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RESEARCH

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The value of shear wave elastography combined with red blood cell distribution width in evaluating arterial erectile dysfunction

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Abstract

Purpose A retrospective study was conducted to determine the value of shear wave elastography (SWE) and red blood cell distribution width (RDW) in the diagnosis of various forms of erectile dysfunction (ED).

Methods With the method of Nocturnal Penile Tumescence and Rigidity (NPTR) and the screening method of Color Duplex Doppler Ultrasound (CDDU), hematological data were collected from 131 individuals, among whom 24 are with psychogenic ED, 48 are with non-arterial ED(NAED) and 59 are with arterial ED(AED) with erectile dysfunction. SWE value of penile corpus cavernosum(CCP) and cavernous arterial flow velocity were measured before (flaccid state) and after (erect state) intracavernous injection (ICI) in all patients.

Results Among the AED patients and other types of ED patients, there were statistically significant differences in the abridged five-item International Index of Erectile Function (IIEF-5), red blood cell distribution width-coefficient of variation (RDW-CV), red blood cell distribution width-standard deviation (RDW-SD), and SWE values (all $P < 0.01$). In the AED patients, the IIEF-5 scores had a significant negative relationship with RDW-CV, RDW-SD, and SWE values, with SWE values having the strongest correlation. ($p < 0.001$, r=-0.638).

Conclusion The combination of RDW level and SWE value demonstrated the greatest performance in diagnosing AED, according to the receiver-operator characteristic(ROC) curve analysis (AUC = 0.870, $p < 0.0001$, cut-off value of 0.75, sensitivity of 74.6%, specificity of 91.7%).RDW and SWE value may develop into an incredibly simple, practical tool for predicting and diagnosing AED.

Trial registration retrospectively registered.

Keywords Arterial erectile dysfunction, Red blood cell distribution width, Shear wave elastography, Penile corpus cavernosum, International Index of Erectile function

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Background

The erection process is an intricate neurovascular process that involves the coordination of the neurological, endocrine, psychological and circulatory systems [1]. The inability of a man to achieve and/or sustain a penile erection that is sufficient for sexual engagement and for an acceptable sexual performance is known as erectile dysfunction(ED) [2]. ED can be classified as being psychogenic, organic (i.e., neurogenic, hormonal, arterial, cavernous, or drug-induced), or a mixture of psychogenic and organic [3]. Vascular variables are crucial in organic ED because of the microcirculation of the penile corpus cavernosum (CCP) [4]. Arterial ED(AED), venous ED, and mixed ED are the three subtypes of vascular ED, with AED being the most prevalent [3].

The diagnosis of ED is therefore very complex, a process that requires differentiating among types of ED and identifying the causes, associated risk factors and potential life-threatening comorbidities. At present, it is mainly diagnosed through history taking, physical examination, laboratory assessment, and specific investigations [3].

Red blood cell distribution width (RDW) is one of the quantitative parameters of routine complete blood cells and reflects the heterogeneity of red blood cells [5].It is a typical marker for differential diagnosis of different types of anemia. Recent studies have shown that RDW can be used as an independent diagnostic marker to predict cardiovascular diseases(CVD) (e.g., hypertension, atherosclerosis, coronary syndrome), tumours, metabolic syndromes and inflammatory diseases [6]. As a condition intimately associated with cardiovascular factors, some scholars believe that ED is an early symptom of subclinical CVD or even an independent marker [7]. According to the association between ED and CVD, we hypothesized that clinically pertinent hematological parameters that can be used to predict or evaluate CVD would also be applicable to ED.

The features of shear wave elastography (SWE) include non-invasion quantification, convenience and high repeatability. SWE has been widely investigated to estimating thyroid, breast, and liver mass stiffness. A number of previous researches have investigated the feasibility of using SWE to quantitatively evaluate CCP stiffness for the diagnosis of ED. SWE provides noninvasive quantitative data on CCP stiffness and its change with age, as demonstrated by Inci et al [8]. Hu et al [9] found that compared with normal tissues, two-dimensional SWE can differentiate CCP lesions secondary to hyperlipidemia by quantifying elastic quantitative values.

Taken together, our aim was to assess RDW level, SWE value and the abridged five-item International Index of Erectile Function (IIEF-5) in patients with AED, nonarterial ED(NAED), and psychogenic ED, and the relationship among these three parameters.

