Diagnostic value of Telomerase Activity in patients with Bladder cancer: a meta-analysis of diagnostic test

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Abstract

Background This article aims to evaluate the diagnostic value of telomerase activity (TA) in bladder cancer (BC) by meta-analysis of diagnostic tests. Methods We conducted a systematic search of articles published on PubMed, Embase, and Web of Science up to June 1, 2019.Stata 15 and Review Manager 5.3 were used for calculation and statistical analyses. Results We use the sensitivity, specificity, positive and negative likelihood ratio (PLR,NLR),diagnostic odds ratio (DOR) and 95% confidengce intervals (CIs) to evaluate the diagnostic value of TA for BC. 22 studies were included in the meta- analyses, with a total of 2867 individuals. The pooled parameters are calculated from all studies: sensitivity of 0.79(95%CI:0.72-0.84), specificity of 0.91(95%CI:0.87-0.94), PLR of 8.91(95%CI:5.91-13.43),NLR of 0.24(95%CI:0.15-0.37), DOR of 37.90(95%CI:23.32-61.59), AUC of 0.92(95%CI:0.90-0.94). We also conducted subgroup based on different stages and grades. Results from subgroup analysis showed that there was no significant difference in TA during the high and low stages BC, but low-grade tumors have lower TA than high-grade tumors. Conclusions For the diagnosis of BC, the overall diagnostic value of TA is high, and is expected to be an alternative to cystoscopy for different staging and grading. The tumor also has a very good diagnostic value.

Background

Bladder cancer (BC) is a malignant tumor with very high invasiveness, whether it is male or female, it ranks very high It is in the top ten in both male and female tumors[1, 2]. BC can generally be identified by painless macroscopic hematuria or microscopic hematuria, but this usually leads to a poor prognosis[3].

Due to BC patients lack specific clinical symptoms, to diagnosis BC as early as possible has a great impact on the treatment and prognosis of patients[4].Generally speaking, urine cytology, histology, and cystoscopy are common methods for diagnosing BC.[5] Cystoscopy is the gold standard for the diagnosis of BC. Its intuitive characteristics are quite reliable for the diagnosis of BC, but this invasive operation will bring great pain to patients, and its expensive charges also affect its clinical frequency of use and late follow-up[6]. For a long time, people have been looking for a harmless, accurate and easy-to-manage way to diagnose BC[7].

Detection of telomerase activity TA is a non-invasive and effective auxiliary test for the diagnosis of BC[8] Telomerase is closely related to the maintenance of the telomere length of tumor cells and the infinite differentiation of cells. Telomerase expresses activity in tumor cells, but it cannot be detected in normal tissues around it[9]. Compared with cystoscopy, the detection of TA only needs to detect the urine or bladder irrigation solution, which greatly reduces the patient's fear of medical examination, and also facilitates follow-up[10].

Non-invasive diagnostic methods have become a hot emerging field. There are also many studies reporting the accuracy of TA in the diagnosis of BC. However, the diagnostic capabilities come from

different research is significantly different and may be affected some limitations, such as sampling errors, internal and internal observer changes. Considering the limitations of a single study, we attempted to perform meta-analysis based on more research samples and statistics to obtain a more accurate diagnostic efficiency for TA in patients with BC. Studies have revealed the relationship between telomere length and various cancers. On this basis, we further explore the relationship between TA and BC, aiming to reveal telomere and telomerase systems's status and role in cancer[11].

Methods

Literature search and eligibility criteria

We systematically retrieved relevant literature in the PubMed, Embase, and Web of Science databases from inception to May 25, 2019. Use TA, BC, urine as search terms. Language was limited to English. We also searched the relevant references directories to avoid missing other related documents.

Studies that meet the following requirements can be included in our research: (1) A patient diagnosed with bladder cancer by the gold standard (cystoscopy); (2) The diagnostic value of TA must be reflected in the research; (3) study Sufficient data be provided: true positive (TP), false positive (FP), false negative (FN), true negative (TN). Repeated articles, insufficient quality studies, studies focusing on other diseases, letters, comments, case reports or editorials were excluded. This process was independently retrieved by two authors.

Data extraction

We included the following data from each study in our meta-analysis: First author, Publication year, region, sample size, four data (TP, FP, FN, TN). Two authors (PL and CDH) extracted information by using the standard Excel worksheet respectively and cross-checked the data. The third investigator (RZJ) will resolve the disputes may arise.

Quality evaluation

We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) to assess the quality of included studies. We used a quantitative method to assess the studies. The QUADAS-2 included 14 items[12]. Each key domain includes two sections: risk of bias and applicability. We could determine the risk of bias is low if all signaling question's answer for a domain are 'yes'. If the answer to any question is 'no', potential bias exists. Concerns about applicability are determined as 'low', 'high', or 'unclear'. 'Yes' as one scores was defined.

