



The diagnostic value of two-dimensional ultrasound score, contrast-enhanced ultrasound score and ultrasound elastography score in prostate cancer

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Background: Prostate cancer (PCa) is a prevalent malignancy in men, with early diagnosis being crucial for treatment and prognosis. This study evaluates the diagnostic efficacy of two-dimensional ultrasound imaging score (2DUS), contrast-enhanced ultrasound score (CEUS), and ultrasound elastography score (UES) in PCa.

Methods: The PCa group consisted of patients diagnosed with primary PCa who underwent radical prostatectomy at the second hospital of Shanxi Medical University between January 2022 and December 2023. The benign lesion group consisted of patients diagnosed with benign prostatic hyperplasia (BPH) through prostate biopsy during the same period. We compared ultrasound scores at PCa and BPH patients using receiver operating characteristic (ROC) curve analysis. The study collected comprehensive patient data and analyzed variations in 2DUS, CEUS, and UES to identify relationships between preoperative ultrasound findings and the pathological states of PCa patients.

Results: PCa patients exhibited significantly higher ultrasound scores ($P < 0.001$). Optimal cut-offs were 2.110 for 2DUS, 3.235 for CEUS, and 2.790 for UES, yielding area under curves (AUC) of 0.789, 0.817, and 0.898. The combined score provided an AUC of 0.933, with 83.33% sensitivity and 90.70% specificity. In the form of that patients with tumor stage III–IV, pathological grade III, poor differentiation, and pelvic lymph node metastasis exhibited significantly higher scores in 2DUS, CEUS, and UES compared to those with tumor stages I–II, pathological grades I–II, moderate and high differentiation without pelvic lymph node metastasis, respectively ($P < 0.05$).

Conclusions: The combined use of 2DUS, CEUS, and UES scores is highly effective for early PCa detection, surpassing individual scores in accuracy, and is beneficial for staging and differentiation.

Keywords: Two-dimensional ultrasound score (2DUS); contrast-enhanced ultrasound score (CEUS); ultrasound elastography score (UES); diagnostic value; prostate cancer (PCa)

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Introduction

Prostate cancer (PCa) is a malignant neoplasm originating in the prostatic tissue and represents the most prevalent form of male malignancy, predominantly affecting elderly individuals (1). Globally, millions of new PCa cases are diagnosed annually, with considerable variation in prevalence across different regions (2). PCa ranks as the third leading cause of mortality among men due to cancer (3). A study has documented that PCa claimed over 400,000 lives in the European Union and its six most populous nations between 1989 and 2020 (4).

The onset of PCa is occult and lacks typical clinical manifestations, which is usually suspected during disease screening due to elevated prostate-specific antigen (PSA) levels, and further prostate biopsy is performed to confirm the diagnosis. PSA is organ-specific rather than cancer-specific, and may also be elevated in non-malignant diseases such as benign prostatic hypertrophy and prostatitis (5). Prostate biopsy for all patients with elevated PSA levels may lead to excessive examination or treatment. Negative biopsies may result in the underdiagnosis of certain PCa patients. Numerous clinical studies have demonstrated a high false negative rate associated with prostate system biopsy, even repeated biopsies fail to achieve satisfactory cancer detection rates (6), thereby increasing the likelihood of complications such as bleeding, infection, and acute

urinary retention.