Methods

Patients

The University Bioethical Committee gave its approval to the study procedure, which was carried out in accordance with the principles of the Helsinki Declaration. Each subject signed the consent form before joining the examination. We enrolled consecutive patients who suffered from ED in our hospital's urology department, from January 2020 to September 2022. Inclusion criterion was: IIEF-5 score less than 21 points. Exclusion criteria were: Congenital penile malformation; CVD (e.g., coronary atherosclerotic heart disease, cerebral infarction, myocardial infarction, etc.); neurological dysfunction (e.g., cerebrospinal cord injury, etc.); hematologic and vascular diseases(e.g.anemia, leukemia, lymphoma, thrombosis, varicose veins, etc.); Endocrine and metabolic disorders (including thyroid dysfunction, diabetes mellitus, gonadal dysfunction, etc.); acute or chronic inflammatory or infectious diseases; systemic diseases (e.g. rheumatoid arthritis, ankylosing spondylitis, etc.); history of genitourinary, pelvic and rectal surgery; history of medication use over a long period of time (including drugs that may influence haematological tests and hormone metabolism (Fig. 1). Fasting blood samples of all participants were collected from the antecubital vein at 7:00 am, for the data of their fasting blood glucose, lipids, sex hormones, routine blood.

Technique

To discriminate between organic ED and psychogenic ED, we performed the nocturnal penile tumescence and rigidity (NPTR) test on each patient while utilizing the RigiScan monitoring device (GOTOP Inc., USA). The patients were advised to refrain from using medications(except for prescription drugs taken routinely) and avoid consuming alcohol or caffeine to assure a restful night's sleep and less attachment. Additionally, they were asked to empty their bladders before sleep. Data were obtained the next morning. To get over the "first night effect," the test was performed three nights in a row. If at least one nocturnal erectile event met the following criteria (tip swelling ≥ 2 cm, base swelling ≥ 3 cm, event duration ≥ 10 min), psychogenic ED was diagnosed; otherwise, organic ED was identified [10–12].

All patients with ED underwent SWE examination, which was performed by using a Aixplorer ultrasound equipment (Supersonic Imagine S.A., Aix-en-Provence, France) with a SuperLinear SL15-4 probe (Frequency:4–15 MHz). In order to relieve the anxiety and nervousness of subjects, all operations were carried out in a quiet and comfortable environment. All individuals underwent supine examinations, with the glans penis held softly and the penis body close to the pubic symphysis. They were required to keep the penis not squeezed,

