·Technology and Methods·

The diagnostic value of urine-based survivin mRNA test using reverse transcription-polymerase chain reaction for bladder cancer: a systematic review

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[Abstract] Background and Objective: Survivin has gradually become an important target in diagnosis, prognosis prediction and treatment of tumor. There are many studies on urine-based survivin mRNA test using reverse transcription-polymerase chain reaction (RT-PCR) as a noninvasive examination for bladder cancer. However, its clinical value remains controversial. This study was to evaluate the diagnostic value of urine survivin mRNA detection with RT-PCR for bladder cancer by a systematic review of related studies. **Methods:** With the search terms such as bladder neoplasm, survivin, RT-PCR, sensitivity, specificity and diagnosis, we systematically searched through PubMed, EMBASE, SCI, Cochrane Library, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Full-text Database (CSJD), China Journal Full-text Database (CJFD), Chinese Medical Association (CMA) digital periodicals and Google Scholar totally from January 1997 to April 2009 for diagnostic trials with RT-PCR detection of urine survivin mRNA for bladder cancer. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) items were used to evaluate the quality of the included studies. Meta-disc software was used to calculate outcome indicators. **Results:** Twenty-six studies, totally 2 416 patients, were eligible. Meta-analysis showed that compared with pathologic examination, the summary values of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and summary receiver operating characteristic curve (SROC) of urine-based survivin mRNA test using RT-PCR for bladder cancer were 88%, 94%, 14.56, 0.13 and 0.9736, respectively. Nested RT-PCR got the highest sensitivity, specificity and SROC and the values were 91%, 95% and 0.9805, respectively. The sensitivity and specificity of general RT-PCR were the second highest, which were 87% and 94%, respectively. The sensitivity of quantitative RT-PCR was 80% and the specificity was 93%. **Conclusions:** Comparing with pathologic examination, the sensitivity and specificity of urine-based survivin mRNA test using RT-PCR are relatively high. It can be used as an important adjunct method for cystoscope in early screening and postoperative monitoring of bladder cancer.

Key words: Bladder neoplasm, survivin mRNA, reverse transcription-polymerase chain reaction, diagnostic test, systematic review

Bladder tumor is one of the most common tumors in the male urinary system. The statistical results of WHO in 2005 showed that bladder cancer ranked the eighth of the male common tumors in China, with the morbidity and mortality of 5/100 000 and 3/100 000, respectively[1]. The American Cancer Association estimated that 68 810 new bladder cancer cases were identified and 14 100 died in the United States in 2008[2]. Among the newly occurred cases, about 70% were superficial bladder cancer which can be treated by endoscopic transurethral resection, but 50%-70% of them will relapse after operation and 10%–20% will progress to muscle-invasive bladder cancer[3]. Therefore, early diagnosis and postoperative monitoring of bladder cancer is beneficial to early treatment and reduce the mortality. At present, cystoscopy and biopsy of lesions as well as urine cytology are considered the golden standards for diagnosis of bladder cancer. However, the former method is an invasive operation and easily leads to urinary tract infection, therefore, it is difficult to be accepted by the patients; the sensitivity of the latter method is low (34%), especially for early low-grade bladder cancer (12%)[4-6]. All these disadvantages limit the early diagnosis and postoperative follow-up of bladder cancer. Thus, discovering a non-invasive means of detecting bladder cancer with high sensitivity and specificity is very significant.

With the rapid development of molecular biology, detection

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of urine tumor molecular markers, such as NMP22, BTAstat, BTAtrak, cytokeratin 20 (CK20), and so on, has become a research hotspot [5]. Survivin, which has double functions of inhibiting apoptosis and regulating cell mitosis, was first discovered by Ambrosini *et al.*[7] in 1997. It is a new member of inhibitor of apoptosis protein (IAP) family. Survivin is widely expressed in human embryonic tissues and various tumor tissues, while only a few normal adult tissues can express it. Survivin gene has gradually become a target of cancer diagnosis, prognosis prediction and treatment. Many studies are involved in the detection of survivin mRNA in urine to diagnose bladder cancer by reverse transcription-polymerase chain reaction (RT-PCR). Unfortunately, the results varied. In this study, the related literatures were objectively evaluated by the systemic review method. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and the area under the receiver operating characteristic curve (SROC) were computed and summarized to evaluate the diagnostic accuracy, so as to provide an objective evidence to evaluate the diagnostic accuracy of bladder cancer by detection of urine survivin mRNA using RT-PCR.