The ultrasound examination offers distinct advantages in the diagnosis of PCa due to its convenience, real-time results, and free from radiation exposure. With continuous advancements in various ultrasound techniques in recent times, it has assumed a pivotal role in the early diagnosis and differential diagnosis of PCa (7,8). The two-dimensional ultrasound imaging (2DU) plays a pivotal role in ultrasound examination, and certain suspicious indicators observed in 2DU may imply the potential presence of malignancy in patients with prostate PCa. However, during this stage, most patients do not exhibit typical clinical manifestations, and relying solely on 2DU score (2DUS) cannot provide an accurate diagnosis. Therefore, a combination of serum specific markers and prostate biopsy results is imperative for diagnostic purposes (9,10). The detection and imaging efficiency of microvessels can be improved through Contrast-enhanced ultrasound (CEU), which involves intravenously administering an ultrasound contrast agent with a diameter comparable to that of red blood cells. This technique leverages the non-linear signals produced by backscattered contrast agent microbubbles, enabling real-time monitoring of blood perfusion in both lesions and surrounding tissues. The field of ultrasound elastography (UE) facilitates the detection of subtle modifications in the internal tissue stiffness, and it is primarily classified into two distinct methodologies: strain elastography (SE) and shear wave elastography (SWE). The implementation of this technique in liver, thyroid, breast, and other organs has produced encouraging outcomes (11-13), facilitating the visualization of rigid lesions that cannot be detected using traditional ultrasound examinations. Even though the utilization of UE in prostate examination is not currently widespread, it holds great potential to become an optimal diagnostic tool in the future.

The survival rate of PCa treated at an early stage surpasses that of other types of cancers, thus emphasizing the significance of early detection and prompt treatment as effective measures to reduce mortality. Due to the limitations of the current diagnostic methods, which exhibit unsatisfactory sensitivity and specificity, there exists a situation where clinically significant PCa cases are missed while benign lesions are excessively examined. Consequently, an increasing number of researchers are dedicated to exploring examination techniques that offer more ideal specificity, sensitivity, and minimal complications in order to enhance the diagnostic efficiency of PCa. The present study aimed to investigate the diagnostic and evaluative

Highlight box

Key findings

- The study reveals that combining two-dimensional ultrasound imaging score (2DUS), contrast-enhanced ultrasound score (CEUS), and ultrasound elastography score (UES) scores significantly improves the diagnostic accuracy for prostate cancer, with an area under the curve (AUC) of 0.933.

What is known and what is new?

- While early detection of prostate cancer is crucial, existing diagnostic methods have limitations.
- This study introduces a novel approach by combining three ultrasound scoring methods, providing a more precise tool for early detection.

What is the implication, and what should change now?

- The study's results suggest that integrating the combined ultrasound scores into clinical practice could enhance early detection and treatment planning for prostate cancer. Immediate actions include further validation of these methods and assessing their cost-effectiveness in various healthcare settings.

roles of 2DUS, CEUS score (CEUS), and UE score (UES) in patients with PCa and benign prostate lesions, aiming to provide simplified and reliable examination methods for follow-up screening of prostate lesions and treatment planning. We present this article in accordance with the STARD reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-137/rc>).

Methods

Study design

The PCa group consisted of patients diagnosed with primary PCa who underwent radical prostatectomy at The Second Hospital of Shanxi Medical University between January 2022 and December 2023. Criteria for inclusion included: (I) the pathological results were verified and confirmed by the pathology department, leading to the generation of a valid pathological report indicating primary PCa, T stage and regional lymph node metastasis were according to the 2017 American Joint Committee on Cancer (AJCC) staging system; (II) the digital rectal examination revealed the presence of a palpable prostatic nodule; (III) the patient was less than 85 years old; (IV) complete clinical characteristics acquisition. Exclusion criteria included: (I) combined with other primary malignant neoplastic diseases; (II) metastatic PCa; (III) history of surgery under general anesthesia within 3 months before enrollment; (IV) with long-term glucocorticoid and immunosuppressant therapy; (V) prior surgical intervention for prostate-related conditions. The benign lesion group consisted of patients diagnosed with benign prostatic hyperplasia through prostate biopsy in The Second Hospital of Shanxi Medical University during the same period. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the second hospital of Shanxi Medical University (No. KYLL20220301) and informed consent was taken from all the patients.

The clinicopathological data of all patients diagnosed with PCa were collected, and the differences in scores obtained from 2DU, CEU, and UE among patients with varying pathological characteristics were compared to elucidate the internal correlation between preoperative 2DUS, CEUS, UES and the pathological conditions of PCa patients.