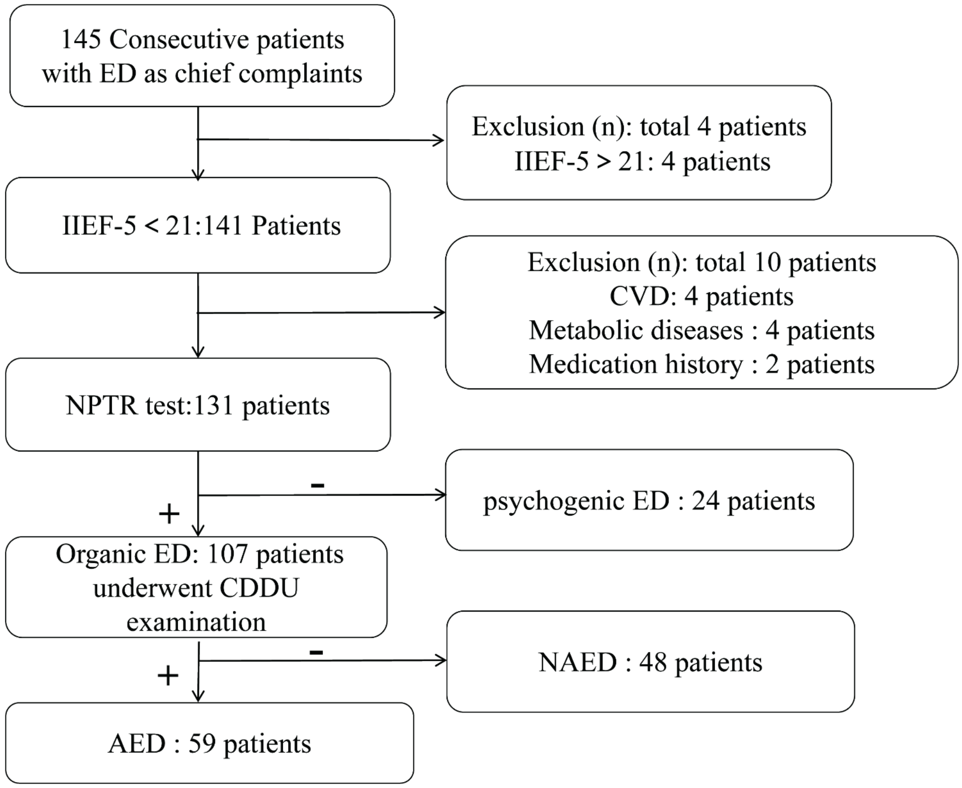

Fig. 1 Summary flow chart of the study

in order not to affect the accuracy of the examination. Sonograms of the anatomy of the entire penis in the flaccid state were obtained (longitudinal and cross-sectional views) by B-mode sonography, and after grayscale sonographic assessment, we switched to SWE mode. We selected the base parts of the CCP to perform SWE in the transverse section to obtain the left and right sides of the CCP, respectively. The image was stored when the color image fills over 90% of the area of interest (ROI). Following the disinfection of the skin surrounding the penis with iodophenol, intracavernosal injection was performed, and the vasoactive drug alprostadil (10ug mixed with 3 ml of normal saline) was injected on one side. The base of the penis was secured with a disposable pressure band to preserve the majority of the vasoactive drug in the CCP and was released after 40 to 60 s. Audiovisual Sexual stimulation (AVSS) equipment was also applied after alprostadil injection to reduce false positive cases caused by external environmental interference and promote penile erection. Patients were asked to masturbate after seeing the pornographic films through a spectacle-style video player. The peak systolic flow velocity (PSV), end-diastolic flow velocity (EDV), and resistance index (RI) were repeatedly obtained at an interval of 6 to 10 min after intracavernous injection (ICI). The initial measurement of SWE values of the bilateral bases of the CCP was done at 5 min post-ICI, then obtained every 5 min until 30 min post-ICI(a total of 6 post-ICI measurements). The ROI was a circular sampling frame with a diameter of 4 mm, and the SWE value of the CCP was obtained. Two successive measurements were carried out and their average value was calculated as the final value and the results were reported in kilopascals (kPa). The same sonographer performed the SWE examination and the image analysis, who had decades of experience in genitourinary ultrasonography, but was not aware of any clinical background of the subject.Ultrasounds for all subjects were performed in a single visit. Doppler criteria for AED after ICI were as follows: PSV < 25 cm/s, EDV < 5 cm/s or RI > 0.9, otherwise classified as NAED [13].

Statistical analysis

All data analyses were performed using SPSS statistical software version 25.0(SPSS Inc., Chicago, IL, USA). Continuous variables were described with mean and standard deviation (mean ± standard deviation), and categorical variables were described with frequency and percentage. The Student's t-test or Mann-Whitney U-test was used to compare continuous variables between the two groups. In cases where the continuous variables had a normal distribution and homogeneity, one-way analysis of variance (ANOVA) was used to assess statistical differences among the three groups, and Bonferroni's method was applied for multiple comparisons. In all other cases, the

Kruskal Wallis H-test was used. Chi-square tests were conducted to compare categorical data, and Pearson's correlation analysis assessed the correlation between two continuous variables. Finally, receiver-operator characteristic (ROC) curves were utilized to determine cut-off values for the corresponding variables to distinguish AED from other types of ED. We also obtained the area under the curve (AUC), sensitivity, specificity for the corresponding variables. It was statistically significant when $P<0.05$.

Results

Patient characteristics

This research involved 131 participants in total, including 24 with psychogenic ED (Group 1), 48 with NAED (Group 2), and 59 with AED (Group 3). Table 1 provides an overview of the patients' demographic features. After statistical analysis, this study found that there were no differences in age, BMI, fasting blood glucose, blood lipids and sex hormones among the above three groups, while the differences in IIEF-5 score, RDW and SWE value were statistically significant. Using the Bonferroni method, we conducted multiple comparisons and observed statistically significant differences in RDW-CV, RDW-SD and IIEF-5 scores when comparing Group 1 and Group 3, Group 2 and Group 3 (all $P<0.05$). Furthermore, when Group 1 and Group 2 were compared, there were meaningful differences in RDW-CV, IIEF-5 score (both $P<0.05$), but no difference in RDW-SD ($P=0.379$), as seen in Table 1; Fig. 2.

SWE value of CCP among types of erectile dysfunction

After the injection of a vasoactive drug, we discovered significant differences in SWE values between groups 1 and 3 and between groups 2 and 3 (both $P<0.05$), but not between groups 1 and 2 ($P=0.385$) (Fig. 3). However, before vasoactive drug injection, there was no significant difference in SWE value among the three groups. We observed a statistically significant difference in SWE values among the three groups when comparing before and after drug injection using the paired t-test method (all $P<0.01$), as detailed in Table 2; Fig. 4.