Materials and Methods

Inclusion and exclusion criteria

Inclusion criteria: (1) the study type was diagnostic trial that providing fourfold table data and was reported in English and Chinese literatures; (2) the objects of study were suspected bladder cancer patients, with no restrictions of age, gender, race and cause of disease; (3) the diagnostic method was detecting survivin mRNA in urine by RT-PCR which was compared to golden standard (pathologic examination); (4) the measurement indicators were summarized sensitivity, summarized specificity, summarized positive likelihood ratio, summarized negative likelihood ratio and the area under SROC.

Exclusion criterion: animal experiment.

Literatures retrieval

With the terms such as bladder neoplasm, survivin, RT-PCR, sensitivity, specificity, diagnosis, and so on as the main search terms, systematic literature search was conducted in PubMed, EMbase, Cochrane Library, SCI, Chinese Biomedical Literature Database (CBM), Chinese Journal Full-text Database (CJFD), Chinese Scientific Journal Full-text Database (CSJD), and Chinese Medical Association (CMA) Journal Digital Search from January 1997 to April 2009. We referred to The Bayes Library of Diagnostic Studies and Reviews as our search strategy that combining keywords and free words. All the search strategies were determined by repeated pre-search. We used Google Scholar and other search engines to find relevant literatures on the Internet, and traced the references of included literatures.

Literature screening and data extraction

Two reviewers independently screened the literatures according to pre-established inclusion criteria and exclusion criteria. In detail, they firstly read the titles and abstracts to exclude obvious ineligible literatures, then read the full texts of the candidate literatures to determine whether they truly meet the inclusion criteria, and finally conducted cross-checking. If the screening results by two reviewers were inconsistent, the final results were determined by negotiation or discussion with another reviewer. Extracted information included author, year, country, the number of included samples, reference standard, trial methods, whether adopting the blind method, and the result indicators (the true positive number, the false positive number, the true negative number and the false negative number), and so on.

Quality evaluation

Two reviewers independently evaluated the quality of included researches based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) [8], and resolved their controversies by discussion. QUADAS quality assessment quantization table has 14 items. Every included literature was assessed by 'yes', 'no' and 'unclear' from the variations (items 1, 2), the bias (items 3–7, 10–12, 14) and the report's quality (items 8, 9, 13), respectively, and identified the causes of bias and variations.

Statistical analysis

The heterogeneity was tested using χ^2 test (RevMan5.0) and assessed by P value and I^2. It was suggested that there was no statistical heterogeneity when $P > 0.05$ and $I^2 < 50\%$. If there was heterogeneity ($P < 0.05$ and $I^2 \geqslant 50\%$), heterogeneous sources were firstly analyzed. If the heterogeneity was caused by the diversity of different RT-PCR detection levels, then sub-group analysis was considered. We drew SROC curves using Meta-Disc software (Version 1.4) and calculated the summarized sensitivity, specificity, positive likelihood ratio, negative likelihood ratio of diagnostic methods.

Results

Literature retrieval

We initially retrieved 207 literatures, 67 repeated documents were removed and 114 literatures were excluded, 26 studies were eventually included [9-34]. There were totally 2416 subjects including 1428 in the case group and 988 in the control group (Figure 1).

Characteristics of included studies

Seven literatures were in English [11-17]; 4 studies were conducted in the United States [12], Egypt [13], Germany [16], and Iran [17], and 22 in China. Four studies were conducted by quantitative RT-PCR [11,12,16,32], 11 were nested RT-PCR [9,10,15,18,19,24-26,30,33,34], the rest were general RT-PCR (Table 1).

