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The appropriate number of preoperative core needle biopsy specimens for analysis in breast cancer

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Abstract

Ultrasound (US)-guided core needle biopsy (CNB) has been recognized as a crucial diagnostic tool for breast cancer. However, there is a lack of guidance for hospitals that are not equipped with adjunctive US. The aim of this study was to assess the sensitivity, specificity, and experience of freehanded CNB in the outpatient department, and to determine the minimum number of tissue strips required to obtain concordance for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), and tumor grade with the excised specimen.

A prospective study was performed on 95 patients undergoing CNB and subsequent surgical procedures. The reliability of immunohistochemical assessments of the pathological type, tumor grade, ER, PR, and HER2 status in CNBs was compared with that of surgical specimens. Concordance between the CNBs and surgical samples was estimated as a percentage agreement, and analyzed using the chi-square test. A $P < .05$ was considered significant.

The concordance rates of ER, PR, and HER2 status and tumor grade status between CNBs and surgically excised specimens were 97.9%, 91.6%, 82.1%, and 84.2%, respectively. The reliability of taking 2 tissue strips was similar to that of taking six tissue strips in distinguishing malignancy from benignancy, and determining the pathological type without the aid of US. Four tissue strips obtained by CNB showed good accuracy comparable to those obtained by surgical specimens in assessing ER, PR, and HER2 status and tumor grade.

Two tissue strips obtained by CNB showed good accuracy in differentiating malignancy from benignancy, while at least 4 strips are recommended to obtain overall conformity of pathological biomarkers.

Abbreviations: CNB = core needle biopsy, ER = estrogen receptor, FISH = fluorescence in situ hybridization, HER2 = human epidermal growth factor receptor-2, IHC = immunohistochemistry, PR = progesterone receptor, US = ultrasound.

Keywords: breast neoplasms, core needle biopsy, immunohistochemistry

1. Introduction

Breast cancer is a leading cause of death in women worldwide. In China, it is 1 of the 5 most commonly diagnosed cancers in women, and about 268,600 new breast cancer cases were predicted in 2015.[1] The key point to tailor individualized treatment is to confirm pathological biomarkers of suspicious lesions, such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and

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All data generated and analyzed during this study are included in this published article (and its Supplementary Information files), and are available from the corresponding author upon reasonable request.

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ki67. These markers help to classify subtypes of breast cancer, predict response to treatment and long-term prognosis. However, there is no consensus on the best technique for histological sampling. Fine needle aspiration cytology has been widely used initially, as it is minimally invasive and well-tolerated. However, its applications are also restricted by its shortcomings, including insufficient samplings, difficulty in discriminating carcinoma in situ from invasive carcinoma as the material was aspirated, experience requirements for both the operator and the pathologist, and the low rate of definitive diagnoses. In light of this, core needle biopsy (CNB) has been established as a valid tool to assess radiologically and clinically-detected breast lesions.[2] CNB provides larger samples[3] with preserved architecture. The concordance rate of CNBs and surgical specimens in distinguishing benign from malignant lesions[4] ranges from 96% to 100%.[2] In addition, CNB provides predictive information such as tumor grade, ER, PR, and HER2 status,[5,6] which is useful for surgery planning and adjuvant/neoadjuvant treatment.

The accuracy of CNBs is known to increase when a higher number of CNB tissue strips are collected. One of the concerns is the dissemination of tumor cells into the adjacent tissue through the transgression and withdrawal of the biopsy needle,[7,8] but this is extremely rare and has little direct effect on patient outcomes.[9–11] Previous studies[4,12–14] have shown that 4 to 5 specimens are required to obtain a definitive diagnosis, but few studies have focused on the optimal number of biopsy cores required to obtain a reliable pathological diagnosis. In addition, achieving high accuracy usually requires the assistance of ultrasonography. However, not all hospitals are equipped to perform this technique, and additionally, there in an increase in cost and delay in referral to the radiological center with this technique.

Therefore, we conducted a prospective study to assess the number of biopsy strips collected by freehand CNB that are required to obtain a result consistent with the postoperative pathological diagnosis, in an outpatient department. Tumor grade and ER, PR, and HER2 status were evaluated, as they are critical parameters to guide the selection of neoadjuvant therapy and postoperative care.

