk prediction model to identify patients with appendicitis were a PPV of  $\geq 95\%$  coupled with a sensitivity of  $\geq 30\%$ . In men aged 16-45 years, the AIRS risk prediction model did not achieve a PPV of  $\geq 95\%$  at any cut-off. Therefore, the use of the risk prediction model cannot be recommended to identify men aged 16-45 years with appendicitis.*

**Table S4: Validation of the Adult Appendicitis Score in women aged ≥46 years**

AAS cut-off*	Sensitivity	Specificity	PPV	NPV
>8	96.4% (93.5-98.3)	41.3% (37.6-45.2)	40.8% (37-44.6)	96.5% (93.7-98.3)
>9	95.4% (92.2-97.5)	49.1% (45.2-53.0)	44.0% (40.0-48)	96.2% (93.6-98.0)
>10	90.0% (85.9-93.3)	60.2% (56.4-63.9)	48.6% (44.3-53.0)	93.5% (90.7-95.6)
>11	82.5% (77.5-86.8)	68.0% (64.3-71.5)	51.9% (47.2-56.6)	90.3% (87.3-92.7)
>12	68.6% (62.8-74.0)	77.5% (74.2-80.7)	56.1% (50.7-61.5)	85.5% (82.4-88.2)
>13	54.3% (48.3-60.2)	84.7% (81.9-87.5)	60.1% (53.8-66.2)	81.6% (78.5-84.4)
>14	45.7% (39.8-51.7)	91.2% (88.8-93.2)	68.4% (61.3-75.0)	80.0% (77-82.8)
>15	31.4% (26.0-37.2)	93.0% (90.8-94.8)	65.2% (56.5-73.2)	76.4% (73.3-79.3)
>16	20.7% (16.1-25.9)	94.8% (92.8-96.3)	62.4% (51.7-72.2)	74.0% (71.0-76.9)
>17	9.64% (6.5-13.7)	97.5% (96.0-98.5)	61.4% (45.5-75.6)	72.0% (69.0-74.6)
>18	6.79% (4.1-10.4)	98.4% (97.1-99.2)	63.3% (43.9-80.1)	71.6% (68.5-74.5)
>19	4.3% (2.2-7.3)	99.3% (98.3-7.37)	70.6% (44.0-89.7)	71.2% (68.2-74.1)
>20	2.5% (1.0-5.1)	99.6% (98.7-99.9)	70.0% (34.8-93.3)	70.9% (67.9-73.8)
>21	0.7% (0.1-2.6)	99.9% (99.2-100.0)	66.7% (9.4-99.2)	70.6% (67.6-73.5)

AAS: Adult Appendicitis Score; NPV: Negative predictive value; PPV: Positive predictive value. 95% confidence intervals given in parentheses.

\*AAS cut-off ≤8 has previously been identified as the optimum cut-off for identifying women aged 16-45 years at low-risk of appendicitis. The maximum AAS score is 24 points, however, as only 3 patients score over 21 points, the validation terminated at the ≤21 cut-off.

*Outcome: The pre-determined value to recommend the use of the risk prediction model to identify patients with appendicitis were a PPV of ≥95% coupled with a sensitivity of ≥30%. In women aged ≥46 years, the AAS risk prediction model did not achieve a PPV of ≥95% at any cut-off. Therefore, the use of the risk prediction model cannot be recommended to identify women aged ≥46 years with appendicitis.*

**Table S5: Validation of the Appendicitis Inflammatory Response Score in men aged  $\geq 46$  years**

AIRS cut-off*	Sensitivity	Specificity	PPV	NPV
$\leq 2$	99.6% (98.0-100.0)	18.3% (14.3-22.9)	49.7% (45.4-54.0)	98.4% (91.3-100.0)
$\leq 3$	95.9% (92.8-97.9)	35.1% (30.0-40.5)	54.5% (49.9-59.1)	91.4% (85.1-95.6)
$\leq 4$	88.1 (83.7-91.8)	46.5% (41.1-52.1)	57.2% (52.3-62.0)	82.9% (76.7-88.0)
$\leq 5$	71.9% (66.1-77.1)	63.4% (57.9-68.5)	61.4% (55.8-66.8)	73.5% (68.0-78.5)
$\leq 6$	51.5% (45.3-57.6)	78.1% (73.2-82.4)	65.6% (58.8-71.9)	66.5% (61.6-71.2)
$\leq 7$	34.1% (28.4-40.1)	88.6% (84.7-91.8)	70.8% (62.2-78.4)	62.4% (57.8-66.8)
$\leq 8$	17.8% (13.4-22.9)	94.9% (92.0-97.0)	73.8% (61.5-84.0)	58.7% (54.4-62.9)
$\leq 9$	6.7% (4.0-10.3)	98.8% (97.0-99.7)	81.8% (59.7-94.8)	56.6% (52.5-60.7)

AIRS: Appendicitis Inflammatory Response Score; NPV: Negative predictive value; PPV: Positive predictive value. 95% confidence intervals given in parentheses.