Statistical analysis

We used Stata 15 (StataCorp LP, University City, Texas, USA) and Review Manager 5.3 for statistical analysis. Using Q test and I^2 to evaluate the heterogeneity of the study, and I^2>50% improvement was significantly heterogeneous[13]. We use the bivariate model to calculate the polled sensitivity, specificity,

positive and negative likelihood ratios (PLRs and NLRs), diagnostic odds ratio (DOR) and its 95% confidence interval (CI)[14]. We calculated the area under the receiver operator characteristic curve (SROC, AUC). AUC varies from 0.5 to 1. If the area is 1, it means that the diagnosis has perfect discrimination. If the area is 0.5, it means that the diagnostic ability is very poor[15]. Deek's funnel plot was used to assess the publication bias, and Fagan plots shows the relationship between the prior probability, the likelihood ration, and posterior test probability[16]. P<0.05 means the results are statistically significant.

Results

Study selection and study characteristics

Fig.1 presented our literature search selection process. Initially we identified a total of 515 studies in the database. 195 duplicates records were removed, After reading the title, abstract and topic, 260 records were excluded. There are 60 articles left to read the full text to assess eligibility. After further reading the full text of these 60 articles, we removed 41 records unrelated to diagnostic value, and 4 duplicates. Similarly, 8 studies were excluded due to insufficient data. Finally, we included 22 studies in our qualitative and quantitative analysis[7, 9, 10, 17-35].

In Table 1, the characteristics of 22 articles were included in this meta-analysis of TA for BC. The years of these articles from 1997 to 2010. 2867 sample individuals from all over the world were included in the study. Most of them were multicenter studies. Sample sizes range from 42-185, among 22 studies, 5 were conducted in Asia (Japan and Israel), 6 from the United States, 10 from Europe (UK, Germany, Italy and Poland), and an African (Egypt) study. The four-flod table data was presented in Table 1.

Quality assessment

Table 1 lists the quality scores for each study. It can be clearly seen that each article scores more than 11 points. According to the QUADAS-2 scoring standard, 18 belong to the middle and high scores.

Pooled diagnostic values

Since the value of I2 is greater than 50%, the random effects model is used to combine sensitivity and specific. The diagnostic value of TA for the detection of BC is shown in Table 2. Its overall sensitivity and specificity are 0.79(95%CI:0.72-0.84) and 0.91(95%CI:0.87-0.94,Figure 2).Youden Index is 0.7.The pooled PLR was 8.91(95%CI:5.91-13.43), NLR was 0.24(95%CI:0.15-0.37), and DOR was 37.90(95%CI:23.32-61.59).The overall SROC curve was shown in Figure 3, and AUC was 0.92(95%CI:0.90-0.94). Fagan plot was shown in Figure 4. The prior probability was 20%,and the post-test probability was 69% of LR-positive, and 6% of LR-negative. The diagnostic accuracy of detecting TA in BC is generally better.

Subgroup analyses

We performed a subgroup analysis of TA based on different stages and grades of the tumor. We specify Tis, Ta, T1 for low stage, T2 and above for high stage. Similarly, we specify that Grade 1 is low grade and

Grade 2-3 is high grade. According to the results of the heterogeneity test, both use a fixed model for meta-analysis, and the results and forest map are shown in Figure 5. In the comparison of the different sub-periods, the P value was >0.05, suggesting that there was no significant difference in TA during the high and low stages（Figure 5）. In different grades, P = 0.001, suggesting that our low-grade tumors have lower TA than high-grade tumors.

publication bias

The Deek's plot shows there was no publication bias (P=0.83, Figure 6)

Discussion

To our knowledge, this is the first meta-analysis of the diagnostic efficacy of telomerase activity for bladder cancer. We found that TA is ideal among various indicators and also proves its excellent diagnostic performance.