2. Methods

2.1. Patients and samples

Breast cancer patients attending the Department of Breast and Thyroid Surgery, Jinan Central Hospital (affiliated with Shandong University) from 2013 to 2015 were considered for the prospective study. A total of 95 patients who underwent CNB and subsequent surgical excision were recruited in this prospective study. Patients who had previously received neoadjuvant chemotherapy and/or endocrine therapy were excluded due to potential treatment effects on the receptor status. Patients who had their histology processed in other hospitals or those with an equivocal or unavailable receptor status were also excluded. The period between CNB and the final surgery ranged from 2 to 3 days. The study (Register No.: KYLL-2016–353) was approved by the Ethics Committee of Scientific Research of Shandong University Qilu Hospital, and was conducted in accordance with the principles of the Declaration of Helsinki. Oral and written informed consent for participation in the study was obtained from all participants.

2.2. Procedure

Biopsies were performed by an experienced surgeon using a 14-gauge needle and a spring-loaded biopsy gun (Bard Magnum). Three to 6 cores containing specimens from different parts of each lesion were obtained without the aid of US. Each core was labeled with the pass number in accordance with the order of the puncture. All specimens were formalin-fixed and paraffin-embedded, and the tissue sections were stained with hematoxylin and eosin. The samples were assessed by an experienced pathologist who was blinded to the identity of the final surgical samples, to exclude potential bias.

2.3. ER, PR, and HER2 determination

The status of the ER, PR, and HER2 biomarkers was assessed using standard immunohistochemical methods in paraffin-embedded, formation-fixed tissue stained with hematoxylin and eosin, and with antibodies to the ER, PR, and HER2 proteins (Dako, Glostrup, Denmark). ER positivity (ER+) and PR positivity (PR+) were defined as the presence of more than 1% positively stained invasive tumor cells with nuclear staining. The level of HER2 expression was scored according to the American Society of clinical Oncology/College of American Pathologists 2013 guidelines: score 0 for no staining or membrane staining in $<10\%$ of the tumor cells; score 1 + for faint/barely perceptible partial membrane staining in $\geq 10\%$ of the tumor cells; score 2 + for weak to moderate complete membrane staining in $\geq 10\%$ of the tumor cells; and score 3 + for strong complete membrane staining in $\geq 10\%$ of the tumor cells. HER2 status was categorized as negative (0 or 1 +), inconclusive (2 +), or positive (3 +) according to the membrane staining. Immunohistochemistry (IHC) of the surgical specimens was defined as the gold standard, and CNB was defined as the test technique.

2.4. Statistical analysis

Statistical calculations were performed using the Statistical Package for Social Sciences (SPSS) version 19.0 software. The concordance, sensitivity, and specificity were calculated using CNBs as the test assessment and the surgical specimens as the gold standard; the Fisher's exact test and the chi-square test were used for performing comparisons. The exact 95% confidence intervals were calculated based on the binomial distribution. A 2-tailed P value $<.05$ was considered statistically significant. The kappa coefficient showed the proportion of agreement.

3. Results

Ninety-five patients meeting the inclusion criteria were enrolled in this study. All patients were diagnosed with malignancies according to the pathology results of the surgical specimens. Except for 1 missed case, all the other patients were also diagnosed as malignant according to the analysis of CNBs. The clinicopathological characteristics are summarized in Table 1. The patients' mean age was 52 years (range: 34 to 80 years). The mean tumor diameter was 3.3 cm (range: 1 to 10 cm). One patient presented with T0 stage, 22 patients presented with T1 stage, 59 patients presented with T2 stage, 10 patients presented with T3 stage, and 3 patients presented with T4 stage disease. Invasive ductal carcinoma was the most common type of breast cancer (97.9%).

Table 1

Clinicopathological characteristics of the patients.

	n
Mean Age (yr) (mean ± SD)	52 (34–80)
Pathological T Stage	
T0	1
T1	22
T2	59
T3	10
T4	3
Histology	
invasive lobular carcinoma	1
ductal carcinoma in situ	1
invasive ductal carcinoma	93
ER status	
Negative	30
Positive	64
PR status	
Negative	47
positive	47
HER2 status	
Score0/1+	39
Score2+	34
Score3+	21

ER = estrogen receptor, HER2 = human epidermal growth factor receptor-2, PR = progesterone receptor, SD = standard deviation.

