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Evaluation of the NMP22 BladderChek test for detecting bladder cancer: a systematic review and meta-analysis

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膀胱癌 Bladder Cancer

- 98%膀胱癌屬上皮細胞來源
- 好發於50~70歲
- 發生率；男:女2:1
- 2018十大癌症死亡人數如右圖，為男性癌症死亡第10名

2018十大致死癌症男女排名


	男性		女性
1	氣管、支氣管和肺癌	1	氣管、支氣管和肺癌
2	肝和肝內膽管癌	2	肝和肝內膽管癌
3	結腸、直腸和肛門癌	3	結腸、直腸和肛門癌
4	口腔癌	4	乳癌
5	食道癌	5	胰臟癌
6	胃癌	6	胃癌
7	攝護腺癌	7	子宮頸及部位未明示子宮癌
8	胰臟癌	8	卵巢癌
9	非何杰金氏淋巴瘤	9	非何杰金氏淋巴瘤
10	膀胱癌	10	白血病

高風險群

1. 無痛血尿：初期膀胱癌患者中約有80~90%
2. 基因：約有38%膀胱癌患者有抑癌基因KDM6A突變
3. 吸菸者、染髮
4. 工作場合時常接觸使用芳香胺，染料，焦油，汽油，柴油，油漆。
5. 台灣南部近海之烏腳病流行區(砷汙染水源)
6. 下盆骨放射治療的患者可能演進成膀胱癌

膀胱癌診斷與存活率

非侵入性：

1.Urinalysis & Cytology:

- **Urinalysis:** 潛血反應
- **Cytology:** 尿沉渣染色後，用顯微鏡檢查是否有異常細胞

2.Urine tumor marker tests

- **UroVysion™: 膀胱癌癌細胞中染色體的變化(FISH)**
- **BTA stat: Bladder tumor-associated antigen**
- **Immunocyt™: mucin and carcinoembryonic antigen (CEA) (Immunocytochemistry)**
- **NMP22 BladderChek® : 膀胱癌患者尿液中含高濃度之核基質蛋白(細胞有絲分裂時表現)**

侵入性：

1. Cystoscopy: 膀胱鏡檢查及切片
   - **估計約有10%的偽陰性**
   - **敏感性受到視野影響 (例: 發炎、出血、尿路上皮病變、嚴重發育不良...等)**
   - **原位癌通常難以與正常膀胱組織區分開**
   - **進階版: Fluorescence Cystoscopy**

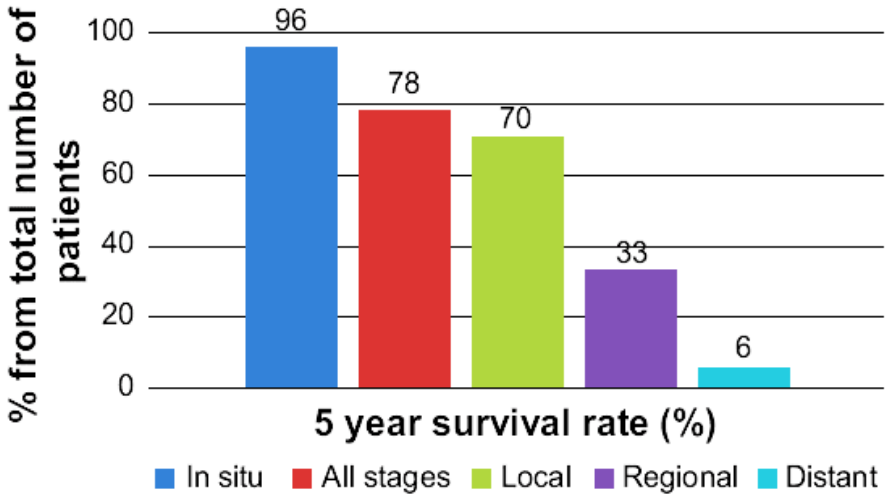

Figure 1 Five-year relative survival rates for bladder cancer in relation to the stage at time of diagnosis.

步驟 1：系統性文獻回顧探討的問題為何？

PICO	Problem (問題)	**bladder cancer test**
	Intervention(介入措施)	NMP22 BladderCheck
	Comparisom(比較)	Urine cytology
	Outcomes(結果)	good discrimination ability for detecting bladder cancer and a high-specificity algorithm that can be used for early detection to rule out patients with higher bladder cancer risk ?