Imaging examination and related scores obtained

2DU examination and related score obtained

All subjects underwent the standard examination procedure

of Siemens S2000 color Doppler ultrasound diagnostic instrument, 2DU scoring rules are as follows: the absence of blood flow signals within and surrounding the prostate nodules was zero; The presence of solid hypoechoic nodules with an irregular shape, indistinct margins, and internal vascularity were each assigned a score of 1. A score <3 indicated a benign condition, while a score ≥ 3 raised suspicion of malignancy.

UE examination and related score obtained

During real-time UE mode check, when 4–5 stable waveforms were observed in the strain curve on the ultrasonic instrument display, image freezing was initiated followed by quantitative analysis of the elastic image at the troughs. The elastic imaging score of suspected lesions can be divided into 1–5 points: A score of 1 was definitely benign (the whole gland shows uniform strain and appears uniform green). A score of 2 was probably benign (symmetrical, non-uniform strain across the gland with an uneven blue-green Mosaic image). A score of 3 was an uncertain nodule (there is no clear lesion in the gray-scale ultrasound image of the whole gland, and the elasticity was blue). A score of 4 may indicate a malignant nodule (the edge of the lesion was green and the center was blue). A score of 5 may indicate a malignant nodule (there was no strain in the whole lesion and its periphery, and the image was blue).

Transrectal CEU examination and related score obtained

The focus will be on the temporal changes in intensification intensity, intensification time, and other parameters in the designated key observation areas identified in the aforementioned 2DU and UE. After the above procedure, QLAB software was used to analyze the imaging data offline. CEU scoring criteria were as follows: (I) the ring enhancement was incomplete; (II) the lesions exhibited varied enhancement patterns; (III) the onset time of enhancement in nodules was delayed compared with that in parenchyma; (IV) the enhancement time of peripheral nodules was the same or later than that of parenchyma; (V) the peak intensity of peripheral nodules was low or equal-echo compared with parenchyma; (VI) the peak intensity inside the nodules was hypoechoic compared with the parenchyma. For each item, if positive, it would be counted as 1 point. The final score was the sum of the six indicators. The higher the score, the higher the likelihood of malignancy.

Table 1 Comparison of clinical data between the two groups

Variables	PCa group (n=278)	Benign lesion group (n=90)	t	P
Age (Years)	70.18±8.64	69.79±9.01	0.21	0.83
BMI (kg/m ²)	24.61±3.88	24.89±3.90	0.341	0.73
Prostate volume (mL)	57.28±9.17	57.16±9.45	0.061	0.95
2DUS	3.94±0.76	1.98±0.42	23.326	<0.001
CEUS	4.98±0.77	2.71±0.48	26.346	<0.001
UES	4.17±0.56	1.87±0.58	33.57	<0.001

Data are presented as mean ± standard deviation. PCa, prostate cancer; BMI, body mass index; 2DUS, two-dimensional ultrasound imaging score; CEUS, contrast-enhanced ultrasound score; UES, ultrasound elastography score.

Clinical data collection

The clinical data of all patients were collected, including age, body mass index (BMI), prostate volume, PSA level, maximum tumor diameter, tumor stage, pathological grade, differentiation degree and pelvic lymph node metastasis.

Statistical methods

SPSS 23.0 software was used to process the data obtained in this study, $P < 0.05$ was considered to be statistically significant. Counting data were expressed as cases and percentages, Chi-squared test was used for comparison between the two groups; Measurement data were expressed as mean ± standard deviation, the independent samples *t*-test was employed to compare the two groups. The receiver operating characteristic (ROC) curve was employed to assess the discriminative diagnostic efficacy of ultrasound score values in PCa analysis.

