Comparisons between magnetic resonance/ultrasound fusion-guided biopsy and standard biopsy in the diagnosis of prostate cancer

A prospective cohort study

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Abstract
Prostate-specific antigen is not useful for detection of prostate cancer in Chinese men. The major problems in prostate cancer patients are overdiagnosis and overtreatment. The objective of the study was to test the hypothesis that targeted biopsy is an accurate diagnostic tool for prostate cancer detection than standard biopsy in Chinese men.

Total, 998 patients whom multiparticulate multiparametric magnetic resonance imaging had revealed at least 1 lesion in the prostate were included in a cohort. Patients were subjected to magnetic resonance imaging (MRI)/ultrasound (US) fusion-guided biopsy followed US-guided biopsy. Benefits of a diagnostic test were evaluated by decision curve analysis. Patients who were diagnosed as having prostate cancer by either of biopsies were subjected to radical prostatectomies followed by whole-mounted pathology (n = 578). Spearman rank correlation was performed between the biopsy results and the subtype of prostate cancer at 99% of confidence level. With respect to whole-mounted pathology, for US-guided biopsy, MRI/US fusion-guided biopsy, and combined data of both biopsies, sensitivities were 0.973, 0.983, and 0.973 and accuracies were 0.837, 0.91, and 0.917, respectively. MRI/US fusion-guided biopsy (P = .165) and combined data of both biopsies (P = .182) had the same specificity to whole-mount pathology. However, a US-guided biopsy had not the same specificity to whole-mount pathology (P = .0003). Decision-making zones for radical prostatectomy of different biopsies were in the order of combined data of both biopsies > MRI/US fusion-guided biopsy > US-guided biopsy.

Only the targeted biopsy is recommended for the diagnosis of prostate cancer.

Abbreviations: ADC = apparent diffusion coefficient, AUC = the area under the curves, DWI = diffusion-weighted image, mpMRI = multiparametric magnetic resonance imaging, MRI = magnetic resonance imaging, PI-RADS v1/v2 = Prostate Imaging Reporting and Data System version 1/ version 2, PSA = Prostate-specific antigen, q = Critical value for Tukey-Kramer Multiple comparisons test, START = Standards of Reporting for MRI-targeted Biopsy Studies, STROCSS = Strengthening the Reporting of Cohort Studies in Surgery, T1W image = T1-weighted image, T2W image = T2-weighted image, TNM = tumor, node, and metastases, US = ultrasound.

Keywords: biopsy, magnetic resonance imaging, pathology, prostatectomy, prostatic neoplasms, ultrasonography

1. Introduction
Prostate-specific antigen (PSA) “gray zone” in Chinese men (10.1–20 ng/mL) is higher than men of western countries (2.5–10 ng/mL)\textsuperscript{[1]} and the incidence rate of prostate cancer in men of the People’s Republic of China is 0.000121%.\textsuperscript{[2]} The major problems for men with prostate cancer are overdiagnosis and overtreatment.\textsuperscript{[3]} PSA is widely used for detection of prostate cancer,\textsuperscript{[4]} but it is not useful for detection of prostate cancer in Chinese men.\textsuperscript{[1]} Therefore, currently, the tumors of the prostate are detected by image-guided biopsies and extended-sextant biopsies in PR China.\textsuperscript{[5]} Saturation biopsy is also used for identification of prostate cancer but it has no significant improvement than extended-sextant biopsies for decision-making of prostatectomy.\textsuperscript{[6]} Nowadays, mpMRI (multiparametric magnetic resonance imaging)\textsuperscript{[7]} and transrectal ultrasound (US)-guided biopsies\textsuperscript{[8]} are used for identification of prostate cancer.

Magnetic resonance imaging (MRI) has high resolution, superior pictures, and images obtained are feasible to assign tumor grades than US.\textsuperscript{[8]} However, MRI-guided biopsy procedure is expensive, burdensome, and time-consuming.\textsuperscript{[9]} Moreover, MRI...
Multiparametric sectors 26 39

Apparent diffusion coefficient

Dynamic contrast-enhanced imaging

Primary and 5-point scale

Secondary (positive and negative)

MRI itself may provide false negative results.\textsuperscript{[11]} MRI also has the high specificity of interobserver variability.\textsuperscript{[12]} Therefore, MRI/US-guided biopsy has a sensitivity to detect tumor of 2.4mm\textsuperscript{[6]} and secondary endpoint of the study was to compare specificity of targeted biopsies and standard biopsies with whole-mount pathology.