步驟 2：系統性文獻回顧的品質如何？(FAITH)

F－研究是否找到 (Find) 所有的相關證據？

良好的文獻搜尋至少應包括二個主要的資料庫(如：Medline, Cochrane考科藍實證醫學資料庫, EMBASE等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science,Scopus或Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用 MeSH 字串及一般檢索詞彙(text words)。在文章的方法(Methods)章節，可以找到詳細搜尋策略的說明，包括使用的名詞

Search strategy：

We searched MEDLINE, Embase, the Cochrane Library, and Web of Science for relevant studies in all languages published from January 1, 1990, to June 1, 2017, with the following terms: (BladderChek OR NMP22BC) AND (Bladder cancer OR urinary bladder neoplasm [MeSH]).

We identified additional studies by screening the reference lists.

評讀結果：☑是 □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

F－研究是否找到 (Find) 所有的相關證據？

1.收錄病人至少已NMP22檢驗過一次
2.分析數據有使用four-fold table

	Disease				
Test	Present	n	Absent	n	Total
Positive	True Positive (TP)	*a*	False Positive (FP)	*c*	*a* + *c*
Negative	False Negative (FN)	*b*	True Negative (TN)	*d*	*b* + *d*
Total		*a* + *b*		*c* + *d*	

3.若數據重複使用，則採用最詳細或最新一次文章發表
4.英文或中文
5.若分析不完整或未，則只有systematic review才收入

Inclusion criteria：

(1)Clinical study comparing the diagnostic effects of the NMP22 BladderChek test with at least one measurement for patients with high bladder cancer risk;

(2) provided sufficient data for constructing the diagnostic four-fold (2 × 2) contingency table;

(3) if data or data subsets were used in more than one article, the article with the most detail or the most recent article was chosen;

(4) written in English or Chinese;

(5) Related studies with unqualified data or that did not provide sufficient data were included only in the systematic review.

評讀結果：☑是 □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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在文章的方法(Methods)章節，可以找到詳細搜尋策略的說明，包括使用的名詞，結果(Results) 章節中可以找到本篇系統性文獻回顧評估的摘要及全文文獻數目、文獻納入與排除的數量及原因。資料可能會以圖表或 PRISMA的流程圖呈現。

Exclusion criteria：

(1) Duplicate publication;

(2) reviews, case reports, letters to editors;

(3) studies in languages other than English or Chinese.

Two reviewers (ZJ Wang and HL Que) independently screened the collected citations for relevance and reviewed full-text articles according to the inclusion criteria.

Disagreements were resolved by consultation with a third reviewer (M Gu).

評讀結果：☑是 □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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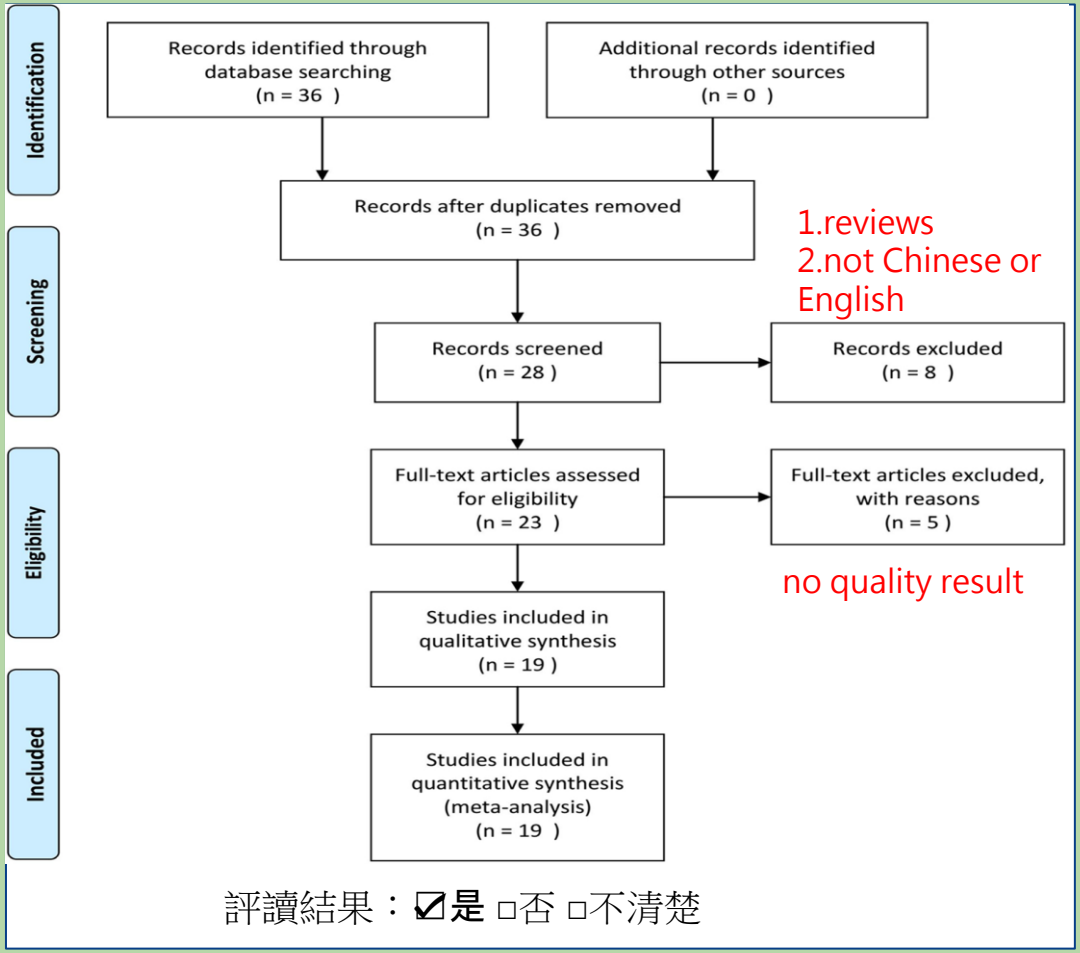