Results

Clinical characteristics

After excluding ineligible data samples, a total of 368 patients were enrolled in this study, comprising 278 patients in the PCa group and 90 patients in the benign lesion group. There were no significant differences in age, BMI, prostate volume between the two groups; the preoperative 2DUS, CEUS and UES of the PCa group were significantly higher than those of the benign lesion group (3.94±0.76 *vs.* 1.98±0.42, $P < 0.001$; 4.98±0.77 *vs.* 2.71±0.48, $P < 0.001$; 4.17±0.56 *vs.* 1.87±0.58, $P < 0.001$). The details can be found in *Table 1*.

Diagnostic value of ultrasound scores in PCa

The optimal cut-off value for diagnosing PCa using 2DUS was determined to be 2.110, with an area under the curve (AUC) of 0.789 (95% CI: 0.708–0.870). The sensitivity and specificity were found to be 73.77% and 61.11%, respectively. The optimal cut-off value for the CEUS in diagnosing PCa was determined to be 3.235, with an AUC of 0.817 (95% CI: 0.728–0.907). The corresponding sensitivity and specificity were found to be 69.77% and 69.23%, respectively. The optimal cut-off value for the UES in diagnosing PCa is determined to be 2.790, with an AUC of 0.898 (95% CI: 0.831–0.965). The corresponding sensitivity and specificity are calculated as 88.64% and 80.49%, respectively (*Figure 1*).

The AUC of 2DUS, CEUS and UES combined in the diagnosis of PCa was 0.933. The sensitivity and specificity are 83.33%, and 90.70% respectively. The combination of three ultrasound scores in the diagnosis of PCa is superior to any single ultrasound score ($P = 0.01$).

The correlation between ultrasound scores and clinicopathological characteristics

In the form of that patients with tumor stages III–IV, pathological grade III, poor differentiation, and pelvic lymph node metastasis exhibited significantly higher scores in 2DUS, CEUS, and UE compared to those with tumor stages I–II, pathological grades I–II, moderate and high differentiation without pelvic lymph node metastasis, respectively ($P < 0.05$) (*Table 2*).

Discussion

The increasing incidence of PCa and the limitations of

current examination methods necessitate the identification of a simple and efficient approach for early diagnosis, which undoubtedly serves as a crucial means to reduce mortality among PCa patients. The objective of this study is to investigate the diagnostic and clinical evaluation efficacy of

2DUS, CEUS, and UES in patients with PCa, aiming to address the limitations associated with current examination methods. The results showed that the combination of these three ultrasound scores exhibited superior sensitivity and specificity in diagnosing and evaluating PCa compared to any individual ultrasound score, indicating potential clinical value for assessing PCa differentiation and tumor staging.

The utilization of 2DU, CEU, and UE is prevalent in clinical settings. The 2DU is a routine clinical color ultrasound examination that provides comprehensive diagnostic information by displaying anatomical and blood flow data of the prostate (14,15). A substantial number of microvessels are generated in PCa, providing essential nutrients for tumor proliferation, metastasis, and invasion. The density of microvessels in PCa is significantly higher compared to that in normal prostate tissue, forming the basis for 2DUS examination.

The CEU examination can be utilized for the diagnosis of microcirculation perfusion in the lesion through contrast agent (16,17), which exhibits a high detection rate for clinically significant PCa and offers a more precise indication for subsequent treatment (18). Moreover, CEU parameters can serve as indicators of PCa angiogenesis, providing guidance for transrectal biopsy to enhance the

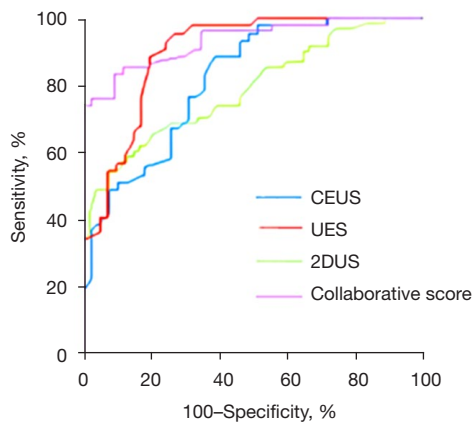


Figure 1 AUC of ultrasound scores in diagnosis of PCa. PCa, prostate cancer; 2DUS, two-dimensional ultrasound imaging score; CEUS, contrast-enhanced ultrasound score; UES, ultrasound elastography score.