BC, as a malignant tumor with high morbidity and mortality, has received wide attention from all walks of life, both in its diagnosis and treatment[36]. as we know, cystoscopy has long been the gold standard for the diagnosis of BC. Although it is quite reliable, as an invasive examination, at least it needs to be operated under local anesthesia, inducing strong discomfort to the patient. [7]. People need a diagnosis that is not only simple, but also minimizing the damage caused by the examination. Measures, which also make the continuous detection and development of BC test methods, which also gradually move people's attention from macro to micro, and began to explore the role of some markers in urine in the detection and diagnosis of BC[18, 19]. Telomeres are composed of repeated gene sequences and related proteins. Their main role is to avoid end-to-end fusion and nuclear cleavage during chromosome division[18]. Telomerase can reverse the fact that telomeres become shorter due to division. This is one of the essential conditions for the permanent life of tumor cells[9]. So we suspect that in tumor cells, telomerase activity is higher than in normal cells. Many scholars have studied the relationship between TA and BC, but due to the factors of detection technology and sample size, the conclusions are not only inconsistent, but even some differences in some evaluation indicators. We integrated and analyzed the research done by relevant authors and included enough samples for meta-analysis, aiming at comprehensive evaluation. Diagnostic validity of TA in BC will provides better guidance for clinical practice.

A number of studies have shown that the sensitivity of the telomerase assay for urothelial carcinoma is lower in voided urine specimens than bladder washings[17, 22, 24]. However, the urine is easier to obtain for the bladder washings, which is beneficial to the patient's cooperation. In our meta-analysis, the overall sensitivity is 0.79 (95% CI: 0.72-0.84), the specificity is 0.91 (95% CI: 0.87-0.94), and the Yoden index is 0.7. AUC is 0.92 (95% CI: 0.90-0.94), which is in line with our expectations, and through these composite indicators, it also shows that TA has a good effect in terms of diagnostic accuracy. In general, the diagnostic test can be considered to have a high value when sensitivity and specificity are >0.7. In the study we included, the results of sensitivity in 16 articles reached this value, which also indicates the

superiority of TA in the diagnosis of BC and is consistent with our predictions. However, the sensitivity values provided in the other 2 studies were significantly lower [17, 22]. The reason we analyze it may be that the technical level of the test, the sample size, and some bias between the samples lead to different final results. In terms of specificity results, 21 of the studies we have included have reached 0.7 or higher, which shows that the results are not very different between the studies, which also confirms our conjecture and indicates that in the diagnosis of BC, the excellent specificity of TA. The higher the value of DOR, the better diagnostic ability of this diagnostic method. In our study, the DOR value was 37.90 (95% CI: 23.32-61.59)，suggesting that the overall accuracy was high. The overall PLR value was 8.91 (95% CI: 5.91-13.43), which means that people with BC have a TA 8.91 times higher than normal, and a total NLR of 0.24 (95% CI: 0.15- 0.37), understood as the normal person suffering from BC is 25%. In the criteria for judging, PLR>10, NLR<0.1, the diagnostic efficiency of this method is higher. From this aspect, it can be concluded that the diagnostic efficiency of TA for BC is suboptimal.

To investigate the TA relationship between different staging and grading, we performed a subgroup analysis. In terms of staging, we drafted Tis, Ta, and T0 as low-stage tumors, while T2-T4 was high. In early grading, grade 1 was a low-grade tumor, and 2 and 3 were high-grade tumors. Thus, through meta-analysis, the association between them was shown. From the results, there was no absolute difference in TA between high-stage and low-stage tumors (P>0.05); and between different grades, meta-analysis. The results showed that the TA of the low-grade tumor was significantly lower than that of the high-grade tumor (P=0.001). We believe that this is because the higher the grade, the lower the degree of differentiation, the stronger the invasive ability, and the higher the TA, which is consistent with the results of Bravaccini[7] et al. Of course, detecting TA is not the only non-invasive method used to aid in the diagnosis of BC, other markers, such as nuclear maxtrix protein (NMP)-22, bladder tumor antigen (BTA), Cytokeratin 20. Studies have reported that BTA and cytokeratin 20 are very insensitive to low-grade tumors. For grade 1 tumors, the sensitivity of BTA and cytokeratin is 13% and 6%, respectively. NMP-22 has a specificity of 70% in the diagnosis of BC. [9, 22, 25]. Therefore, even on some individual indicators, these markers may work better, but the diagnostic performance should pay more attention to the composite indicators. As can be seen from our meta-analysis, the overall diagnostic ability of TA is better.

We follow the PRISM guidelines for meta-analysis[37]. However, at present, our meta-analysis has limitations. First, in the research we have included, most of the research samples are from Europe and the United States, Asia is less, and there is only one in Africa, which may lead to deviations in our research due to differences in races. Third, in each group of controlled studies, the patients studied may have other diseases besides BC. Since the mechanism is not clear, the interaction between the diseases may lead to higher or lower accuracy of the results. Finally，in the subgroup analysis, we combined the different stages and graded tumors into a self-control. Due to the influence of the original data, it was not able to be detailed enough in different stages and grades. Compared with cystoscopy, although not further clinically applied, TA does have a higher advantage in diagnosing BC with its relatively high sensitivity and non-invasive mode of operation. A larger sample size, tighter design, and longer follow-up randomized controlled trials are also needed to validate.