步驟 2：系統性文獻回顧的品質如何？(FAITH)

A－文獻是否經過嚴格評讀 (Appraisal)？

應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)。

在文章的方法章節，可以找到所使用的文獻品質評讀標準的描述，而結果章節則會列出每篇研究品質的評讀結果。

Data extraction and quality assessment

We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [11] to assess methodological quality. The QUADAS-2 scale contains four domains: patient selection, index test, reference standard, and flow and timing. We assessed all domains for potential risk of bias and the first three domains for concerns regarding applicability. Each question was assigned a “yes,” “no,” or “unclear” response when every eligible study was evaluated.

1.使用QUADAS-2 評讀
2.分為誤差風險(四部分評核)
與臨床運用疑慮兩部分(三部分評核)
3.每個評核部分皆有關鍵性問題，以yes，no，nuclear回答
4.若評核區塊有一題為no，則列為高，反之則為低，若有nuclear則為不清楚

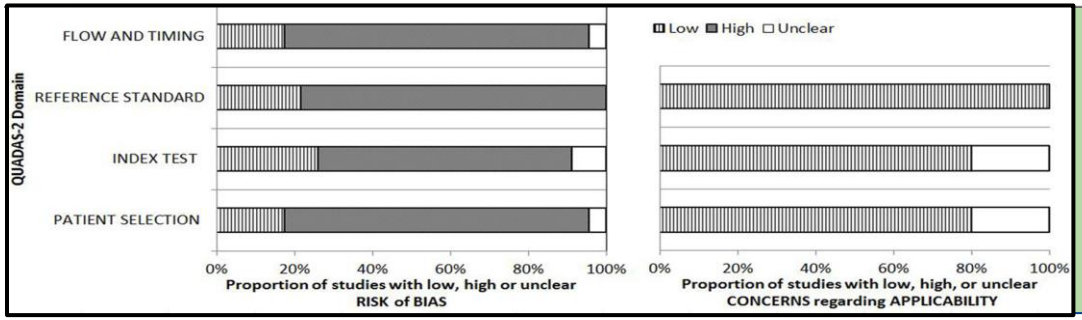
評讀結果：☑是 □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

A－文獻是否經過嚴格評讀 (Appraisal)？

Table 1. **Risk of Bias and Applicability Judgments in QUADAS-2**

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	



1.雖有QUADAS-2評分，但沒有提供每篇文章審查結果之list。

評讀結果：☑**是** □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

I－是否只納入 (Included) 具良好效度的文章？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。

在文章的方法章節，可以找到文章評估的方式，以及是由誰完成評估的，在結果章節則會提供審查者意見一致性的程度。

Data extraction and quality assessment

Two reviewers (ZJ Wang and HL Que) extracted the relevant data independently.

A consensus reviewer (MGu) resolved any disagreement among the data extraction and quality assessment.