\*AIRS cut-off  $>2$  has previously been identified as the optimum cut-off for identifying men aged 16-45 years at low-risk of appendicitis. The maximum AIRS score is 10 points.

*Outcome: The pre-determined value to recommend the use of the risk prediction model to identify patients with appendicitis were a PPV of  $\geq 95\%$  coupled with a sensitivity of  $\geq 30\%$ . In men aged  $\geq 46$  years, the AIRS risk prediction model did not achieve a PPV of  $\geq 95\%$  at any cut-off. Therefore, the use of the risk prediction model cannot be recommended to identify men aged  $\geq 46$  years with appendicitis.*

**Table S6: Ultrasound scan findings other than appendicitis\***

	Age 16-45 years		Age ≥46 years	
	Men n=31	Women n=247	Men n=10	Women n=36
<b>Gastrointestinal</b>	<b>12</b>	<b>17</b>	<b>0</b>	<b>3</b>
Inflammatory bowel disease	3	2	0	0
Suspected colorectal cancer	0	0	0	1
Diverticulitis	0	1	0	0
Intra-abdominal abscess	3	4	0	1
Other gastrointestinal	6	10	0	1
<b>Hepatobiliary</b>	<b>6</b>	<b>14</b>	<b>5</b>	<b>3</b>
Gallstones	3	6	5	2
Other hepatobiliary	3	8	0	1
<b>Gynaecological</b>	<b>-</b>	<b>189</b>	<b>-</b>	<b>21</b>
Benign ovarian cyst	-	120	-	8
Pelvic Inflammatory disease	-	16	-	1
Suspected ovarian cancer	-	1	-	2
Other gynaecological	-	52	-	10
<b>Urological</b>	<b>4</b>	<b>7</b>	<b>4</b>	<b>6</b>
Urinary tract infection	1	1	0	0
Renal stones	1	1	1	2
Other urology	2	5	3	4
<b>Other</b>	<b>9</b>	<b>20</b>	<b>1</b>	<b>3</b>
Hernia	2	0	0	1
Miscellaneous	7	20	1	2

A total of 158 ultrasound scans were reported to show appendicitis (these patients are not included in the table)

**Table S7: Diagnostic performance of ultrasound for diagnosis of appendicitis, in sub-group of patients with imaging findings other than appendicitis**

	Ultrasound
Proportion of scanned patients with final diagnosis of appendicitis	11.7% (38/324)
<b>Scan findings for appendicitis</b>	
Positive	2.5% (8/324)
Equivocal	66.7% (216/324)
Negative	29.9% (97/324)
Missing	0.9% (3/324)
<b>Performance for appendicitis</b>	
AUC	0.55 (0.50-0.60)
Sensitivity	10.5% (2.9-24.8)
Specificity	98.6% (96.4-99.6)
PPV	50.0% (15.7-84.3)
NPV*	89.1% (85.2-92.4)

\*Main analysis based on scans reported as either 'negative' (i.e. excluding appendicitis) or 'equivocal' (i.e. unable to either exclude or confirm appendicitis) both being classified as negative scans; yielding NPV 89.1% for ultrasound. If only scans reported as 'negative' are classified as negative, then the NPV for ultrasound was 99.0% (95% confidence interval 94.4%-100%).



**Table S8: Computed tomography scan findings other than appendicitis**

	Age 16-45 years		Age ≥46 years	
	Men n=114	Women n=145	Men n=166	Women n=224
<b>Gastrointestinal</b>	<b>68</b>	<b>40</b>	<b>100</b>	<b>117</b>
Inflammatory bowel disease	16	11	11	11
Suspected colorectal cancer	3	1	10	10
Diverticulitis	12	8	28	37
Obstruction	3	0	5	11
Intra-abdominal abscess	7	1	18	13
Other gastrointestinal	27	19	28	35
<b>Hepatobiliary</b>	<b>8</b>	<b>5</b>	<b>21</b>	<b>25</b>
Gallstones	2	2	14	14
Pancreatitis	2	0	3	0
Other hepatobiliary	4	3	4	11
<b>Gynaecological</b>	<b>-</b>	<b>65</b>	<b>-</b>	<b>39</b>
Benign ovarian cyst	-	28	-	15
Pelvic inflammatory disease	-	21	-	4
Suspected ovarian cancer	-	5	-	6
Other gynaecological	-	11	-	14
<b>Urological</b>	<b>24</b>	<b>24</b>	<b>23</b>	<b>22</b>
Urinary tract infection	1	8	2	4
Renal stones	19	9	17	10
Other urology	4	7	4	8
<b>Other</b>	<b>14</b>	<b>11</b>	<b>22</b>	<b>21</b>
Other suspected malignancy	2	2	5	6
Hernia	3	1	5	7
Miscellaneous	9	8	12	8