Quality evaluation of included studies

Twenty-six studies were consistent with 8 items of QUADAS criteria. The other 6 items were described below: 22 studies involved diagnosed bladder cancer patients [9-11,13,15,17-25,27-34]; only 1 study used the blind method (RT-PCR operator is unaware of the clinical data) [14], 2 gave a detailed description of the inclusion criteria and exclusion criteria of study objects [16,17], 4 gave a partial description and the remaining studies did not

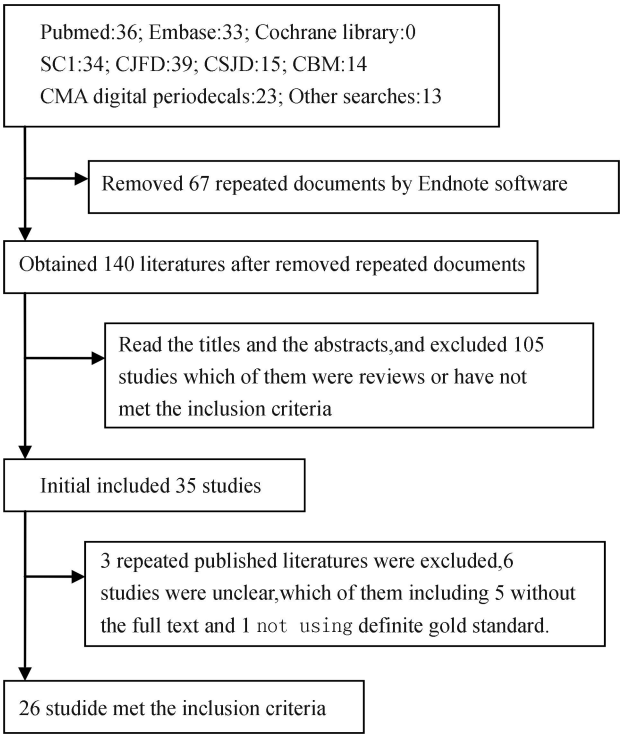

Figure 1 The flow chart of literature screening

describe [12,13,26,29]; 21 studies did not report whether the control group accepted the gold standard examination[9,11,13,15,16,18-25,27-34]; 10 studies did not report the sequences of PCR primers[9,17-20,22-24,27,31]; All the studies did not describe in detail the operation methods of cystoscopy and pathological examination (Table 2).

Meta analysis

There were statistical heterogeneity among 26 studies (P < 0.001, I^2 = 60%). Meta analysis was carried out by random effect model and the results showed that SEN_{sum} was 0.88 (95% CI: 0.86-0.90) (Figure 2), SPE_{sum} was 0.94 (95% CI: 0.92–0.96) (Figure 3), +LRsum was 14.56 (95% CI: 8.85–23.95) and -LRsum was 0.13 (95% CI: 0.09–0.18), SROC (AUC) was 0.9736 (Figure 4). The heterogeneity may be related to the diverse detection levels of different RT-PCR techniques. Sub-group analysis was carried out according to the different RT-PCR techniques and the results were as follows: (1) Nested RT-PCR test results from 11 studies were compared with the golden standard, no statistical heterogeneity was found (P = 0.19, I^2 = 27%). Meta analysis showed that SEN_{sum} was 0.91 (95% CI: 0.89–0.93), SPE_{sum} was 0.95 (95% CI: 0.92–0.97), $+LR_{sum}$ was 13.76 (95% CI: 9.14–20.71), $-LR_{sum}$ was 0.10 (95% CI: 0.07–0.16), and SROC (AUC) was 0.9805. (2) Quantitative RT-PCR test results from 4 studies were compared with the golden standard, statistical heterogeneity was found (P = 0.0005, I^2 = 83%). Meta analysis showed that SEN_{sum} was 0.80 (95% CI: 0.72–0.86), SPE_{sum} was 0.93 (95% CI: 0.89–0.96), $+LR_{sum}$ was 9.88 (95% CI: 5.94–16.44), $-LR_{sum}$ was 0.26 (95% CI: 0.15–0.46), and SROC (AUC) was 0.9616. (3) General RT-PCR test results from 11 studies were compared with the gold standard, and statistical heterogeneity was found (P = 0.02, I^2 =