Conclusions

Overall, our study demonstrates that TA has a high overall diagnostic value and demonstrates its superiority in BC, and is expected to be an alternative to cystoscopy for different staging and grading. The tumor also has a very good diagnostic value. We hope to have further research to confirm our findings.

Abbreviations

Bladder Cancer,BC；Telomerase Activity,TA；Quality Assessment of Diagnostic Accuracy Studies 2, QUADAS-2;TP, true positives; FP, false positives; FN, false negatives; TN, true negatives; ROC, Receiver Operating Characteristic; SROC, summary receiver operator characteristic PLRs, positive likelihood ratios; NLRs, negative likelihood ratios; DORs, diagnostic odds ratios; CI, confidence intervals.

Declarations

Notes

Lei Peng, Dehong Cao, Lujia He, Zhengju Ren contributed equally to this work.

Ethics approval and consent to participate

Not applicable. There are no details on individuals reported within the manuscript, so we don’t have the consent for publication.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

Conceived and designed the experiments: PL. Analyzed the data: CDH and RZJ. Contributed reagents/materials/analysis PL, CDH and RZJ. Wrote the manuscript: PL, LJZ and CDH. All authors have read and approved the final manuscript.

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Figures

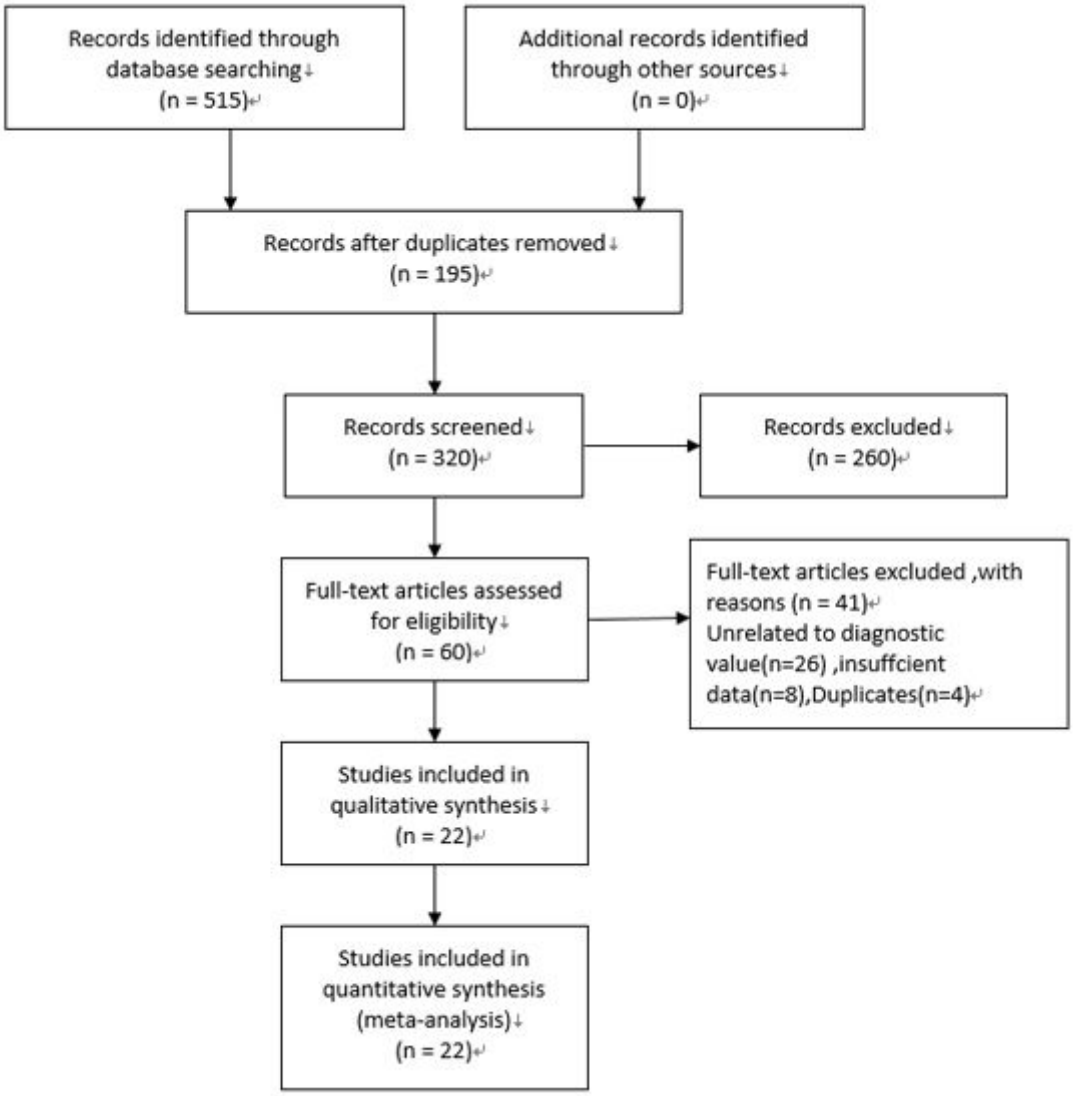

Figure 1

Flow diagram of studies selection process.