1.由兩位作者獨立評估文章
2.當有意見不符時則由共識審核員進行評估解決
3.但無提供審查者的意見一致性

評讀結果：□是 □否 ☑不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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Table 1: Basic characteristics of eligible studies in our meta-analysis

Study	Ethnicity	Case number	Mean age (year; range)	Male/female	Proportion of smoking patients (%)	Specific details of index test used	Total sensitivity (%)	Total specificity (%)
P.M.J. Moonen (2005)	Caucasian	106	66.4 (26.9–86.1)	79/27	NA	NMP22BC, Cytology	63.63%	90%
S. Tritschler (2006)	Asian	100	67.9	71/29	NA	NMP22BC	65.00%	40
A. Kumar (2006)	Asian	131	67 (32–91)	117/14	NA	NMP22BC, Cytology	84.80%	77.6%
Y. Lotan (2007)	Caucasian	1328	58.7 (18–96)	756/572	36.1%	NMP22BC	56.96%	85.8%
Y. Lotan (2008)	Caucasian	1502	62.5 (46–92)	1175/327	45%	NMP22BC	NA	NA
H. Steiner (2008)	Caucasian	183	60.1 (36.8–83.8)	123/60	100%	Dipstick, NMP22BC, Cytology, UroVysion	5.56%	82.5%
V K. Arora (2009)	Asian	53	59 (33–83)	48/5	66.04%	NMP22BC, Cytology, Cystoscopy	78.95%	80
H S. Choi (2009)	Asian	1070	59.31	650/420	NA	NMP22BC	77.50%	88.8
E O. Kehinde (2011)	Asian	178	55.3 (16–77)	NA	80%	Cytology, NMP22BC, UroVysion	82.00%	66.0%
T. Smrkolj (2011)	Caucasian	108	68.3	74/34	NA	Cytology, NMP22BC	17.70%	100.0%
E C. Hwang (2011)	Asian	1021	65	776/245	NA	NMP22BC	22.58%	97.97
L. Sagnak (2011)	Asian	164	30.8	56/108	NA	NMP22BC	100.00%	85.2%
M A. Maghrebi (2012)	Asian	105	53.48 (16–77)	81/24	NA	NMP22BC	61.30%	96
G. Hatzichristodoulou (2012)	Caucasian	200	61.3 (48–75)	142/58	NA	NMP22 ELISA, NMP22BC	59.00%	93.0%
G. Ludecke (2012)	Caucasian	13	< 50	NA	NA	UBC rapid, NMP22BC, BTA stat	NA	NA
E. Coskuner (2012)	Asian	95	60.7 (27–88)	78/17	NA	NMP22BC	44.40%	98.4%
P O. Sullivan (2012)	Caucasian	475	69 (59–77)	389/96	76%	Cytology, microscopy, NMP22BC, NMP22 ELISA	37.70%	96.40%
HX. Li (2013)	Asian	175	62.4 (23–89)	142/33	NA	LBC, FISH, NMP22BC	67.60%	88.1%
R. Ritter (2013)	Caucasian	198	70 (20–90)	151/47	NA	UBC ELISA, Cytology, NMP22BC, UBC rapid	16.40%	95.3%
F A. Yafi (2014)	Caucasian	109	69 (33–96)	90/19	89%	dipstick, BTA Stat, NMP22 BC, ImmunoCyt	58.00%	85
L. Turkeri (2014)	Asian	303	56.6	146/157	NA	NMP22 BC, RisikoCheck	45.00%	95.0%
M D. Bell (2016)	Caucasian	91	74 (45–96)	76/15	89%	Dipstick, BTA Stat, NMP22 BC, ImmunoCyt	NA	NA
Y. Lotan (2017)	Caucasian	1016	20–90	786/230	NA	Cytology, NMP22 ELISA, NMP22 BC, UroVysion	11.0%	NA

Abbreviations: NMP22BC, NMP22 BladderChek; ELISA, Enzyme-linked immunosorbent assay; LBC, liquid-based cytology; FISH, fluorescence in situ hybridization; NA, not available.

雖有QUADAS-2評分，但沒有提供每篇文章審查結果之list，無法得知是否只納入良好效度之文章。

評讀結果：□是 □否 ☑不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

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在文章的方法章節，可以找到文章評估的方式，以及是由誰完成評估的，在結果章節則會提供審查者意見一致性的程度。

對文章進行了deeks' funnel plot，p值為0.75分析結果顯示沒有publication bias

Data extraction and quality assessment

There was no statistically significant publication bias across the studies, the slope coefficient had a p-value of 0.75 (-19.11, 14.05).