3.1. Hormonal status, HER2 status and tumor grade concordance

Among the CNB specimens, the ER status was negative in 31 and positive in 63 specimens. Among the surgical specimens, 30 cases were negative and 64 cases were positive for ER. The concordance rate of ER assessment between the CNB and surgical specimens was 98.9% (kappa value: .975; $P < .001$), with a discrepancy in 1 case (Table 2).

Among the CNB specimens, the PR status was negative in 52 and positive in 42 specimens. Among the surgical specimens, 47 cases were negative and 47 cases were positive for PR. The concordance rate of PR assessment between the CNB and surgical specimens was 92.6% (kappa value: 0.851; $P < .001$), with a discrepancy in 7 cases (Table 2). Out of the 7 discrepancies, six positive specimens certified by postoperative histology were underestimated as negative in the CNB analysis, and only 1 negative specimen was overestimated as positive by the CNB analysis.

Table 2

Concordance between CNB and surgical specimen for ER and PR status.

	Surgical specimen				
Biopsy	Negative/ low	Positive/ high	Concordance rate, %	Kappa	*P* value
ER status					
Negative	30	1	98.9	0.975	$P < .001$
Positive	0	63			
PR status					
Negative	46	6	92.6	0.851	$P < .001$
Positive	1	41			

CNB = core needle biopsy, ER = estrogen receptor, PR = progesterone receptor.

Table 3

Concordance between CNB and surgical specimen for HER2 status.

	Surgical specimen					
CNB	Score1+	Score2+	Score3+	concordance rate, %	Kappa	*P* value
Score0/1+	37	5	1	83	0.737	$P < .001$
Score2+	2	24	3			
Score3+	0	5	17			

CNB = core needle biopsy, HER2 = human epidermal growth factor receptor-2.

Among the CNB samples, the HER2 scores were as follows: score 0/1+, 43 cases; score 2+, 29 cases; and score 3+, 22 cases. Among the surgical specimens, the HER2 scores were as follows: score 0/1+, 39 cases; score 2+, 34 cases; and score 3+, 21 cases. The concordance rate of HER2 status between the CNB and surgical specimens was 83% (kappa value: 0.737; $P < .001$), with a discrepancy in 16 cases (Table 3).

The concordance rate of tumor grade between the CNB and surgical specimens was 84.2%. Consistent with previous studies,[15] our results showed that the tumor grade was more likely to be underestimated by preoperative CNBs. Nine cases were underestimated and six were overestimated when 5 and 6 cores were collected, respectively. Detailed information is shown in Table 4.

3.2. The optimal number of CNB specimens to detect malignancy and achieve overall concordance

It is not difficult to understand that the diagnostic accuracy of CNB increases with an increase in the number (one core, 77.9%; 2 cores, 93.7%, 3 cores, 96.8%; four cores, 98.9%; five cores, 98.9%; and six cores, 98.9%) of the CNB specimens collected (Table 5, Fig. 1). The above results demonstrated good concordance between the CNB and surgical specimens in evaluating IHC-assessed ER, PR, and HER2 status, and tumor grade, based on CNB with six passes, in each patient. There is a lack of studies assessing the minimal and optimal number of CNB specimens required to obtain a reliable result. Thus, we next sought to determine the minimum number of CNB samples needed to achieve the best concordance with surgical specimens with reference to detecting malignancy and gaining overall concordance. We performed a chi-square test to investigate the difference between the contiguous numbers of core biopsies in the diagnosis of malignancy, ER, PR, and HER2 status, and tumor grade. We observed that for the diagnosis of a malignancy, 2 cores are significantly more reliable than 1 ($P < .001$), while there is no significant increase in reliability upon further increasing the number of tissue strips ($P > .05$). For this reason, at least 2

Table 4

Discordance in the tumor grade between CNBs and excised specimens.

	First	Second	Third	Fourth	Fifth	Sixth
Underestimated	21	13	12	10	9	9
Overestimated	14	8	6	6	6	6
Total	35	21	18	16	15	15

CNB = core needle biopsy.

Table 5

Concordance (positive and negative) between each pass of the CNB and surgical specimen for histological and biomarker status.