The objective of the study was to test the hypothesis that MRI/US fusion-guided biopsy is an accurate diagnostic tool for prostate cancer detection than US-guided biopsy in Chinese men at the level I of evidence\textsuperscript{[13]} without conflict of interest. The secondary endpoint of the study was to compare specificity and sensitivity of targeted biopsies and standard biopsies with whole-mount pathology.

2. Material and methods

2.1. Reagents

Hematoxylin, cosin, and formalin were purchased from Mark Specialties, Germany.

2.2. Ethical consideration and consent to participate

The study had been registered in research registry (www.researchregistry.com), UID No.: researchregistry3969, dated 15 January 2004. The protocol (UR/CL/17/04, dated 9 January 2004) had been approved by the Heilongjiang Provincial Hospital review board. The study had adhered to Standards of Reporting for MRI-targeted Biopsy Studies (START) Consortium,\textsuperscript{[14]} 1964 Declarations of Helsinki,\textsuperscript{[15]} and the law of China. The work has been reported in line with the STROCSS (Strengthening the Reporting of Cohort Studies in Surgery) criteria.\textsuperscript{[16]} All enrolled patients had been signed an informed consent form before commencement of the study regarding pathology, radiology, anesthesia, surgery, and publication of the finding in all formats (hard and/or electronics) including patients’ personal information (image or photograph if any) irrespective of time and language.

2.3. Inclusion criteria

Men who had aged 18 years and above, admitted to Department of Urology of the Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China and Heilongjiang Provincial Hospital, Harbin, China from 16 January 2004 to 1 January 2018 with complains of a sudden urge to urinate, dribbling urine after the finish of urinating, difficulties in starting to urinate or emptying urinary bladder, a weak flow when urinating, a feeling that urinary bladder had not emptied properly, pelvic pain, hip pain, back pain, erectile dysfunction, and weight loss were included in the study. Men who had mpMRI that revealed at least 1 lesion in the prostate (as per PI-RADS v1/v2; Table 1),\textsuperscript{[17]} an elevated level of PSA (the 4 prostate-specific Kallikreins biomarker monoclonal antibody technique tests were performed for the study: total PSA, free PSA, intact PSA, and Human Kallikrein\textsuperscript{[11]} and an abnormal digital rectal examination (Patients were lied on their side on an examination table, with their knees brought up toward their chest. The evaluator had slid a finger gently into the rectum of patients, Table 2) were included in the cohort. Total, 998 men who had signed an informed consent form and agreed to radical prostatectomy (if required) were included in the study.

The demographic characteristics of the enrolled patients are presented in Table 3.

2.4. Exclusion criteria

Patients who had already diagnosed with prostate cancer contraindicated with mpMRI, and not signed an informed consent form were excluded from the study. Patients who had mpMRI that revealed no lesion in the prostate,\textsuperscript{[17]} normal level of PSA (<3–5.5 ng/mL as per age, Table 4),\textsuperscript{[18]} not subjected to MRI/US fusion-guided biopsies, US-guided biopsies, biopsies-related residual hemorrhage, or not agreed for radical prostatectomy (if required) were excluded from the study.

START Flow diagram of the study is presented in Figure 1.

2.5. mpMRI

All enrolled patients were subjected to mpMRI by a 3.0-T MRI (Excite HDXT, GE Healthcare) with 4 sequences–MR spectroscopy, diffusion-weighted imaging, triplanar T2-weighted, and dynamic contrast-enhanced images.\textsuperscript{[19]} Images were acquired with a 16-channel surface coil (NORAS, GmbH, Germany) and

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Table 1

| Parameters                                      | PI-RADS v1 | PI-RADS v2 |
|------------------------------------------------|------------|------------|
| Magnetic resonance spectroscopic imaging       | Maximum 16 | 1–5 dominant only |
| T2-weighted imaging                            | Suggested, size was not used | Dominant for transition zone, size (>15mm) was used |
| Diffusion-weighted imaging                     | Suggested, size was not used | Dominant for the peripheral zone, size (>15mm) was used |
| Multiparametric sectors                        | Primary and 5-point scale | Secondary (positive and negative) |
| Considerations for decision making             | b-value images (b value <1400) | b-value images (b value >1400) |

PI-RADS v1: Prostate Imaging Reporting and Data System version 1.
PI-RADS v2: Prostate Imaging Reporting and Data System version 2.