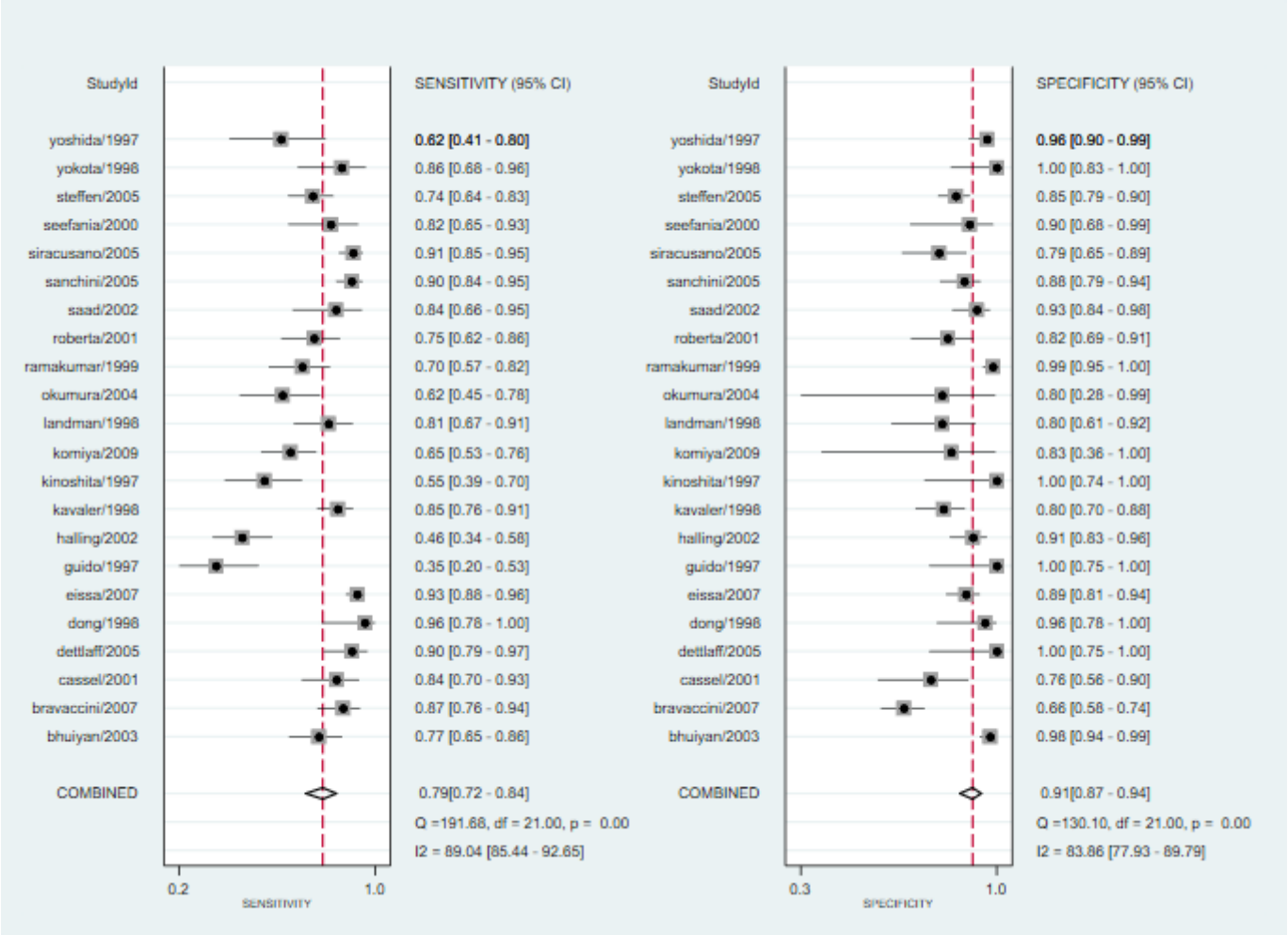

Figure 2

Forest plot of pooled sensitivity and specificity of Telomerase Activity for Bladder Cancer.