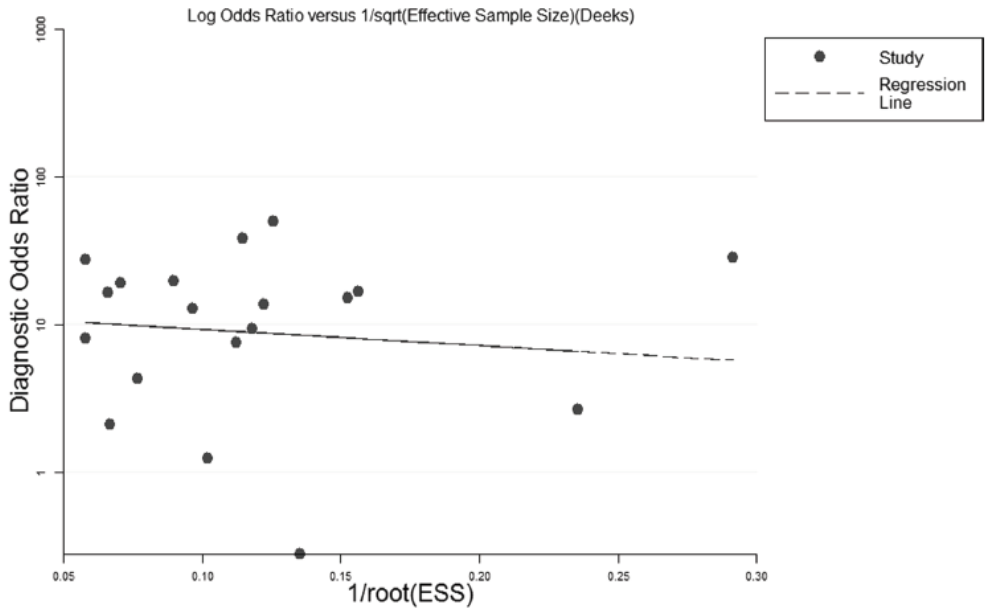


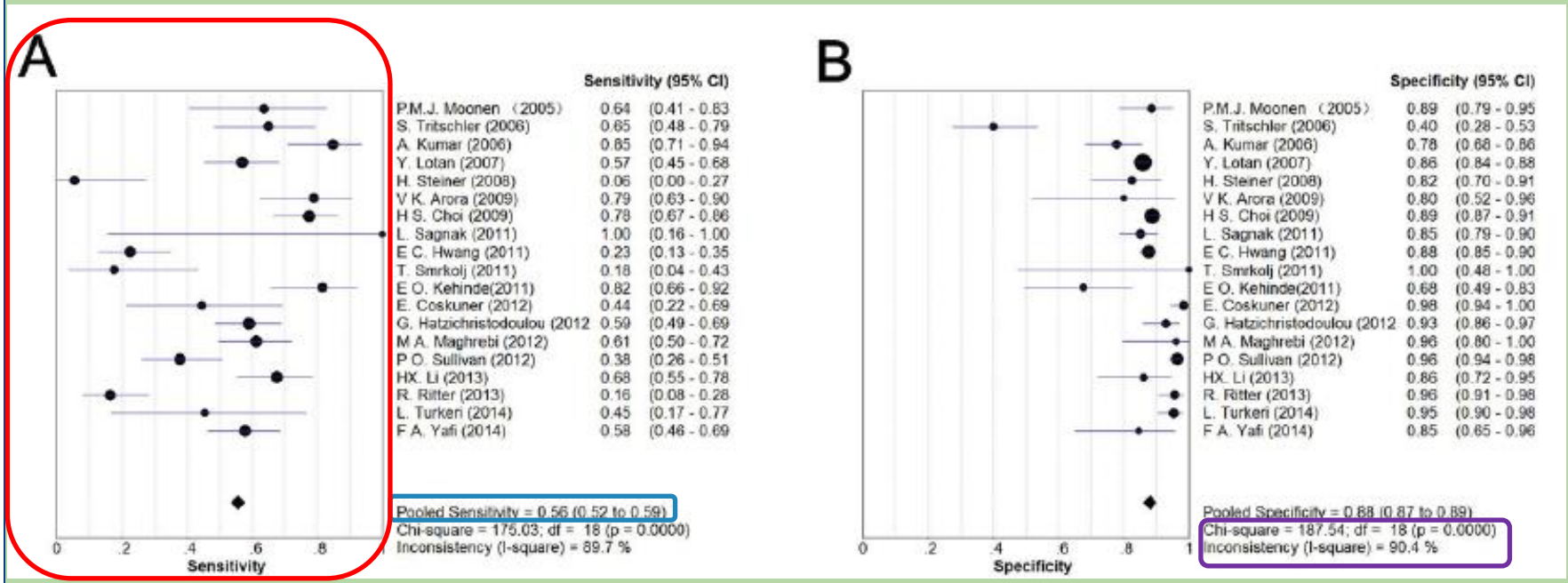
Figure 5: Deeks' funnel plot asymmetry test for studies in the systematic review.