Table 1 The general characteristics of the 26 included studies

Reference	Country	Number of cases	Diagnosis method	Blind method	TP	FP	FN	TN
Kenney *et al.*, 2007[12]	America	118	Quantitative RT-PCR	Unclear	19	7	5	87
Ziaee *et al.*, 2006[17]	Iran	38	General RT-PCR	Unclear	18	9	2	9
Moussa *et al.*, 2006[13]	Egypt	167	General RT-PCR	Unclear	79	4	5	79
Weikert *et al.*, 2005[16]	Germany	68	Quantitative RT-PCR	Unclear	24	0	11	33
Hou *et al.*, 2006[11]	China	70	Quantitative RT-PCR	Unclear	40	4	0	26
Wang *et al.*, 2004[15]	China	66	Nested RT-PCR	Unclear	24	0	6	36
Pu *et al.*, 2008[14]	China	173	General RT-PCR	Yes	104	2	11	56
Jiang *et al.*, 2006[21]	China	85	General RT-PCR	Unclear	32	2	3	48
Wang *et al.*, 2004[28]	China	63	General RT-PCR	Unclear	38	0	2	23
Li, 2008[22]	China	90	General RT-PCR	Unclear	47	6	13	24
Wang *et al.*, 2007[27]	China	110	General RT-PCR	Unclear	76	1	4	29
Yuan *et al.*, 2006[33]	China	83	Nested RT-PCR	Unclear	53	3	0	27
Zhang *et al.*, 2005[34]	China	120	Nested RT-PCR	Unclear	59	3	11	47
Lu *et al.*, 2007[24]	China	86	Nested RT-PCR	Unclear	54	1	2	29
Cao *et al.*, 2004[18]	China	96	Nested RT-PCR	Unclear	51	1	5	39
Wang *et al.*, 2006[30]	China	64	Nested RT-PCR	Unclear	47	1	1	15
Pu *et al.*, 2003[25]	China	51	Nested RT-PCR	Unclear	31	1	0	19
Wu *et al.*, 2007[31]	China	128	General RT-PCR	Unclear	51	1	17	59
Chen *et al.*, 2006[19]	China	48	Nested RT-PCR	Unclear	32	1	0	15
Lin *et al.*, 2007[23]	China	78	General RT-PCR	Unclear	45	1	3	29
Huang *et al.*, 2007[20]	China	67	General RT-PCR	Unclear	41	0	8	18
Wang *et al.*, 2005[29]	China	52	General RT-PCR	Unclear	22	0	18	12
Xu *et al.*, 2005[32]	China	79	Quantitative RT-PCR	Unclear	28	2	12	37
Wan *et al.*, 2008[26]	China	123	Nested RT-PCR	Unclear	60	4	12	47
Guo, 2006[9]	China	111	Nested RT-PCR	Unclear	40	4	8	59
He, 2006[10]	China	182	Nested RT-PCR	Unclear	141	0	11	30

TP, true positive; FP, false positive; FN, false negative; TN, true negative.

