

A novel biomarker panel to rule out acute appendicitis in pediatric patients with abdominal pain 登.登登.★

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Child appendicitis

- Appendicitis is common pediatric disease
 - Peak incidence in the second decade of life
- 正確診斷 pediatric appendicitis 的障礙
 - 沒辦法精準的描述症狀
 - 50% 的兒童沒有 adult appendicitis 的典型症狀(e.g. shifting pain, focal RLQ tenderness)
 - Lab results(CRP, WBC count, others): highly variable in sensitivities or specificity
- 診斷 appendicitis 越來越依賴 imaging study
 - US: suboptimal sensitivity:78-100%, specificity:88-98%
 - CT: sensitivity:92-100%, specificity:87-100%
 - Ionizing radiation exposure : 10-15 times lifetime risk for malignancy compared between 1 y/o to 50 y/o

目的

- 評估利用 Biomarker alone or combination 來排除 acute appendicitis 的準確度
- 評估這些 biomarker 對 CT scan 使用上可能的影響(potential impact on CT scan utilization rate)

Method

- 12 academic and academically affiliated community hospital ER across U.S.
- 2011/3-2011/11
- Prospective observational investigation
- WBC and plasma protein marker in possible acute appendicitis case

method

- Inclusion criteria:
 - S/S like acute appendicitis(RLQ, generalized abdominal pain)
 - 症狀 < 72 hr
 - 2 y/o-20 y/o
- Exclusion: previous appendectomy, metastatic cancer, bleeding disorder, active autoimmune disease, abdominal trauma, invasive abdominal procedure, prior diagnostic imaging

Outcome collection

- Primary outcome: appendicitis or not
 - Surgical pathology
 - Discharge diagnosis
 - Result of plasma protein biomarker
 - Study end point: diagnostic accuracy of biomarker as negative predictor
- Secondary outcome and end point
 - Potential reduction of unnecessary CT scan for negative biomarker result

biomarker

- WBC count
 - CRP
 - Myeloid-related protein 8/14 complex (calprotectin)
 - Hyaluronan
 - Serum amyloid A protein
 - Matrix metalloproteinase 9
- Analysis were blinded to clinical information, result were not showed to treating physician at clinical study site

Optimal cutoff point

- Value(A): $x(\text{WBC})+y(\text{CRP})+z(\text{MRP } 8/14)$
- Cutoff value selection
 - Maximizing true negative test result
 - Minimizing false negative test result

Patient characteristics	Appendicitis n (n/N%)	Not appendicitis n (n/N%)	P value
Total N = 503	n=144 (28.6%)	n=359 (71.4%)	
Age, y			
Median (IQR)	12 (10-16)	12 (8-16)	
<12	77 (53%)	189 (53%)	.9214
Sex			
Male	87 (60%)	156 (43%)	.0008
Ethnicity			
White	90 (63%)	247 (69%)	.3510
Black	10 (7%)	30 (8%)	χ ² test
Hispanic	32 (22%)	64 (18%)	
Asian	4 (3%)	3 (1%)	
Other/unreported	8 (5%)	15 (4%)	
Symptom duration, h			
0-12	34 (24%)	102 (28%)	.6676
12-24	55 (38%)	122 (34%)	χ ² test
24-48	31 (22%)	72 (20%)	
48-72	24 (17%)	63 (18%)	
Similar abdominal pain previously			
Yes	14 (10%)	60 (17%)	.0511
Associated symptoms			
Periumbilical pain with migration to RLQ	100 (69%)	141 (39%)	<.0001
Anorexia	105 (73%)	198 (55%)	.0003
Vomiting	92 (64%)	132 (38%)	<.0001
Nausea	109 (76%)	225 (63%)	.0065
Physical examination			
Fever (>99.6°F, 37.5°C)	36 (25%)	59 (16%)	.320
RLQ tenderness	143 (99%)	309 (86%)	<.0001
Rebound tenderness	73 (53%)	73 (21%)	<.0001
Rigidity and guarding	102/137 (73%)	110/243 (32%)	<.0001
Rovsing sign	49/137 (36%)	38/340 (11%)	<.0001

Patient characteristics	Appendicitis n (n/N%)	Not appendicitis n (n/N%)	P value
Total N = 503	n=144 (28.6%)	n=359 (71.4%)	
Imaging			
US	68 (47%)	231 (64%)	.0006
CT	53 (37%)	132 (37%)	1.0
Both US and CT	21 (15%)	76 (21%)	.1042
No imaging	41 (28%)	65 (18%)	.0113
Other	3 (2%)	7 (2%)	*n too small
Alternative diagnoses			
Abdominal pain		186 (52%)	
Constipation		29 (9%)	
Ovarian cyst		27 (8%)	
Gastroenteritis		25 (7%)	
UTI		13 (4%)	
Colitis		4 (1%)	
Perforated appendix by symptom duration (n ¹), h	n ¹ /n (%)		
0-12	1/34 (3%)		
12-24	0/55 (0%)		
24-48	6/31 (19%)		
48-72	6/24 (25%)		

Age distribution

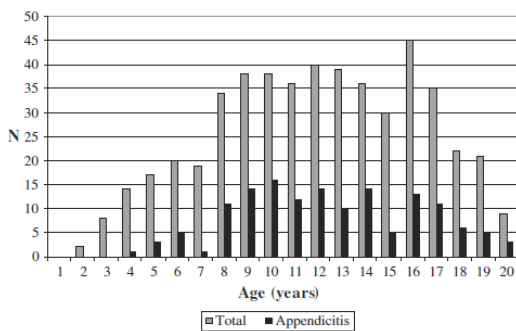


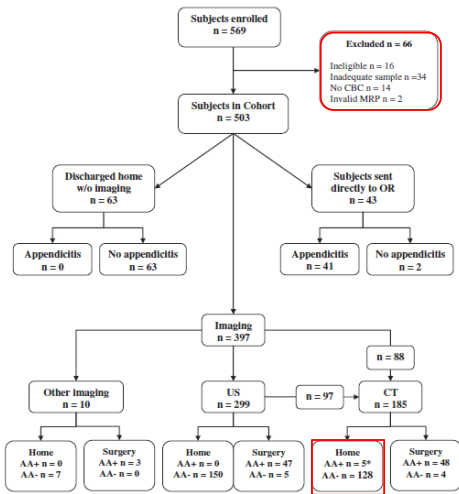
Fig. 1. Age distribution.