	Core biopsy (n = 95)						
	First	Second	Third	Fourth	Fifth	Sixth	Surgical specimen (n = 95)
Malignancy found	74	89	92	94	94	94	95
Tumor size							
TIS	1	1	1	1	1	1	1
T1	3	7	11	13	15	16	22
T2	15	18	29	30	35	36	59
T3	2	5	5	5	5	5	10
T4	1	2	2	2	2	2	3
Pathological type	62	84	89	91	91	91	95
ER	70	85	90	92	93	93	95
PR	62	78	83	86	86	87	95
Her2	43	53	60	70	76	78	95
Grade	60	74	77	79	80	80	95
Overall concordance	24	34	44	52	56	59	95

CNB = core needle biopsy, ER = estrogen receptor, HER2 = human epidermal growth factor receptor-2, PR = progesterone receptor.

specimens are required to confirm the diagnosis of malignancy. In terms of overall concordance (ER, PR, and HER2 status, and tumor grade), little difference was observed between obtaining 4 and 5 cores ($P = .558$), 5 and 6 cores ($P = .656$), and between obtaining 4 and 6 cores ($P = .656$). Detailed data explaining how the core numbers affected the concordance between surgical specimens and CNBs are listed in Supplementary Table 1, http://links.lww.com/MD2/A44. A comparison of immunohistochemical staining for the hormonal receptors and HER2 between CNBs and surgical specimens is shown in Figure 2.

4. Discussion

The demand for an accurate preoperative assessment of biomarker status has been growing in recent years. The determination of ER and PR[16] status plays a particularly important role in predicting patients' responses to endocrine therapy and long-term outcomes, and the HER2 status helps to identify candidates for trastuzumab therapy.[5] Both gene expression assays and molecular subtype classification are valid tools to help stratify patients who may benefit from neoadjuvant chemotherapy or more conservative surgical procedures, and provide potential candidate targets for new therapies; pertuzumab and everlorimus are examples of such therapies. Since gene expression assays are not routinely available, IHC-based CNB can provide a reliable diagnosis,[17–23] supply histological information, and assist in individual treatment planning.[24]

However, most studies have reported its application with the aid of ultrasonography guidance, which is not available in many developing countries. Here, we report our experience and accuracy of freehand CNB in comparison with the results of postoperative pathology.

The diagnosis made based on CNB was concordant with that made based on the surgical specimens in 98.9% of patients, which is consistent with the results of previous studies (92%-100%).[5] A concordance between the assessment of ER and PR status in the CNB and surgical specimens was found in 93 (98.9%) and 87 (92.6%) cases, respectively. PR status in CNB should be treated cautiously because of the reported heterogeneous distribution of PR within the tumor.[25] Out of the discrepancies found in ER and PR determination, most were underestimated by CNB, which may be attributed to sampling error and tumor heterogeneity (without the aid of ultrasonography, the core biopsies were not able to sample the worst area to reflect the whole tumor status).[6] While under the ultrasonography guidance, there is a higher tendency of upscoring in CNB than in surgical specimens.[26] This is probably related to the freshness of the histopathological specimens, shorter interval from sampling to fixation, and better fixation in formalin, leading to better preservation and exposure of the antigen.[27] Therefore, some studies have suggested that the hormone receptor status in CNB specimens is more reliable than that in surgical specimens [26,28] and both surgical specimens and CNBs should be considered when planning therapeutic strategies. Other studies recommend repeating these assessments in CNB, especially when the results of surgical specimens are negative; this ensures that eligible patients do no miss out on endocrine treatment.[25]