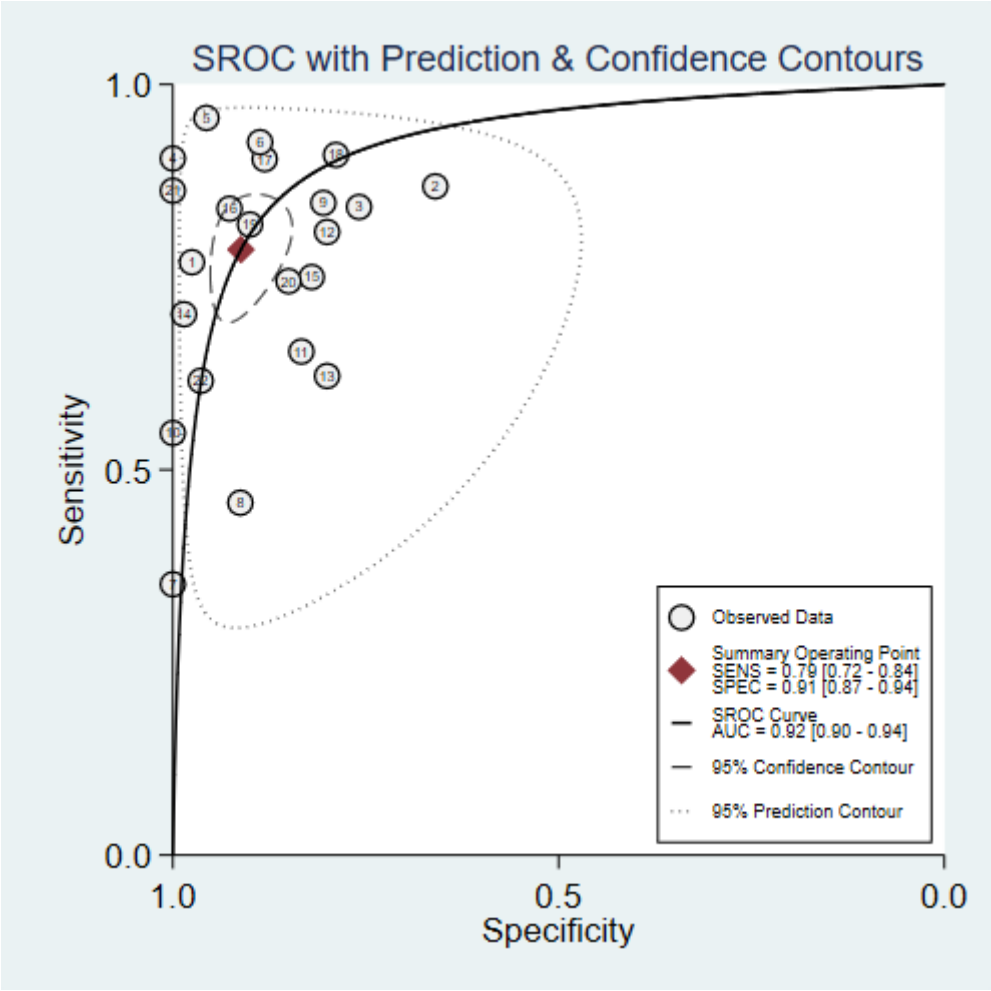

Figure 3

The SROC curve of Telomerase Activity for Bladder Cancer.