Table 2

| Observation          | Conclusion                |
|----------------------|---------------------------|
| Smooth surface       | Normal                    |
| Larger size          | Enlarged prostate         |
| Hard and lumpy       | Prostate cancer           |

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an endorectal coil (IN2-989603212881, Imaging Solutions). The images of mpMRI were subjected to evaluation by a team of experts (authors and urologist(s); with minimum three years of experience of diagnostic radiology)[20]. Scoring was performed as per PI-RADS v1/v2 guidelines in axial T1W/T2W images, the sagittal T2W images, and diffusion-weighted images[21].

### 2.6. Biopsies

Patients whom lesions had identified on mpMRI subjected to MRI/US fusion-guided biopsy (UroNav, Invivo) by a physician followed an inserting of US transducer (CeramTec Suzhou Ltd., Suzhou, PR China) into rectum of men and transrectal US-guided biopsy (SonoScape, GE Healthcare) in the same session by the other physician who was blind for the MRI lesion(s) locations.[22] Men who had faced >1 MRI/US fusion-guided biopsy sessions, the results of the first successful biopsy session was considered in this analysis. One physician had performed all MRI/US fusion-guided biopsies and the other physician (one person) had performed all transrectal US-guided biopsies. Total of 12 cores (7 from the peripheral zone, 3 from the transitional zone, and 2 from anterior zone) had been taken by US-guided biopsies and 9 cores (5 from the peripheral zone, 3 from the transitional zone, and 1 from anterior zone) had been taken by MRI/US fusion-guided biopsies.

| Characteristics | Data |
|-----------------|------|
| Sample size     | 998  |
| Age, y          | 59.12± 9.15 |
| PSA, ng/mL      | 4–10, 10.1–20 |
| Prostate volume, cm³ | Low: 58.52± 7.13, Moderate: 610, High: 201 |
| No. of lesions  | 1: 558, 2: 246, 3: 194 |
| Time from mpMRI, days | MRI/US fusion-guided biopsies: 41± 3, US-guided biopsies: 42± 1 |
| Complains       | A sudden urge to urinate: 547, Dribbling urine after the finish of urinating: 645, Difficulties in starting to urinating: 445, Difficulties emptying urinary bladder: 812, A weak flow when urinating: 902, A feeling that urinary bladder has not emptied properly: 889, Pelvic pain: 245, Hip pain: 345, Back pain: 412, Erectile dysfunction: 249, Weight loss: 137 |

Constant data were represented as a number (percentage) and continuous data were represented as mean±SD. mpMRI= multiparametric magnetic resonance image, PSA= prostate-specific antigen, US= ultrasound.

### 2.7. Beneficial score analysis

Benefits of a diagnostic test were evaluated by decision curve analysis by authors. The net benefit was calculated as per Equation 1.[23]

\[
\text{Net benefit} = \frac{\text{Accurate cancer present}}{\text{Sample size}} - \left( \frac{\text{False positive}}{\text{Sample size}} \times \frac{\text{Threshold probability}}{1 - \text{Threshold probability}} \right) \tag{1}
\]

If the interpreters disagreed, the final decision on prostatectomy had taken by urologist oneself.

### 2.8. Radical prostatectomy

A team of experts was concluded for surgeries in men who had diagnosed as prostate cancer (either of biopsies) by a urologist who had at least 3 years of experience (single surgeon approach). Small incisions (2–3 cm) had made in the belly of patients. A urologist had controlled a robotic system of surgical tools from outside the body. A system lets the surgeon used natural wrist movements and a 3-dimensional screen during surgery. The prostate and some tissue (lymph nodes) around it, including the seminal vesicles, were removed.[24] The samples were collected from the resected prostate.

### 2.9. Whole-mount pathology

Radical prostatectomy specimens were fixed in 40% buffered formalin overnight at room temperature. Cut-off the prostate was made and mounted on a slide (3-mm thickness) with formalin, stained with hematoxylin and eosin, and subjected to detect the risk of cancer (as per TNM staging). One genitourinary
pathologist (blinded for the core samples) reviewed all pathologic specimens. The sensitivity and accuracy of biopsy methods were calculated with respect to whole-mounted pathology by authors and urologist(s) (images and specimens were compared).