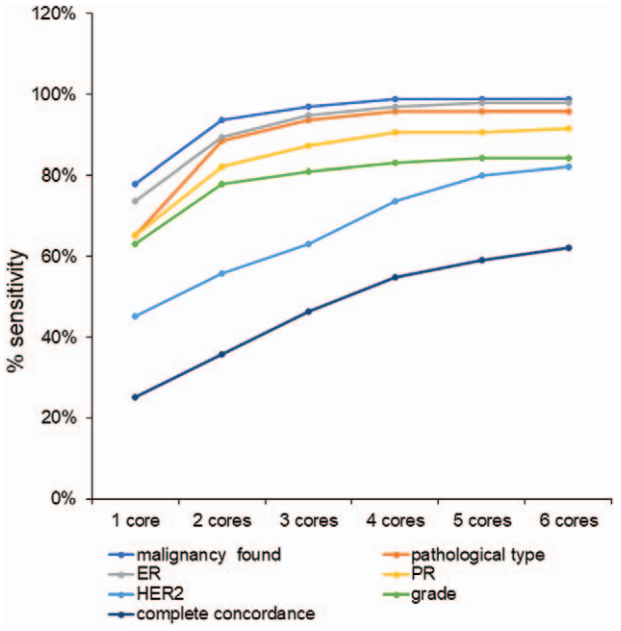

Figure 1. Cumulative sensitivity of the core needle biopsies (CNBs).

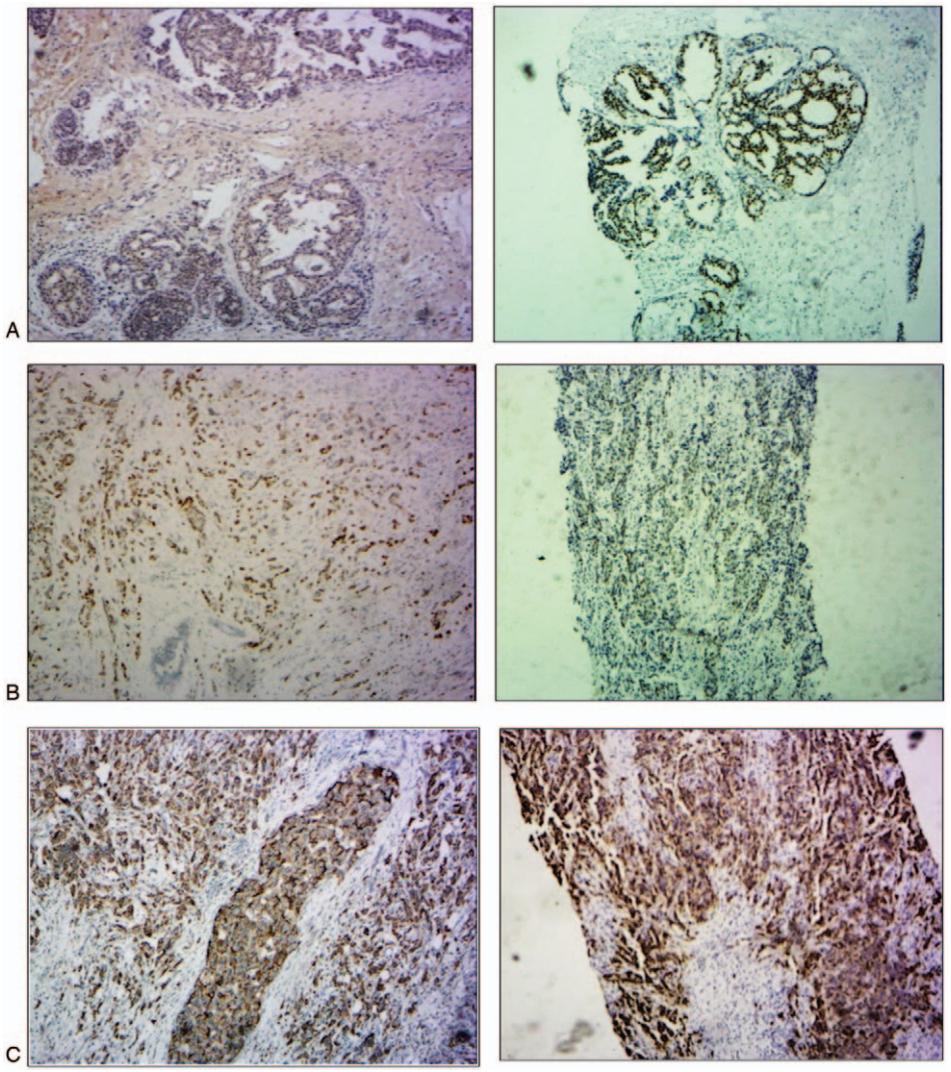

Figure 2. Comparison of the immunohistochemical staining between the CNBs and surgical specimens. A. Estrogen receptor, (ER) staining (left, immunohistochemistry (IHC) staining of surgical specimens; right, IHC staining of 2 passes of CNBs showing concordance). B. Progesterone receptor (PR) staining (left, IHC staining of surgical specimens; right, IHC staining of four passes of CNB showing concordance). C. Human epidermal growth factor receptor-2 (HER2) staining (left, IHC staining of surgical specimens; right, IHC staining of one pass of CNB showing concordance).