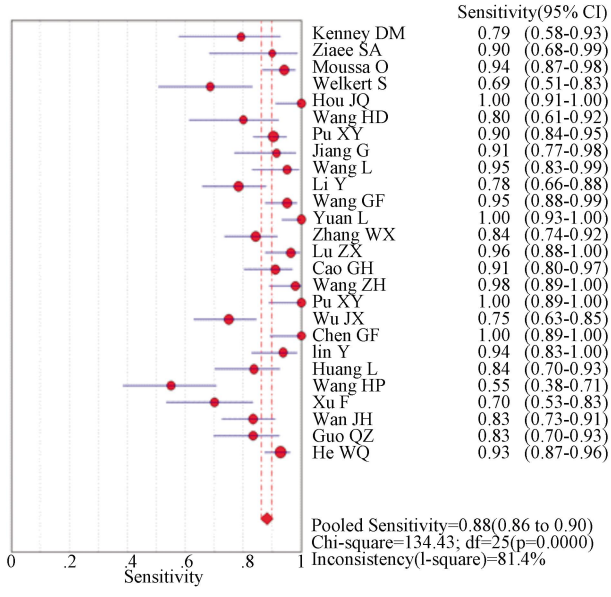

Figure 2 The meta-analysis forest map of sensitivity of urine-based survivin mRNA test using RT-PCR for bladder cancer

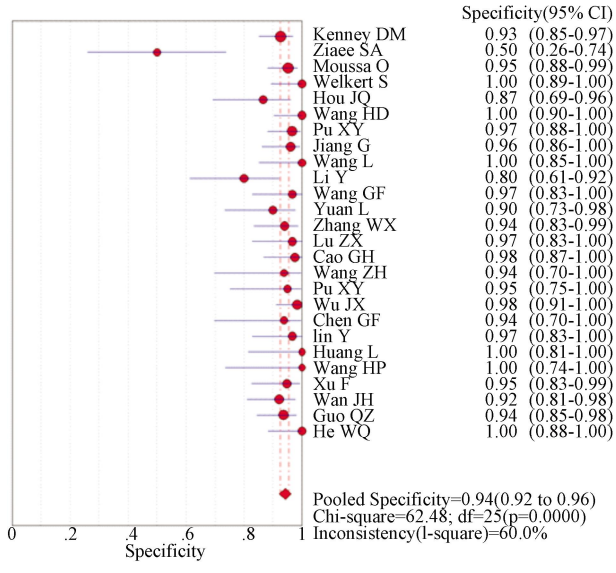

Figure 3 The meta-analysis forest map of specificity of urine-based survivin mRNA test using RT-PCR for bladder cancer

Table 2 The quality evaluation of various studies included in the systematic review

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Kenney *et al.*, 2007[12]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Ziaee *et al.*, 2006[17]	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Moussa *et al.*, 2005[13]	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Weikert *et al.*, 2005[16]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Hou *et al.*, 2006[11]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang *et al.*, 2004[15]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Pu *et al.*, 2008[14]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Jiang *et al.*, 2006[21]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang *et al.*, 2004[28]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Li, 2008[22]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang *et al.*, 2007[27]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Yuan *et al.*, 2006[33]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhang *et al.*, 2005[34]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Lu *et al.*, 2007[24]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Cao *et al.*, 2004[18]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang *et al.*, 2006[30]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Pu *et al.*, 2003[25]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Wu *et al.*, 2007[31]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Chen *et al.*, 2006[19]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Lin *et al.*, 2007[23]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Huang *et al.*, 2007[20]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Wang *et al.*, 2005[29]	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Xu *et al.*, 2005[32]	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Wan *et al.*, 2008[26]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Guo, 2006[9]	No	No	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
He, 2006[10]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes

54%). Meta analysis showed that SEN_{sum} was 0.87 (95% CI: 0.84–0.89), SPE_{sum} was 0.94 (95% CI: 0.91–0.96), + LR_{sum} was 15.90 (95% CI: 5.29–47.82), -LR_{sum} was 0.13 (95% CI: 0.08–0 . 23), and SROC (AUC) was 0.9596.