Table 2 The correlation between ultrasound scores with clinicopathological characteristics

Variables	2DUS			CEUS			UES		
	Mean ± SD	t	P	Mean ± SD	t	P	Mean ± SD	t	P
Tumor stages		7.53	<0.001		3.76	<0.001		8.21	<0.001
I-II (n=176)	3.78±0.40			4.83±0.59			3.97±0.49		
III-IV (n=102)	4.22±0.57			5.12±0.67			4.49±0.54		
Pathological grades		7.96	<0.001		7.77	0.001		6.58	<0.001
I (n=67)	3.78±0.52			4.78±0.53			4.11±0.46		
II (n=179)	3.97±0.50			5.00±0.62			4.21±0.49		
III (n=32)	4.23±0.71			5.28±0.64			4.49±0.55		
Differentiation degrees		5.06	0.007		12.61	<0.001		10.67	<0.001
Poor (n=8)	4.52±0.67			5.36±0.78			4.38±0.52		
Moderate (n=76)	3.95±0.58			5.03±0.60			4.14±0.49		
High (n=194)	3.89±0.54			4.71±0.54			4.20±0.55		
Pelvic lymph node metastasis		3.02	0.003		2.29	0.02		4.68	<0.001
Yes (n=95)	4.05±0.54			5.10±0.73			3.97±0.49		
No (n=183)	3.86±0.47			4.90±0.66			4.02±0.60		

2DUS, two-dimensional ultrasound imaging score; CEUS, contrast-enhanced ultrasound score; UES, ultrasound elastography score; SD, standard deviation.

positivity rate and minimize complications arising from multiple biopsies. Additionally, these parameters hold certain value in the treatment and evaluation of PCa efficacy (19). The potential of CEU in diagnosing PCa is comparable to that of MRI, but it offers a relatively simpler procedure and lacks any obvious contraindications except for a low likelihood of contrast agent allergy. Recent studies, including the confirmatory study by Grey *et al.* (20), have reported that multiparametric ultrasound (mpUS) demonstrates a lower accuracy in diagnosing PCa compared to multiparametric MRI (mpMRI). This is further supported by the work of Pepe *et al.* (21), which questions the incremental value of mpUS in cognitive MRI/transrectal ultrasound (TRUS) fusion prostate biopsy. Our findings, in conjunction with these studies, underscore the importance of mpMRI as the preferred imaging modality before prostate biopsy, in line with international guidelines.

The utilization of UE, an emerging technology derived from the original ultrasound, has also demonstrated advancements in the diagnosis of PCa. The transrectal SWE elastic modulus has been demonstrated in several studies to possess a significant diagnostic advantage for PCa, with high specificity and sensitivity (22-24). The limitation of UE lies in the potential interference caused by tissue perfusion or respiratory motion, which can affect the generation of elastic images. However, this interference is minimal when performing prostate examinations. SWE has shown a high level of diagnostic performance in PCa, and also has a potential predictive ability for the aggressiveness of the disease. A meta-analysis has shown that both SWE and 18F-fluorocholine PET/CT imaging exhibit superior diagnostic performance compared to other investigated imaging techniques, with SWE being particularly advantageous for early detection of PCa (25). The recent advancements in prostate-specific membrane antigen (PSMA) PET/CT, as demonstrated by Pepe *et al.* (26,27), offer a promising alternative for targeted biopsy guidance in PCa diagnosis. Our study's findings on ultrasound-based diagnostic scores can be considered in conjunction with PSMA PET/CT to optimize diagnostic strategies and improve patient outcomes.