Relationships among several statistically significant variables and ROC curve

We further performed Pearson's correlation analysis on the data from the three groups to assess the correlation among SWE values, IIEF-5, and RDW. The results showed that in group 3, IIEF-5 and SWE values showed a significant inverse correlation (r=-0.638, $p<0.001$); in both group 2 and group 3, RDW-CV and RDW-SD indicated a weak inverse correlation with IIEF-5, details of which are presented in Table 3; Fig. 5.

SWE value and RDW level for predicting AED were assessed by ROC curve analysis. The AUC of SWE value was 0.656, the cut-off value was 13.95 kPa, the sensitivity was 52.5%, and the specificity was 73.6%. The AUC of

Table 1 Characteristics of patients with erectile dysfunction

	Group1($N=24$)	Group2($N=48$)	Group3($N=59$)	P Value
Age, year	30.71 ± 4.74	31.42 ± 10.25	31.73 ± 8.2	0.768
BMI, kg/cm2	22.94 ± 3.76	22.57 ± 2.35	22.55 ± 1.74	0.528
IIEF-5 score	15.42 ± 3.46†§	11.08 ± 4.38‡	8.97 ± 4.03	< 0.001
Glu, mmol/L	5.1 ± 0.56	5.13 ± 0.45	5.09 ± 0.53	0.485
Routine blood				
RDW-CV, %	11.9 ± 0.68†§	12.22 ± 0.8‡	13.03 ± 0.92	< 0.001
RDW-SD, fL	38.95 ± 3.17†§	39.67 ± 2.66‡	42.78 ± 3.66	< 0.001
Blood lipids, mmol/L				
TC	4.37 ± 0.73	4.68 ± 0.86	4.35 ± 0.84	0.384
TG	1.2 ± 0.92	1.27 ± 1.55	1.22 ± 1.77	0.265
HDL-C	1.31 ± 0.29	1.31 ± 0.25	1.34 ± 0.32	0.498
VLDL	0.5 ± 0.2	0.42 ± 0.29	0.44 ± 0.26	0.277
LDL-C	2.35 ± 0.46	2.48 ± 0.56	2.52 ± 0.57	0.237
Sex hormones				
FSH, mIU/L	4.76 ± 2.29	4.51 ± 5.61	4.11 ± 1.82	0.760
LH, mIU/L	4.43 ± 1.82	4.84 ± 3.72	4.53 ± 2.18	0.988
Testosterone, nmol/L	15.69 ± 4.91	16.63 ± 4.34	16.34 ± 4.05	0.491
Estradiol, pmol/L	139.64 ± 101.74	138.08 ± 115.12	138.33 ± 104.67	0.730

Notes: Abbreviations: BMI, body mass index; Glu, glucose; RDW-CV, red blood cell distribution width-coefficient of variation; RDW-SD, red blood cell distribution width-standard deviation; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; VLDL, very low-density lipoprotein; LDL-C, Low density lipoprotein-cholesterol

†P: $P>0.05$ when compared between group 1 and group 2; ‡ P: $P<0.05$ when compared between group 2 and group 3;§$P<0.05$ when compared between group 1 and group 3. †, ‡, §: Compared using the Bonferroni's method