A specimen of biopsies and whole-mount pathology were evaluated having cancer “yes or no” per lesion only.

A tumor was detected by biopsies but whole-mount pathology examination was failed in the detection of the tumor was considered as a false positive. No prostate cancer was detected by biopsies, but the case clearly had prostate cancer biochemically and developed mpMRI so a prostate was removed and postoperatively tumor was showed in whole-mount pathology examination (Fig. 2) was considered as a false-negative.

2.10. Cost of diagnosis

Cost for MRI/US fusion-guided biopsy and US-guided biopsy for each individual was reported by calculating the cost of the hospital (stay and operating room charges), pathology (whole-mount pathology), consultant charges (radiologist, urologist, expert team charges), imaging (MRI and US), and pharmacy.\textsuperscript{25}

2.11. Statistical analysis

InStat (GraphPad, USA) was used for statistical analysis purposes. $\chi^2$ test for independence was used for comparisons of biopsies results.\textsuperscript{51} DeLong test was used to compare the area under the curves (AUCs) for different biopsies. Two-tailed paired $t$ test following Tukey-Kramer Multiple comparisons tests (considering critical value \(q\) >8.243) was used for cost analysis of biopsy methods.\textsuperscript{26} Spearman Rank Correlation (considering Spearman Rank Correlation constant \(r\) values 0.7213 to 0.73 as significant) was performed between the biopsy results and the subtype of prostate cancer (low, intermediate, high risk). The

![Figure 1](image1.png)  
**Figure 1.** START Flow diagram of the study. Radical prostatectomy was performed at 44 ± 4 days after mpMRI by a urologist (single surgeon approach). mpMRI = multiparametric magnetic resonance imaging, MRI = magnetic resonance imaging, PSA = prostate-specific antigen, US = ultrasound. Level of Evidence: I.

![Figure 2](image2.png)  
**Figure 2.** Whole-mount prostate tissue section of men (age 62 years, stained with hematoxylin and eosin). Red arrows indicated the tumor lesion.
results were considered significant at 99% of confidence level. Intention-to-treat analysis method was adopted.

3. Results

With respect to whole-mounted pathology, a US-guided biopsy had 0.973 sensitivity and 0.837 accuracies. Whereas MRI/US fusion-guided biopsy had 0.983 sensitivity and 0.91 accuracies. Moreover, combined data of both biopsies had 0.973 sensitivity and 0.917 accuracies (Table 5, whole-mounted pathology was considered as “criterion standard”). The area under the curve values for detection of prostate cancer was in the order of MRI/US fusion-guided biopsy procedure < US-guided biopsy procedure < combined biopsies procedure < whole-mounted pathologies.

After MRI/US fusion-guided and US-guided biopsies, a panel of surgeons was concluded for radical prostatectomy in 578 men (at 44±4 days after mpMRI). MRI/US fusion-guided biopsy (P=.163) and data of combined biopsies (P=.182) had the same specificity to whole-mount pathology. However, a US-guided biopsy had not the same specificity to whole-mount pathology (P=.0003, Table 6). The MRI/US fusion-guided biopsy results of the subtype of prostate cancer were correlated with whole-mounted pathology results (r=0.7296). However, the subtype of prostate cancer results of US-guided biopsies was not correlated with whole-mounted pathology results (r=0.7104). Decision-making zone for radical prostatectomy of different biopsies was in the order of combined data of both biopsies > MRI/US fusion-guided biopsy > US-guided biopsy (Fig. 3; Tables 7 and 8).

MRI/US fusion-guided biopsy was expensive for patients than US-guided biopsy (¥6474.83 ± ¥286.15 vs. ¥2339.65 ± ¥75.87, P<.0001, q=757.8, Fig. 4).

4. Discussion

MRI/US fusion-guided biopsy had high sensitivity, accuracy, specificity, and AUC than a US-guided biopsy and no significant difference for treatment zone between combined biopsies and targeted biopsy methods. Moreover, MRI/US fusion-guided biopsies had detected more numbers of high-risk prostate cancer (Gleason score ≥7, tumor volume >0.5 mm) than US-guided biopsies (24 vs. 18). These results were in line with available studies.[5,6,27] In respect to the results of the study, a targeted biopsy was a good option for diagnosis of prostate cancer in Chinese men.