評讀結果：□是 □否 ☑不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

T－作者是否以表格和圖表「總結」 (Total up) 試驗結果？

應該用至少 1 個摘要表格呈現所納入的試驗結果。若結果相近，可針對結果進行統合分析 (meta-analysis)，並以「森林圖」(forest plot) 呈現研究結果，最好再加上異質性分析。在文章的結果章節，可以找到摘要的圖表，以及作者對系統性文獻回顧結果的解釋。



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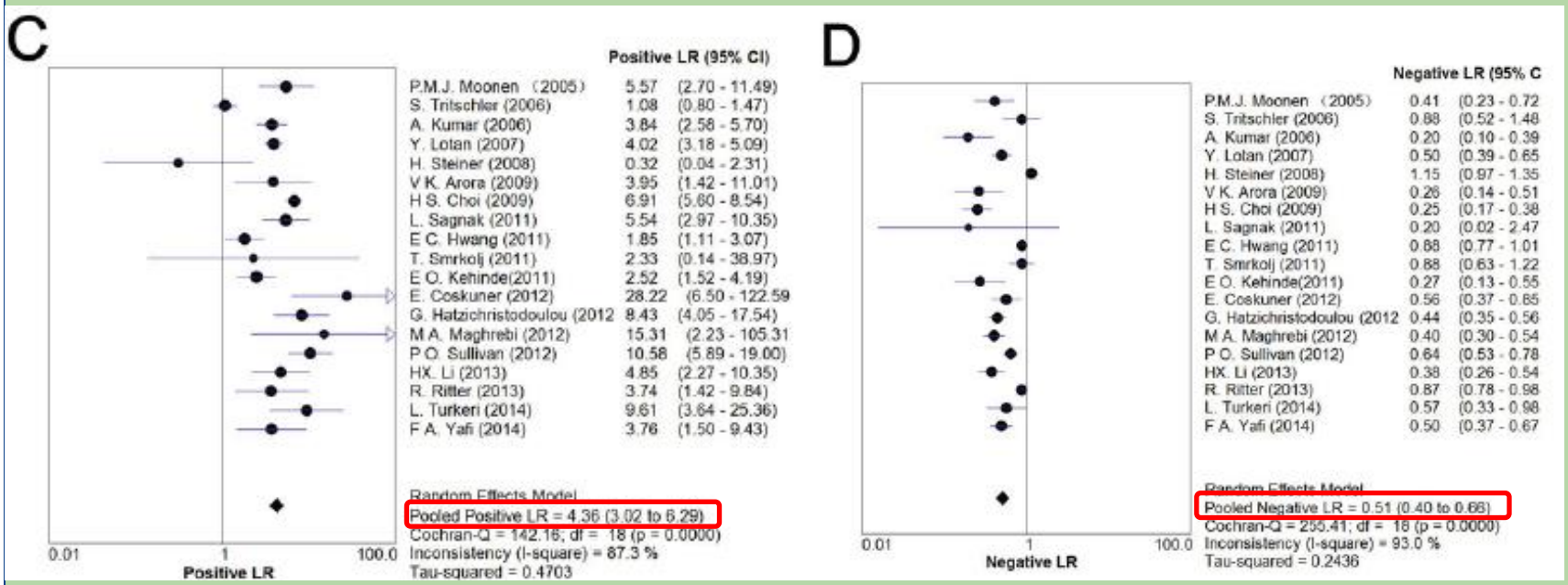