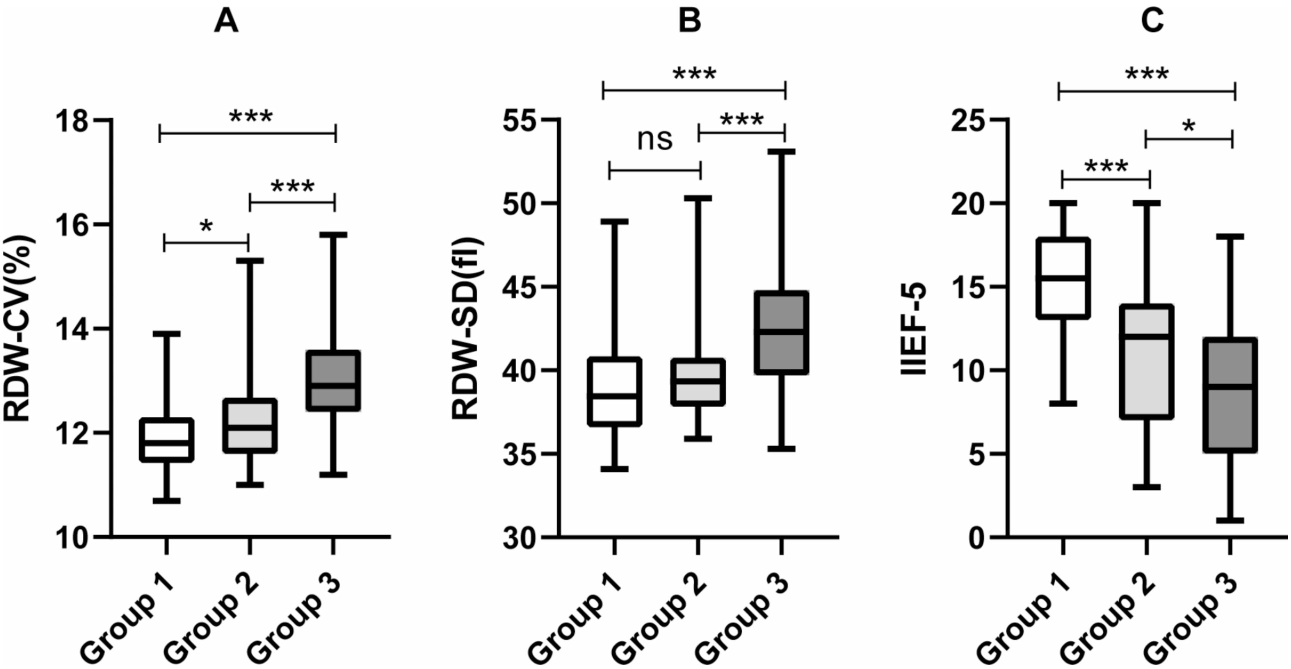

Fig. 2 The combined box plots comparing data characteristics of RDW (A, B) and IIEF-5 score (C) among three groups; *, $p<0.05$; ***$p<0.001$; ns, no significance

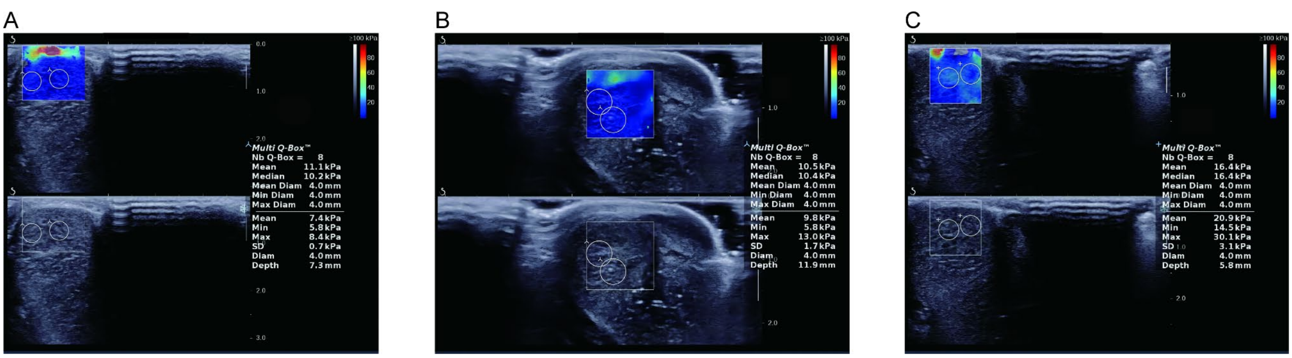

Fig. 3 Shear-wave elastography of three groups of participants after vasoactive drug injection (**A**. Group 1 ; **B**. Group 2 ; **C**. Group 3)

Table 2 Differences of SWE values before and after ICI in various groups

SWE value of CCP, kPa	Group1(*N*=24)	Group2(*N*=48)	Group3(*N*=59)	*P* Value
Before ICI	21.24 ± 6.55	21.58 ± 7.81	22.21 ± 6.82	0.616
After ICI	10.08 ± 4.02*‡	11.08 ± 4.78†§	13.53 ± 5.19¶	0.01

Notes: * P: $P<0.05$ when compared between group 1 and group 3; † P: $P<0.05$ when compared between group 2 and group 3;‡ P: $P<0.05$ when compared SWE value before and after ICI in group 1; § P: $P<0.05$ when compared SWE value before and after ICI in group2; ¶ P: $P<0.05$ when compared SWE value before and after ICI in group 3. *,†: Compared using the Bonferroni method. ‡, §,¶: Compared using paired t-test method

RDW-CV levels was 0.856, the cut-off value was 12.15%, the sensitivity was 84.7%, and the specificity was 61.1%. The AUC of RDW-SD levels was 0.809, the cut-off value was 41.9 fl., the sensitivity was 59.3%, and the specificity was 86.1% (Fig. 6). The diagnostic effects of the above three parameters did not differ statistically significantly from one another (all $P>0.05$).