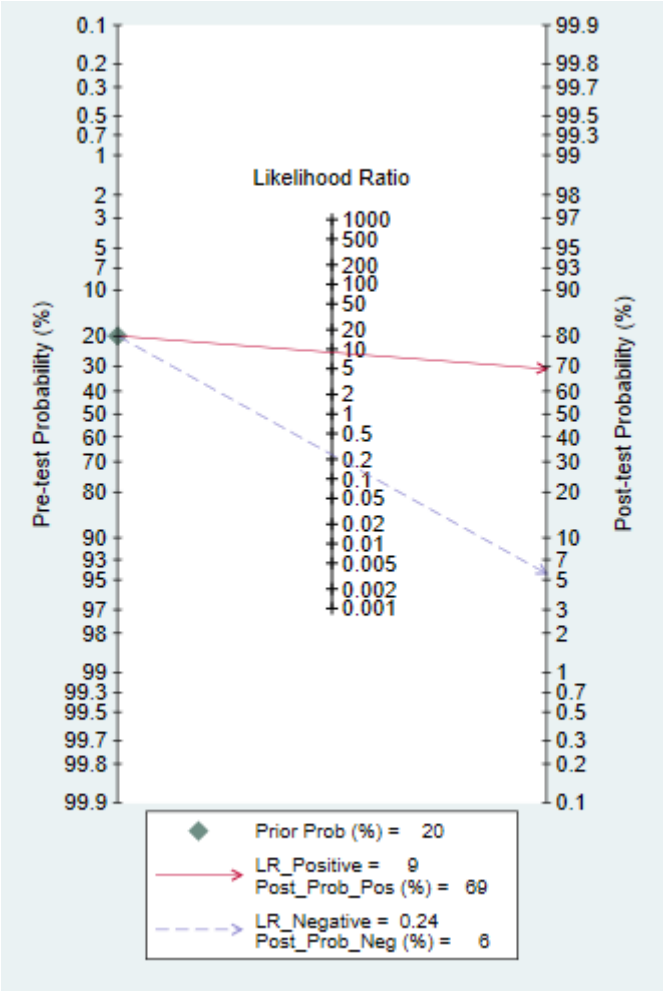

Figure 4

Fagan diagram evaluating the overall diagnostic value of Telomerase Activity for Bladder Cancer.

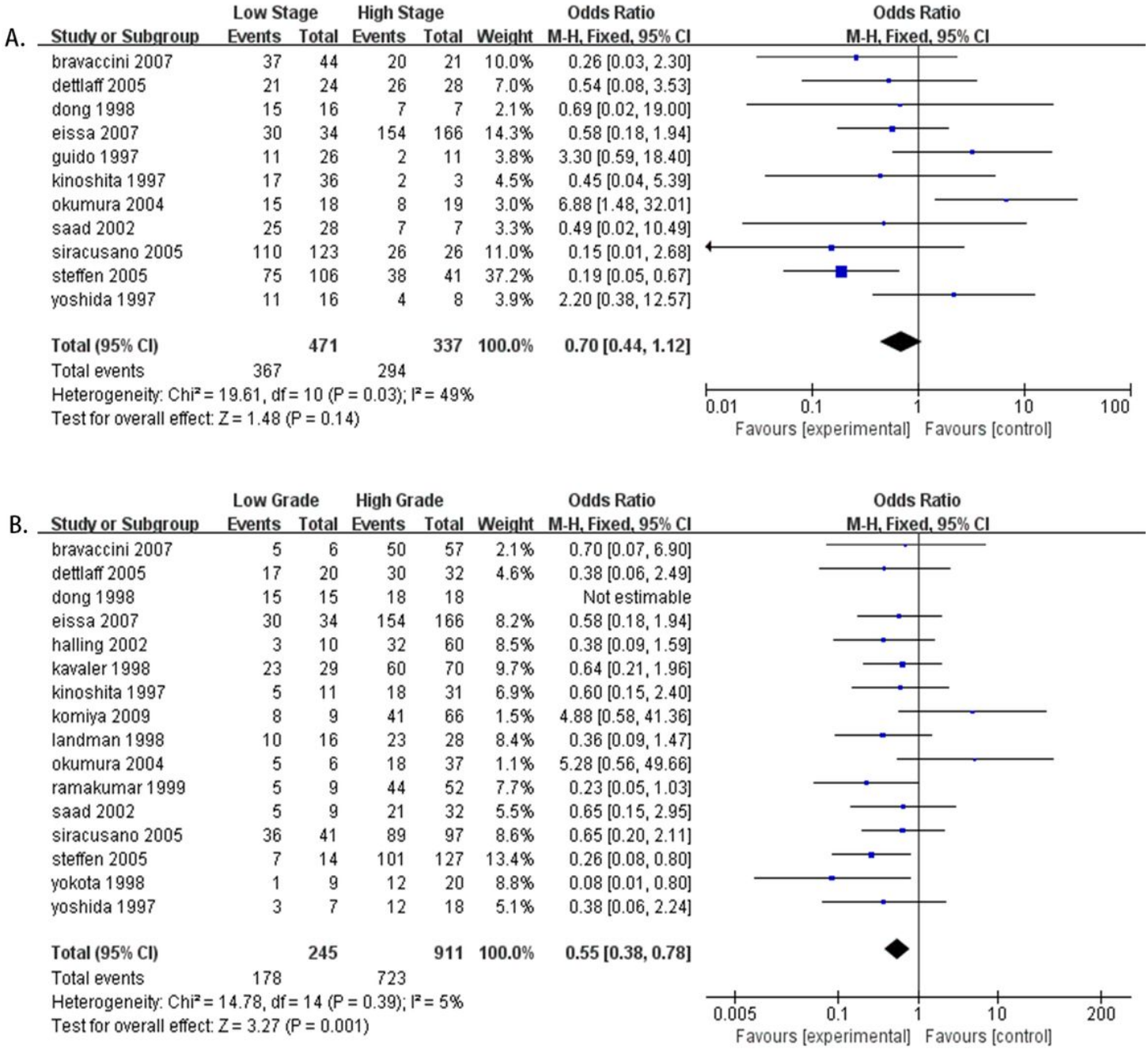

Figure 5

Forest plot of pooled different stages and grades of Telomerase Activity for Bladder Cancer. A: Forest plot of different stages; B: Forest plot of different grades