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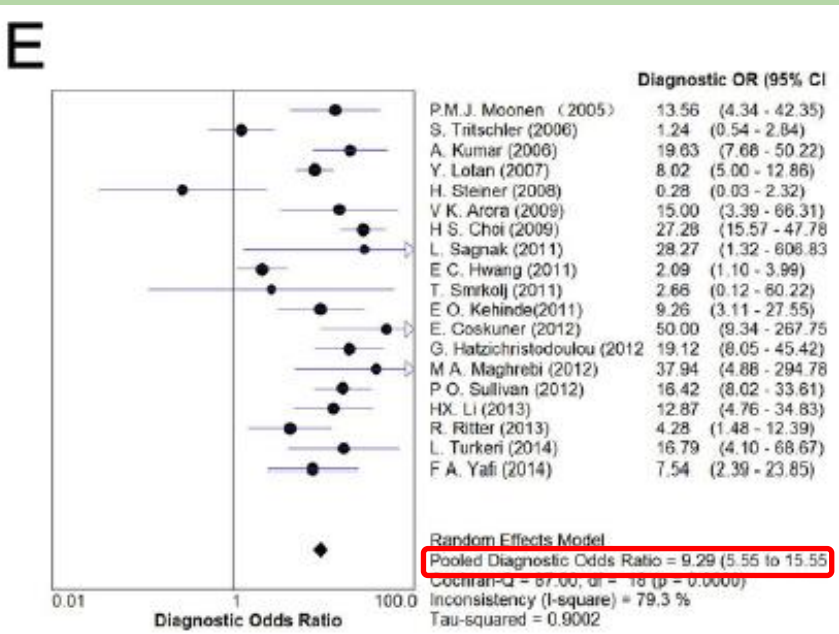

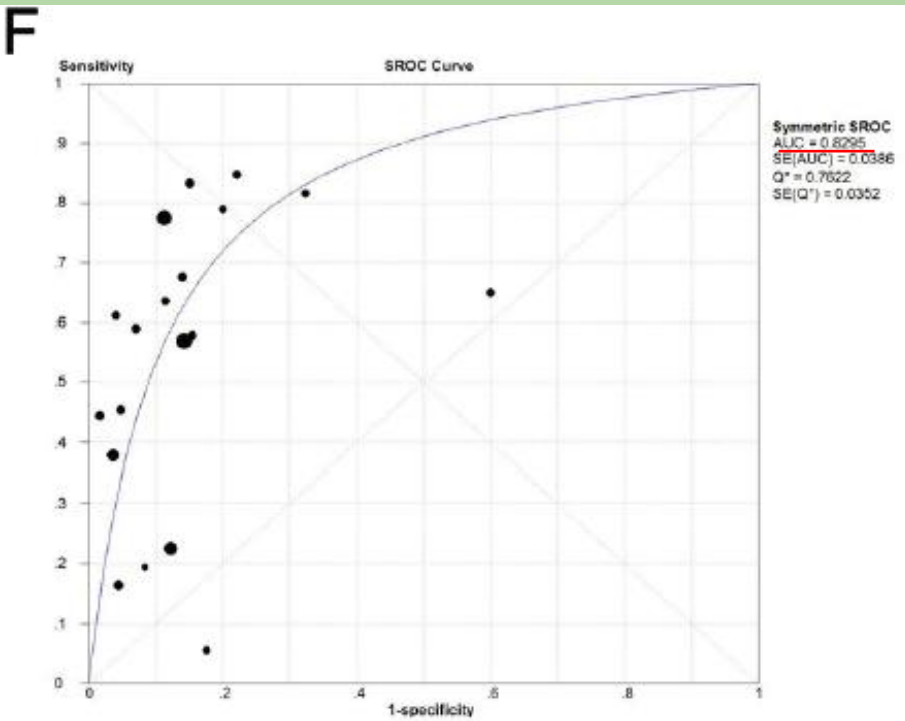

評讀結果：☑**是** □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

H－試驗的結果是否相近－異質性 (Heterogeneity)

？在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著 (卡方檢定)。根據每篇個別研究中不同的 PICO 及研究方法，探討造成異質性的原因。

在文章的結果章節，可以找到研究結果是否具異 質性，及造成異質性可能的原因探討。森林圖中可以找到異質性的卡方檢定結果。

Diagnostic performance

Significant heterogeneity was observed among the 19 studies in our meta-analysis. Accordingly, we performed meta-regression analysis to explore the origins of the heterogeneity. Figure 3 shows that the heterogeneity was suggested across the studies, and among eight factors, study quality was identified as statistically significant, indicating that the quality of the studies was responsible for the relatively high heterogeneity.