Discussion

Our analysis suggested that diagnosis of bladder cancer by

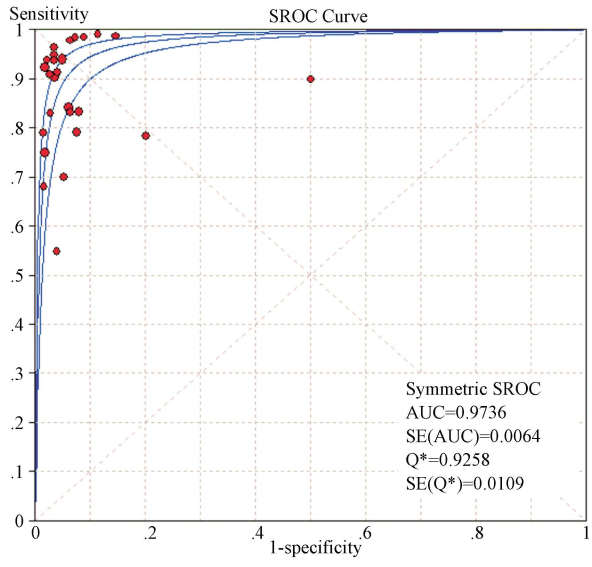

Figure 4 The SROC curve of urine-based survivin mRNA test using RT-PCR for bladder cancer

detecting survivin mRNA using RT-PCR has high sensitivity and specificity. Among the three PCR techniques, nested RT-PCR has the highest sensitivity and specificity, but it is technically difficult to operate and currently carried out less in common laboratories. The sensitivity and specificity of quantitative RT-PCR is much lower and the possible reasons are mainly as follows: (1) A high threshold (≥ 25 000 copies [12] or 1000 copies [16]) of result judgment was set, which may reduce the number of true positive cases, and thus affect the sensitivity. (2) Inner reference genes were not unified, including β-actin [12], ABL[11], porphobilinogen deaminase[16], glyceraldehyde-3-phosphate dehydrogenase [32]. This may also affect the results since excluding samples and judging results depend on inner reference genes. (3) The sequences of primers or probes will also have a great impact on the results. The experimental equipments of quantitative RT-PCR are very expensive. Quantitative RT-PCR experiments are also strict with primers. All these reasons, to a certain extent, restrict its application. The sensitivity and specificity of general RT-PCR range between nested RT-PCR and quantitative RT-PCR. General RT-PCR is widely used and it can be carried out in common laboratories. Since all these three detection techniques can be affected by processing and storage time of samples, RNA quality, the sources of diagnostic reagents and instruments, and operators, setting standard operation procedures and techniques is necessary. If so, detection of urine survivin mRNA by RT-PCR may be used as one of the principal adjunct means of cystoscopy for the bladder cancer screening and postoperative monitoring.

All 26 studies included in our evaluation system were based on current world-recognized golden standard for diagnosis of bladder cancer as a reference criteria, therefore, disease classification bias and summary bias would unlikely happen. All judgments of the golden standard test results from the literatures were carried out under the condition that evaluators did not know the experimental results to be evaluated, therefore, the golden standard test result interpretation bias could not happen. The judgment of RT-PCR results, especially quantitative RT-PCR results, could not be easily affected by subjective factors, thus test interpretation bias could not happen too. At the same time, study designs were not the same and there were certain differences in methodological quality. For example, a relatively small number of samples and different sample constituent ratios affected sensitivity and specificity; most studies did not describe whether non-bladder cancer patients were verified by golden standard, and multi-reference bias or part confirmation bias was likely to occur; some studies partly described the selection and exclusion criteria of study objects, and disease spectrum bias possibly occurred; poorly reported literatures could also affect assessment on their quality.

Therefore, we made the following recommendations for future diagnostic studies: (1) Cross-sectional studies those were standardized designed should be carried out as much as possible. Suspected cases should be included. (2) Adequate samples should be estimated before the experiment. (3) The golden standard tests and the tests to be evaluated should be carried out simultaneously, and the diagnostic process and results should be evaluated blindly to reduce the assessment bias. (4) Adopt the standards for reporting of diagnostic accuracy (STARD)[35] as far as possible to improve the quality of diagnostic test reports. (5) The characteristics of the study objects, inclusion and exclusion criteria, steps, conditions, reagents, and so on, of reference tests and diagnostic tests should be described in detail for the sake of study repetition and practical application.

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