Cost of MRI/US fusion-guided biopsy was higher than US-guided biopsy for any individual. These results were in line with available studies.[5,6,23] However, after proper diagnosis, the cost of overdiagnosis and overtreatment, which is a major drawback for any condition of prostate cancer in situ could be

### Table 5

Comparisons of diagnostic parameters of different biopsy methods.

| Parameters                  | Biopsy methods               |
|-----------------------------|------------------------------|
|                             | MRI/US fusion-guided | US-guided | Combined | Whole mount pathology |
| Sample size                 | 998                        | 998       | 998      | 578                   |
| Accurate cancer present     | 499 (50)                  | 429 (43)  | 502 (50) | 499 (86)              |
| Accurate cancer absent      | 409 (41)                  | 406 (40)  | 413 (42) | 79 (14)               |
| False positive              | 15 (2)                    | 58 (6)    | 12 (1)   | 0 (0)                 |
| False negative              | 58 (6)                    | 78 (8)    | 54 (5)   | 0 (0)                 |
| Inconclusive results        | 17 (2)                    | 27 (3)    | 17 (2)   | 0 (0)                 |
| The area under the curve    | 0.58                      | 0.66      | 0.71     | 0.84                  |

One physician had performed all MRI/US fusion-guided biopsies and the other physician (1 person) had performed all transrectal US-guided biopsies. Data were represented as a number (percentage). MRI = magnetic resonance image, US = ultrasound.

### Table 6

Results of biopsy methods regarding radical prostatectomy.

| Parameters                  | Biopsy methods               |
|-----------------------------|------------------------------|
|                             | Whole-mount pathology | MRI/US fusion-guided | US-guided | Combined |
| No. of biopsies (sample size) | 578                        | 998                 | 998       | 998       |
| Core                        | 3                           | 5                   | 3         | 1         | 7         | 3         | 2         | 12        | 6         | 3         |
| The number of positive biopsy cores to define tumor | ≥1                  | ≥1                  | ≥1        | ≥1        |
| Condition                   | <=6                         | 0                   | 79 (14)   | 424 (43)  | 464 (46)  | 392 (39)  |
| Low-risk cancer             | 6                           | <0.1                | 181 (32)  | 210 (21)  | 245 (25)  | 245 (25)  |
| Intermediate-risk cancer    | 3+4 (Low volume)            | 0.1–0.4             | 198 (33)  | 220 (22)  | 187 (19)  | 220 (22)  |
| High-risk cancer            | >3+4 (High volume)          | 0.4–0.5             | 99 (17)   | 120 (12)  | 84 (8)    | 120 (12)  |

Data were represented as number (percentage). Level of evidence: I. Radical prostatectomy was performed at 44±4 days after mpMRI by a urologist (single-surgeon approach). The P value for χ² test for independence respect to whole-mount pathology for MRI/US fusion-guided biopsy, US-guided biopsy, and combined biopsies were 0.165, 0.0003, and 0.182, respectively. MRI = magnetic resonance imaging, US = ultrasound.
overcome. In respect to the value factor of biopsies, the further trial is required to justify the expenditure of MRI/US fusion-guided biopsy, considering total charges from mpMRI to radical prostatectomy including hospital stay and medicines for MRI/US fusion-guided biopsy and US-guided biopsy for the Chinese men. A human study with level I (Table 9) of evidence that had followed START checklist revealed that targeted biopsy was successful in detection of high-risk prostate cancer and standard biopsy fusion with targeted biopsy was successful in detection of low-risk prostate cancer. This is because of the higher sensitivity of targeted biopsy.\(^5\) However, one additional targeted biopsy after standard biopsy may increase chances of metastasizing.\(^5\) With respect to consideration of risk factor, a prospective cohort study advised urologist to perform targeted biopsy only in case of detection of prostate cancer.

The rate of false positive seems very high. Inflammation may interfere with interpretation of MRI by ghost prostate cancer. There are several reasons for false-positive prostate cancer as radiology read, importing/segmentation of images, MRI quality, and biopsy accuracy. One of the strongest reason for false-positive lesion was inflammation of the prostate.\(^23\) A further trial is required to addressed false-positive results combined with novel inflammatory biomarkers.