評讀結果：☑**是** □否 □不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

H－試驗的結果是否相近－異質性 (Heterogeneity)？

Meta-Regression(Inverse Variance weights)

Var	Coeff.	Std. Err.	p - value	RDOR	[95%CI]
Cte.	-1.333	1.6785	0.4475	----	----
S	0.415	0.3530	0.2697	----	----
male	2.399	1.5375	0.1531	11.01	(0.34;356.76)
comparison	1.278	0.8205	0.1538	3.59	(0.56;22.97)
ethnicity	-1.106	0.7557	0.1773	0.33	(0.06;1.83)
histological	-1.929	1.4741	0.2231	0.15	(0.01;4.08)
primary	0.200	0.6940	0.7800	1.22	(0.25;5.87)
quality	1.006	0.3969	0.0320	2.73	(1.11;6.71)
number	1.178	0.9317	0.2379	3.25	(0.39;26.72)
year	1.476	1.0016	0.1747	4.38	(0.45;42.17)

Tau-squared estimate = 0.8849 (Convergence is achieved after 10 iterations)
Restricted Maximum Likelihood estimation (REML)

Figure 4: Meta-regression analysis of heterogeneity across eligible studies. Male, whether the male/female ratio > 50%; comparison, whether compared with other novel diagnostic methods; ethnicity, Asian/Caucasian population; histological, whether histological examination of bladder cancer was performed; primary, whether bladder cancer recurrence was detected; quality, the quality of all included studies as assessed by QUADAS-2; number, where case number > 400; year, whether publication year was after 2011.

The heterogeneity test and meta-regression analysis showed significant heterogeneity across the included studies, and the quality of these studies may be the potential origin of the relatively high heterogeneity. The included trials involved two main types of diagnostic trials, i.e., case–control and cross-section, and the differences in patient enrollment, study design, and data collection between the two types contributed to the high heterogeneity.

評讀結果：☑**是** □否 □不清楚

步驟 3：研究結果之意義為何？

1. Overall sensitivity and specificity were 56% (52–59%) and 88% (87–89%), respectively; pooled PLR and NLR were 4.36 (3.02–6.29) and 0.51 (0.40–0.66), respectively; DOR was 9.29 (5.55–15.55) with an AUC of 0.8295.

- Good discrimination ability for detecting bladder cancer and a high-specificity algorithm that can be used for early detection to rule out patients with higher bladder cancer risk.

1. The mean sensitivity for Ta, T1, ≥ T2, Tis, G1, G2, and G3 disease was 13.68%, 29.49%, 74.03%, 34.62%, 44.16%, 56.25%, and 67.34%, respectively.

- It also has better potential for screening higher-grade and higher-stage tumors, and better diagnostic performance in Asians.

Disscussion

- 根據NMP22 BladderCheck檢測細胞有絲分裂時之蛋白質而言：

1. 尿液濃度不夠時是否影響檢測結果？
2. 血尿或膿尿是否影響檢測結果？

- NMP22 BladderCheck與Urine Cytology之差異？
- NMP22 BladderCheck的診斷表現較好，但Meta-Regression分析之時，人種卻又不為異質性之原因之一？

Disscussion

Conclusion

The NMP22 BladderChek test has a slightly higher sensitivity compared to cytology, without a relevant loss in specificity. Furthermore it is an easy test with instant result. However, no extra tumours were detected by adjunction of the NMP22 BladderChek test.

Moonen PM, Kiemeney LA, Witjes JA. European urology. 2005; 48:951–6

比起尿液cytology，NMP22 test可以在不失專一性情況下，擁有高一點的敏感性

Results Bladder cancer was diagnosed in 103 patients. Cystoscopy alone identified 91.3% of the cancers (94/103; 95% confidence interval [CI], 84.1%-95.9%). The combination of cystoscopy with the NMP22 assay detected 99.0% of the malignancies (102/103; 95% CI, 94.7%-100%; $P = .005$). The NMP22 assay detected 8 of 9 cancers that were not visualized during initial cystoscopy, including 7 that were high-grade. The sensitivity and specificity of the NMP22 test alone were 49.5% (51/103; 95% CI, 39.5%-59.5%) and 87.3% (493/565; 95% CI, 84.2%-89.9%), respectively. Voided cytology detected only 3 of the malignancies missed during initial cystoscopy and did not significantly increase the sensitivity of cystoscopy (94.2%; 95% CI, 87.7%-97.8%; $P = .08$).

單做膀胱鏡敏感度為91.3%，加做NMP22 敏感度提升到99%

Grossman et al., JAMA Jan 18, 2006

討論：導入 NMP22 BladderChek test 篩檢膀胱癌？

同意:2人

證據不足，無法確定:3人

不同意：4人