Imaging utilization

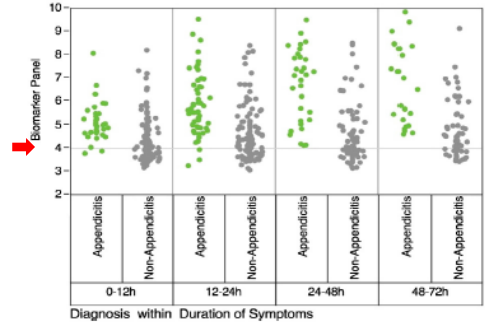
Hospital type, prevalence of appendicitis, imaging utilization

Hospital type	N	Appendicitis % (n/N)	CT % (n/N)	US % (n/N)	CT and US % (n/N)
All hospitals	503	28.6% (144/503)	36.8% (185/503)	59.4% (299/503)	19.3% (97/503)
Children's hospitals	216	32.9% (71/216)	27.8% (60/216)	45.4% (98/216)	10.2% (22/216)
Tertiary care centers	135	26.7% (36/135)	39.3% (53/135)	79.3% (107/135)	28.1% (38/135)
Community hospitals	152	24.3% (37/152)	47.4% (72/152)	61.8% (94/152)	24.3% (37/152)

Imaging totals greater than 100% because those with both CT and US are also included in individual totals for CT and US.



Biomarker and duration of S/S



Biomarker panel result

	Biomarker panel negative	Biomarker panel positive	Total
No appendicitis	155	204	359
Acute appendicitis	5	139	144
Total	160	343	503

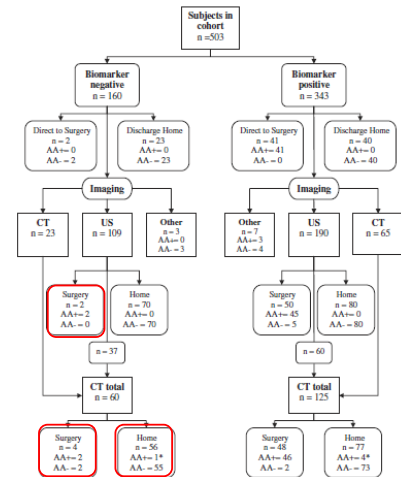
Duration of symptoms (n)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	NLR (95% CI)
All patients (503)	96.5% (92%-99%)	43.2% (38%-48%)	96.9% (93%-99%)	0.08 (0.03-0.19)
<24 h (313)	94.4% (88%-98%)	43.3% (37%-50%)	95.1% (89%-98%)	0.13 (0.06-0.31)
>24 h (190)	100% (94%-100%)	43.0% (35%-51%)	100% (94%-100%)	0

NPV = negative predictive value; NLR = negative likelihood ratio.

WBC (<10 k/uL)+normal CRP

-sensitivity:97.2%(93-99%), NPV: 96.8%(92-99%), specificity: 33.7%(29-39%)

-True negative :121, false negative:4



False negative biomarker results

Pt.	Age/sex	Duration sx at enrollment, h	US	CT	PCI VAS
A	16/F	0-12	P	P	47
B	12/M	12-24	ND ^a	N ^a	100 ^a
C	14/F	12-24	I	ND	67
D	13/M	12-24	P	ND	37
E	8/M	0-12h	I	P	23

Pt.	Age/sex	Clinical course	Pathology results
A	16/F	Surgery at index visit	"Mild acute appendicitis"
B	12/M	Discharged, returned in 48 h, CT neg. Surgery after sx duration 60-72 h	"Mild mucosal acute appendicitis"
C	14/F	Surgery at index visit	"Mild acute appendicitis"
D	13/M	Surgery at index visit	"Appendicitis"
E	8/M	Surgery at index visit	"Acute appendicitis and periappendicitis"

discussion

- CT scan in negative biomarker panel: 32.4%(60/185)
 - False negative biomarker results (5/185, 3.5%): 症状発生時間 < 24小時
 - Perforated appendix: 1.1 % (1/89) for symptoms < 24 hr, 0% in negative biomarker results
- Negative biomarker panel result in patient symptoms > 24 hour reliably excluded acute appendicitis

Limitation

- 當病人出院診斷非appendicitis時缺乏有制度的後續追蹤
- 72小時再回診的病人會被記錄到, 但如果病人跑去別的醫院就無法得知後續結果
- 因為acute appendicitis with false negative biomarker 的個數很少, one missed false negative patient 對這研究會有顯著的影響

Conclusion

- 對於臨床上懷疑appendicitis的兒童及青少年族群, 3 marker panel of WBC+ CRP+ MRP 8/14 有高敏感性, 高陰性預測值及 low negative likelihood ratio
- 如果根據negative biomarker panel 結果來決定影像檢查的使用, 最高可減少32%的CT使用率, 避免不必要的輻射暴露。