When we used the above three parameters to jointly diagnose AED, the AUC was 0.870, the 95% confidence interval was 0.778 to 0.934, the P value was <0.0001, and the cut-off value was >0.75, the sensitivity was 74.6%, and the specificity was 91.7% (Fig. 7).

Discussion

Most studies on ED state that it is a common disorder in male over 40 years of age and that it becomes more common with age. More troublingly, studies revealed that the prevalence of ED in male younger than 40 years is rising,

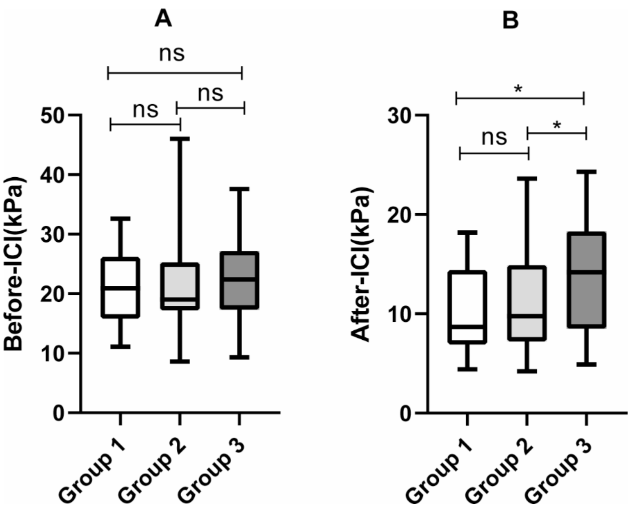

Fig. 4 Comparison of SWE values among three groups before ICI (**A**) and after ICI(**B**); *, $p < 0.05$; ns, no significance

with at least one in four new ED clinicpatients being under the age of 40 due to their frequent display of smoking and illicit drug use habits [14–17]. In parallel, ED is emerging as an important role in reflecting the overall health status of men, with important implications in the cardiovascular field [18–21]. In a sample of males with ED between the ages of 20 and 89, Chew et al. [22]. found ED as a predictor of CVD events.They found that patients with ED under 40 years of age had a higher relative risk of CVD events than the elderly population. Collectively, these earlier observations and our current studies may indicate that ED is a sentinel marker of early health deterioration that can motivate men to develop long-term healthy lifestyles, assess cardiovascular risk and the value of subsequent medical interventions.Therefore, to distinguish patients with organic ED from healthy individuals, additional subclinical markers are required.

Previous researches have shown that RDW level are significantly higher in acute heart failure and can predict the development of carotid plaque in atherosclerosis [23, 24].A meta-analysis demonstrated that patients with acute coronary syndromes with lower level of RDW have a lower risk of major adverse cardiovascular events and that RDW can be used to predict prognosis of associated disease [25, 26]. The most major and prevalent subtype of ED is AED, whose occurrence is related to endothelial dysfunction, atherosclerosis, and inflammation [27, 28]. The current study proved that there was a statistical difference in RDW-CV and RDW-SD levels among

Table 3 Relationships between several statistically significant variables

	Group1($N=24$)		Group2($N=48$)		Group3($N=59$)	
	P	*r*	*P*	*r*	*P*	*r*
After ICI vs. IIEF-5	0.615	-0.108	0.07	-0.382	< 0.001	-0.638
After ICI vs. RDW-CV	0.890	-0.030	0.412	-0.121	0.103	0.214
After ICI vs. RDW-SD	0.055	0.396	0.596	-0.078	0.235	0.157
IIEF-5 vs. RDW-CV	0.483	-0.150	0.001	-0.457	0.002	-0.401
IIEF-5 vs. RDW-SD	0.284	-0.228	0.008	-0.378	0.015	-0.316

Notes: Abbreviations: After ICI, SWE value of CCP after vasoactive drug aprostadil injection