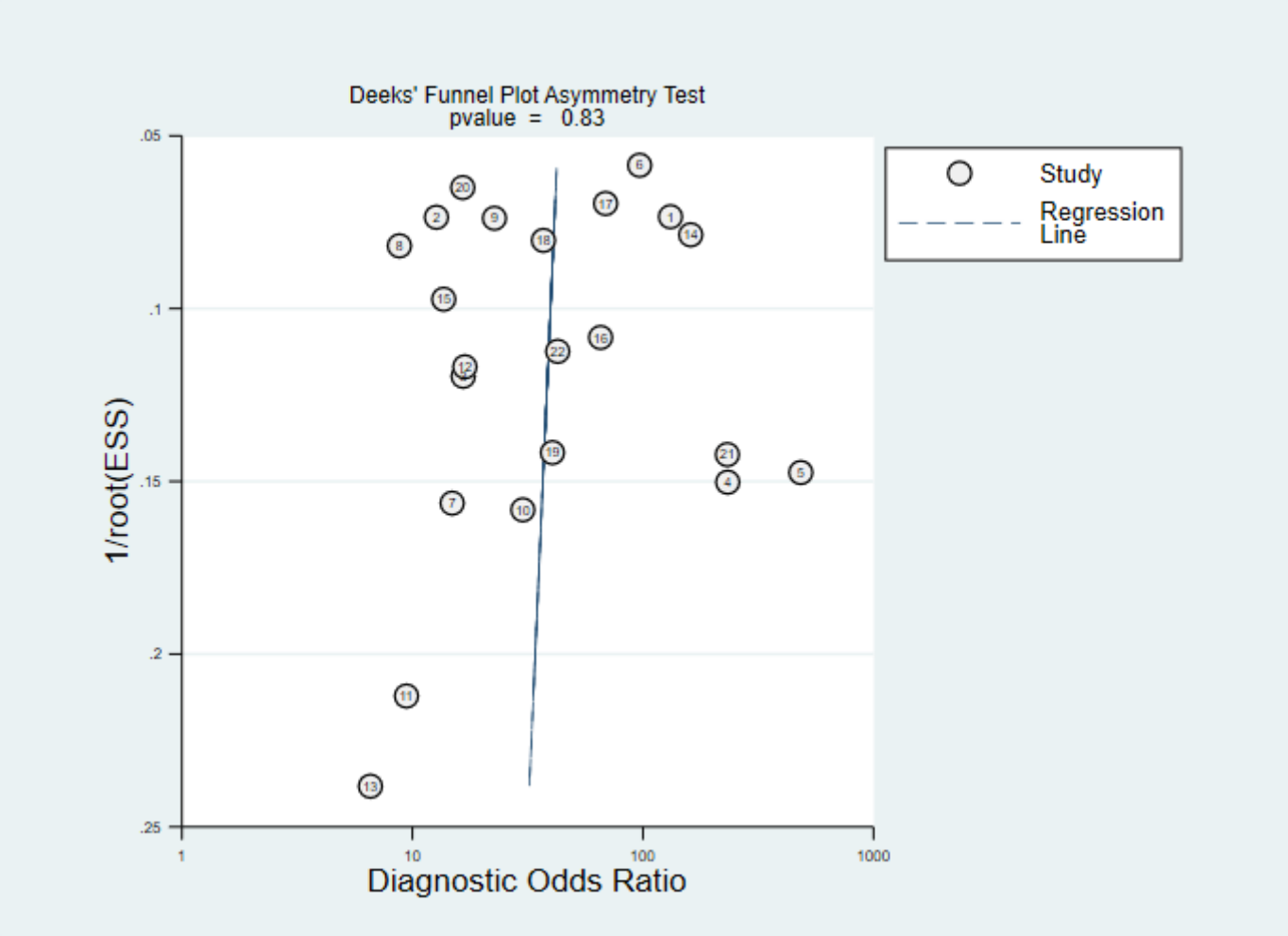

Figure 6

Deek's funnel plot to evaluate the publication bias.

Supplementary Files

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- supplement1.pdf