The consensus among previous studies is that ultrasound serves as the most convenient modality for guiding biopsies, thereby highlighting its inherent advantage in this regard. Although no single technique can provide sufficient diagnostic accuracy, the combination of 2DUS, CEUS, and UES can effectively enhance the ultrasound's diagnostic accuracy in PCa. The diagnostic advantage of combining

the 2DUS, CEUS, and UES surpasses that of any individual ultrasound score due to their complementary advantages in diagnosing the aforementioned ultrasounds. SE-guided biopsy enhances the detection of PCa compared to conventional ultrasound, as it leverages the increased tissue hardness associated with PCa to accurately identify subtle tissue changes and guide biopsy procedures. However, in cases where the tumor is small or the prostate volume is large, the detection ability of SE may be insufficient and low-grade lesions could be missed (28,29). In this case, the anatomical information and blood flow information of the prostate obtained by 2DU probe can be combined with CEUS to provide evidence, so as to significantly improve the diagnostic effect. The incorporation of real-time SE combined with transrectal CEU in a prospective study involving patients with PSA levels ≥ 4.0 ng/mL significantly augmented the sensitivity and overall accuracy for accurately identifying PCa (30).

The assessment of cancer disease may benefit from specific ultrasound score values, in addition to their utility in ultra-early diagnosis and differential diagnosis of PCa. The serious condition and poor prognosis of malignant tumors have been consistently associated with higher tumor stage, higher pathological grade, lower degree of differentiation, and lymph node metastasis (31-33). The correlation between the aforementioned three ultrasound scores and specific pathological features of PCa was analyzed. It was observed that there were variations in 2DUS, CEUS, and UES among PCa patients with different tumor stages, pathological grades, differentiation degrees, and pelvic lymph node metastasis. The aforementioned ultrasound scores were found to be elevated in patients with tumor stages III-IV, pathological grade III, poor differentiation, and pelvic lymph node metastasis. This suggests a significant correlation between the ultrasound scores and the key pathological characteristics of PCa, indicating that higher ultrasound scores may serve as an indicator of increased malignancy in PCa. The recent review by Avolio *et al.* (34) underscores the growing significance of micro-ultrasound in PCa diagnosis. While our study primarily focuses on 2DUS, CEUS, and UES, the integration of micro-ultrasound into diagnostic protocols may offer additional benefits, such as enhanced resolution and improved visualization of micro-architectural changes within the prostate tissue.

This study has provided preliminary evidence on the beneficial role of utilizing multiple prostate ultrasound scores for PCa screening and assessing prostate diseases.

However, further research is needed to determine which patients would benefit from timely examination using a combination of multiple ultrasounds. If all patients undergoing physical examination or suspected of having PCa are subjected to the three ultrasound methods, it may result in inefficient utilization of medical resources and contribute to medical congestion. While our study provides valuable insights into the diagnostic value of 2DUS, CEUS, and UES for PCa, we were unable to perform a detailed cost analysis due to the limited availability of comparative cost data in the literature. Future research is warranted to explore the cost-effectiveness of these imaging modalities in different healthcare settings. Additionally, while our study provides robust evidence of the diagnostic efficacy of our mpUS protocol, we acknowledge the absence of external validation for the actual detection rate in a new cohort. This is a recognized limitation of our study, and we are planning future research to address this gap. The validation of our multiple prostate ultrasound scores protocol's actual application value will be crucial for its integration into clinical practice.

Conclusions

In conclusion, the 2DUS, CEUS, and UES of PCa patients hold significant value in the diagnosis and clinical evaluation of the disease. These modalities offer essential reference information for early screening of individuals with prostate lesions and identification of suitable candidates for biopsy. Besides, the ultrasound score values are closely correlated with the malignancy level of PCa, thereby providing valuable insights for disease assessment and formulation of treatment plans.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-24-137/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-137/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the second hospital of Shanxi Medical University (No. KYLL20220301) and informed consent was taken from all the patients.

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