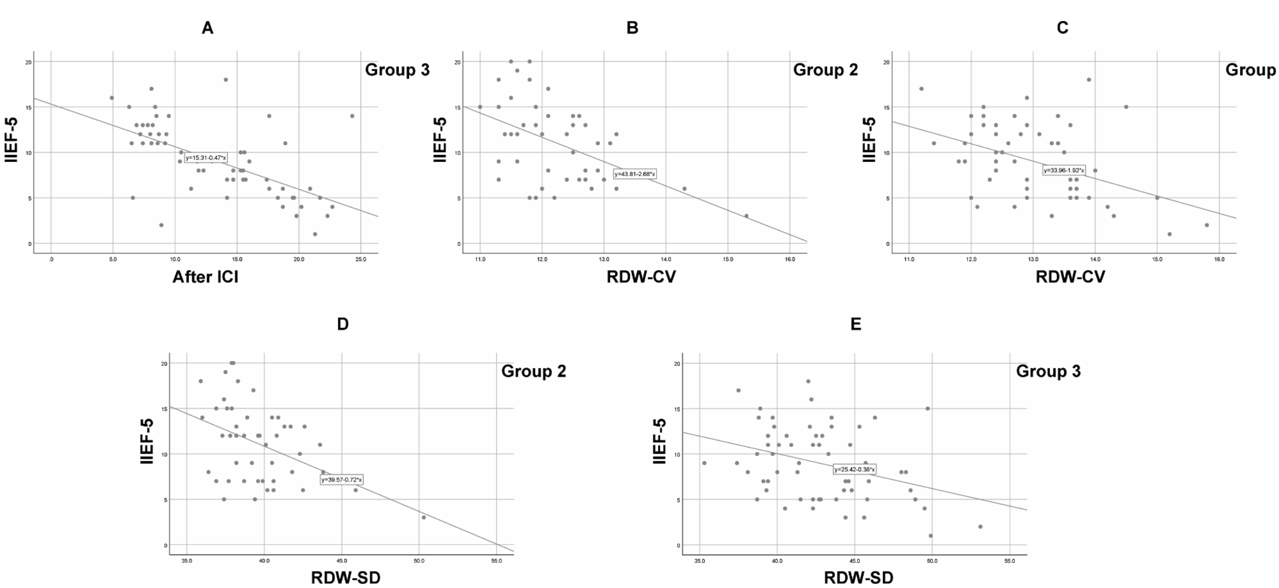

Fig. 5 Correlation among IIEF-5 score, SWE value and RDW levels in ED patients

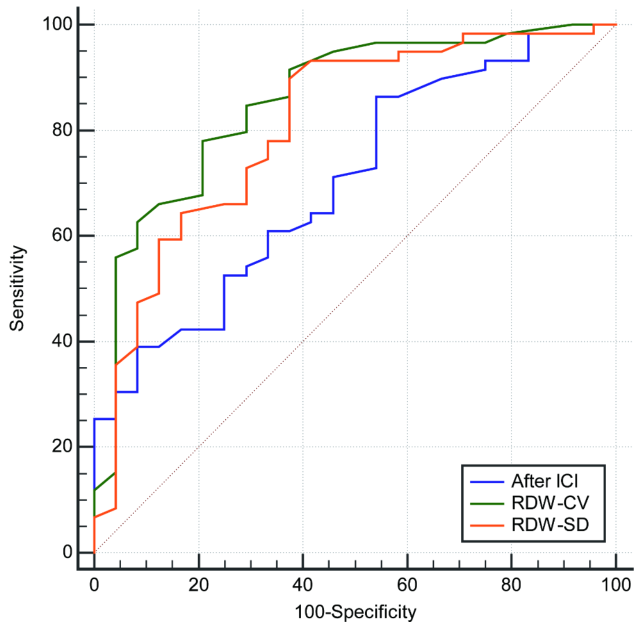

Fig. 6 ROC curve of RDW-CV, RDW-SD and SWE value after ICI for diagnosis of AED

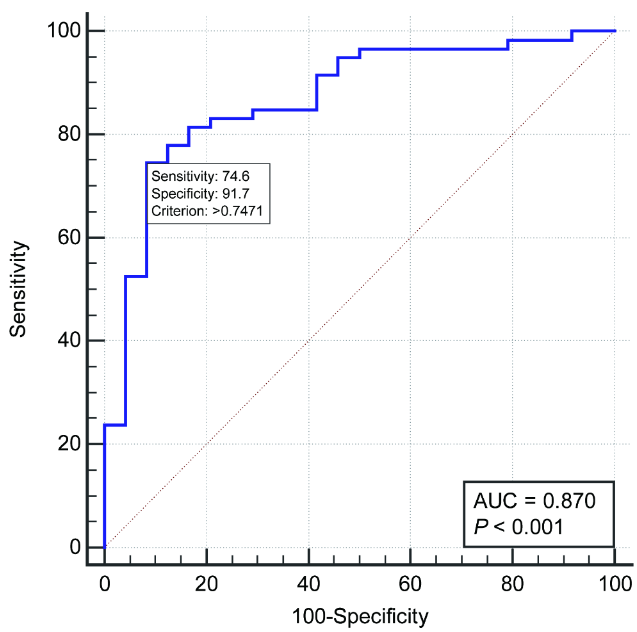

Fig. 7 ROC curve of combined diagnosis of AED by RDW and SWE values after ICI

patients with AED and other types of ED. A possible reason for this has been suggested: The role of systemic factors including oxidative stress and inflammation is the plausible explanation for the association between RDW and AED. A low-grade systemic inflammatory response, increased activity of the adrenergic and neuroendocrine systems and activation of the renin-angiotensin system are associated with increased erythropoiesis, leading to altered erythrocyte maturation processes, heterocytosis and higher RDW. Oxidative stress can also effectively increase RDW in acute inflammatory conditions by damaging the erythrocyte membrane and inducing the release of immature erythrocytes from the bone marrow into the peripheral blood [29–31].

In recent years, numerous academics have studied the association among neutrophils, platelets and AED [32]. However, so far, the relationship between red blood cells, especially RDW and AED has not been investigated. In the present finding, we showed that both RDW-CV and RDW-SD were substantially higher in patients with AED than in psychogenic ED and negatively correlated with IIEF-5 scores. Furthermore, the analysis of ROC curves showed that RDW-CV had a high diagnostic efficacy, with values greater than 12.15% being better ones for the prediction of AED. As confirmed in previous studies [33], AED patients had higher Atherosclerotic Cardiovascular Disease risk scores, which means they had higher endothelial dysfunction and greater severity of atherosclerosis. Considering the association between AEDs and CVD, RDW is likely to be a marker of their connection. Increased RDW levels may be able to predict the risk of CVD in ED patients in addition to representing a higher risk of AED.

A study by Zhou et al [34] found that SWE could be used to quantitatively assess the stiffness of CCP, and SWE values were significantly lower in the AED and non-vascular groups after ICI. The SWE values after ICI were substantially greater in the AED than those in the non-vascular ED (12.17 kPa and 8.04 kPa, respectively), which generally agrees with the findings of the present investigation. CCP is composed of many smooth muscle cells(SMCs), fiber collagen and a meshwork of small arteries and capillaries of various sizes. During tumescence, the arterial SMCs within the CCP relax, the vessels dilate, and arterial blood flows. The white membrane subsequently