**Table S9: Normal appendicectomy rates by duration of pre-operative clinical observation**

<i>Table S9: Normal appendicectomy rates by duration of pre-operative clinical observation</i>					
<i>Duration of clinical observation</i>	Age 16-45 years		Age ≥46 years		Overall
	Men	Women	Men	Women	
<i>&lt;24 hours</i>	8.0% (53/666)	16.7% (69/413)	0.5% (1/196)	2.9% (5/173)	8.8% (128/1448)
<i>24-47 hours</i>	14.3% (30/210)	18.8% (45/240)	3.5% (3/86)	6.5% (6/93)	13.4% (84/629)
<i>≥48 hours</i>	10.0% (3/30)	31.9% (15/47)	20.0% (2/10)	8.7% (2/23)	20.0% (22/110)

**Table S10: Readmission rates†**

	Readmission rate
Postoperative readmissions in patients who had appendix-related surgery*	
Overall	7.4% (166/2242)
Positive appendicectomy	7.1% (137/1928)
Normal appendix	10.2% (23/226)
Diagnostic laparoscopy	6.8% (6/88)
Total readmissions in patients who did not have any surgery	
Overall	7.7% (136/1774)
Ultrasound only	6.6% (41/619)
CT only	8.8% (50/568)
Ultrasound and CT	10.0% (13/130)
MRI*	19.1% (4/21)
No imaging	6.4% (28/436)

†Data on postoperative readmissions not collected for the 37 patients who were initially discharged and operated on a readmission.

\*Including appendicectomy or diagnostic laparoscopy, but excluding other procedures.

**Table S11: Accuracy of intra-operative diagnosis**

		Final histopathology		
		Normal appendix	Appendicitis	Total
Surgeon's intraoperative diagnosis	Normal appendix	144 (69.6)	63 (30.4)	207
	Appendicitis	90 (4.6)	1889 (95.4)	1979
	Total	234	1952	2186

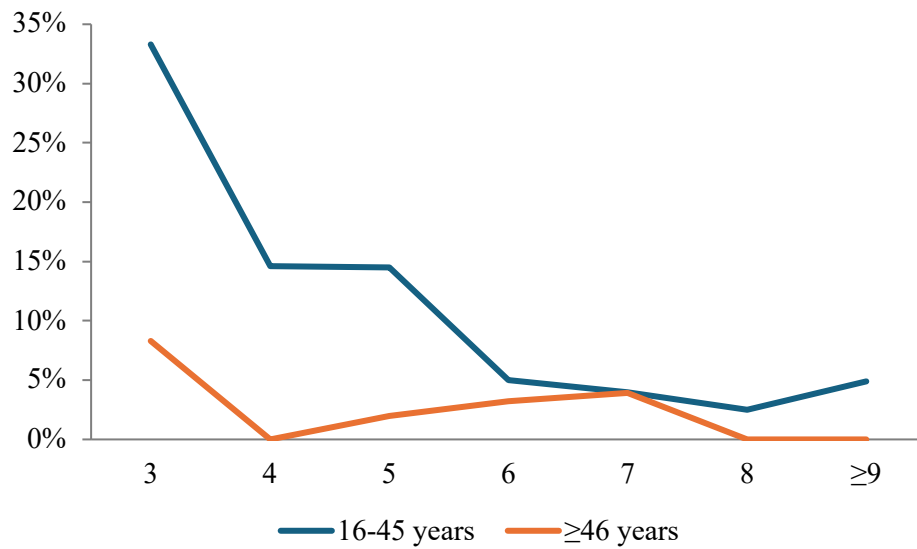
Kappa=0.614 (95% confidence interval 0.558-0.670)

**Figure S1. Normal appendicectomy rates stratified by risk scores**

**a) NAR in women stratified by AAS**



**b) NAR in men stratified by AIRS**



AAS: adult appendicitis score; AIRS: Appendicitis Inflammatory Response Score; NAR: normal appendicectomy rate