In limitations of the study, for examples, the risk of the metastasize owing to biopsies and upgrade of the condition of prostate cancer during the course of treatment or follow-up was not evaluated. The possible explanation for not evaluating such parameters was that the study only enrolled patients who had subjected to radical prostatectomy (if prostate cancer was diagnosed) for a prospective cohort. The available studies have enrolled prostate cancer patients, may or may not be operated during the study. Therefore, these studies have evaluated the upgrade of the condition of cancer during follow-up.\(^5,27\) The lack of history of a prostate cancer diagnosis, mpMRI that had revealed no lesion in the prostate of patients were not included in the cohort; however, such patients might have an intermediate or low risk of prostate cancer.\(^23,59\) The image analysis was performed by authors only; the expert opinions over images by the external examiners had not taken. The study was failed in a finding of the reason behind the diagnosis that why cancer had detected in MRI/US-fusion guided biopsy alone or US-guided biopsy alone. The study was not concentrated on apparent diffusion coefficient (ADC) related to prostate cancers clinical risk. The possible reason is that ADC value used for evaluation of efficacies of chemotherapies not much effective in diagnosis and prognosis of cancer. Large time for study enrollment. Only 2% to 4% of the whole cohort were high-risk disease (Gleason >3+4/4+3), these findings were contrasted to literature suggested: the Asian population had more high-risk prostate cancer compared to the white population! The possible justification for the same is at the time of enrollment, all men might be in a benign stage of prostate cancer.

| Table 7 | True-positive and false-positive rates of biopsies methods. |
|---------|----------------------------------------------------------|
| Biopsies methods | MRI/US fusion-guided | US-guided | Combined |
| True positive rate | 0.5 | 0.43 | 0.50 |
| False positive rate | 0.02 | 0.06 | 0.01 |

MRI = magnetic resonance imaging, US = ultrasound.

Figure 3. Decision curve for radical prostatectomy. One physician had performed all MRI/US fusion-guided biopsies and the other physician (one person) had performed all transrectal US-guided biopsies. Level of Evidence: I. Radical prostatectomy was performed at 44 ± 4 days after multiparametric magnetic resonance imaging by a urologist (single surgeon approach). MRI = magnetic resonance imaging, US = ultrasound.

| Table 8 | Net benefits of biopsies methods. |
|---------|----------------------------------|
| Threshold probability | Weighting factor | MRI/US fusion-guided | US-guided | Combined |
| 0 | 0 | 0.5 | 0.43 | 0.50 |
| 0.1 | 0.11 | 0.5 | 0.42 | 0.50 |
| 0.2 | 0.25 | 0.5 | 0.42 | 0.50 |
| 0.3 | 0.43 | 0.49 | 0.41 | 0.50 |
| 0.4 | 0.67 | 0.49 | 0.40 | 0.50 |
| 0.5 | 1 | 0.49 | 0.37 | 0.49 |
| 0.6 | 1.5 | 0.48 | 0.34 | 0.49 |
| 0.7 | 2.33 | 0.465 | 0.29 | 0.48 |
| 0.8 | 4 | 0.44 | 0.2 | 0.46 |
| 0.9 | 9 | 0.37 | 0.09 | 0.4 |
| 0.99 | 99 | −0.99 | −5.31 | −0.69 |

MRI = magnetic resonance imaging, US = ultrasound.

\(*\) Threshold probability.

\(\dagger\) Estimated probability.
cancer. The other controversial matter that the study began in 2004 following START criteria. The possible justification for the same is Chinese Department of Health is following START criteria since 1995.

5. Conclusion
A prospective cohort study with level I of evidence concluded that the targeted fusion-guided biopsy had high sensitivity, accuracy, specificity, the area under the curve, and ability to detect the significant prostate cancer than standard biopsy. The study is recommended magnetic resonance/ultrasound fusion-guided biopsy only to a urologist before the decision of prostatectomy.

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Author contributions
All authors had read and approved a submission for publication. Guangbin Zhu had performed conceptualization, investigation, and data curation. Quan Wang had performed formal analysis, visualization, funding acquisition, and written the manuscript for the intellectual content. All authors were agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 9

| Level | Prognosis Study |
|-------|-----------------|
| I     | Prospective cohort study, power calculation, and all patients enrolled at a same time point in the disease |
| II    | Prospective cohort study, power calculation, and patients enrolled at different stages of the disease |
| III   | Systematic review and meta-analysis on randomized clinical studies |
| IV    | A case study with the power calculation |
| V     | Case study without a comparison |
| VI    | Expert opinion |

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