HER2 amplification is related to worse outcomes, which is also an indicator for trastuzumab treatment. The concordance rate of HER2 status was only 83%, as concordance was found in 78 cases; this was much lower than that for ER and PR in the corresponding cores, consequently affecting the therapeutic strategy. Based on our results, the sensitivity of inconclusive samples (2 +) was obviously lower than that of the negative (0 or 1 +) and positive (3 +) samples (68.6% vs. 94.9% and 80.9%). One study implied that the sensitivity of CNB is influenced by the definition of HER2 positivity. The sensitivity increases from 80% to 97.7% after altering the definition of HER2 positivity from IHC 2+ or 3+ or FISH (fluorescence in situ hybridization) +, to IHC 3+ or FISH+. Borderline tumor properties may contribute more to the differences in HER2 determination. The aim of this study was to compare IHC-based concordance between the CNB and surgical specimens. We did not include FISH as an adjunctive method to discriminate HER2 positivity from HER2 negativity. The relatively small sample size was also responsible for the differences.

Another aspect that needs special attention is the false-negative rate of CNB,[20,29–33] which can be attributed primarily to histological interpretation.[34] In terms of the comparison of pathological type in our study, four (4.2%) cases of infiltrating ductal carcinoma were underestimated as ductal carcinoma in situ by CNB. The reported false negative rate of atypical ductal hyperplasia diagnosis ranges from 11.6% to 48%.[35–39] The reasons for the above can be separated into 2 aspects: one is the heterogeneity of carcinoma,[40] which is a mixture of intraductal and infiltrating components; the other is the use of either an inappropriate image guiding technique (stereotactic guidance instead of US), or an inappropriate biopsy system. In our study, this phenomenon is more likely to have been a result of the use of a freehand non-monitored CNB technique. Some studies suggested that additional core biopsies and other IHC markers (CD44, CK5/6, calponin, and p63[41–43]) are required.[44]

Although US-guided automated CNB has become a widely practiced method for investigating suspicious lesions,[45] few

studies have investigated the correlation between the number of CNBs and the accuracy of hormonal and biomarker status determination.[13–15,46] To our knowledge, no universal standard has been established regarding the number of specimens that are most effective and economical. Concerns over potential cell displacement and neoplastic seeding of the needle tract remain, although this phenomenon is rare and may not translate to neoplastic seeding. This is not only because the rates of cell displacement vary from 2 to 63%, but also because the reported local recurrence rate obtained by percutaneous biopsy is higher than that of surgical specimens (1.1%–3.7% vs 0.3%–2.1%), especially in triple negative breast cancer with invasive ductal carcinoma, or grade 3 breast cancer. Most studies reported that the mean number of CNB specimens obtained ranges from 3 to 5. Tamaki[47] reported that 4 cores obtained by CNB can achieve a diagnostic accuracy of 100% in terms of ER and PR. In our study, we propose that 2 strips are the minimum number of specimens required to determine a diagnosis of malignancy. In order to obtain a reliable diagnosis from the perspective of the concordance of parameters (ER, PR, and HER2 status and tumor grade) between CNBs and surgically excised specimens, at least 4 strips obtained by CNB are required.

5. Conclusions

In summary, the purpose of this study was to determine the minimum number of CNBs required to achieve concordance with the postoperative pathology. A minimum of 2 strips are required to determine a diagnosis of malignancy, while 4 or more specimens are recommended to achieve complete concordance of the pathology parameters (ER, PR, HER2 status, and tumor grade) between CNBs and surgically excised specimens.

Author contributions

TS performed the core needle biopsies, WG made the pathological diagnosis, and both TS and WG collected and interpreted the data. HZ performed the statistical analyses of the data, literature search, and wrote the paper. QY and TS conceived and designed the study, and reviewed and modified the paper. All authors have read and approved the final manuscript.
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