constricts the veins to restrict venous blood outflow. The number of smooth muscle trabeculae in the ROI gradually decreases, while blood engorgement, and SWE value decreases [35, 36]. Secondly, previous studies found that inadequate blood perfusion in the AED patients led to a decrease in SMCs and an increase in fiber collagen in the CCP [37, 38]. The increase in SMCs reduced SWE values, whereas the increase in collagen fibers led to the opposite result [8, 39, 40], which may explain the higher correlation in the AED group than in the other groups. Patients with AED have penile arterial vascular endothelial dysfunction and/or atherosclerotic load, resulting in a more significant reduction of blood flow in erectile tissue compared to other types of ED [41]. Thus, in the erectile state, AED patients have less blood flow, more vascular smooth tissue and collagen fibers in the zone of interest of the CCP, and they have higher SWE values. Additionally, the findings of this research are in accordance with the studies that the more severer the erectile dysfunction is, the lower the IIEF-5 score is and the higher the SWE value becomes.

IIEF-5 score is a semi-quantitative grade parameter, which is subjective, while SWE can accurately, non-invasively and quantitatively assess the stiffness of CCP. And the SWE value has a good correlation with the stiffness of the CCP of the AED patient, which can evaluate the severity of the AED, and has a high efficiency in the diagnosis of AED in combination with the RDW.

Meanwhile, our study has some limitations. First, the small sample size of this study may result in selection bias as the experimental results are influenced by individual heterogeneity. Second, the lack of a healthy control group may also affect the performance of each parameter. Third, we could not guarantee that each participant would respond equally to alprostadil. More participants and a more comprehensive examination will be refined in the future.

Conclusions

This study demonstrates that RDW-CV, RDW-SD, and SWE values are significantly different in patients with AED compared to those with NAED and psychogenic ED. These parameters show a negative correlation with IIEF-5 scores, indicating their potential as diagnostic markers. The combination of RDW and SWE values provides a high diagnostic accuracy for AED, making them valuable tools for predicting and diagnosing this condition. Despite some limitations, such as the small sample size and lack of a healthy control group, our findings suggest that these parameters could be developed into practical indicators for AED diagnosis and severity assessment.

Abbreviations

RDW	Red blood cell distribution width
SWE	Shear wave elastography
ED	Erectile ysfunction
NPTR	Nocturnal Penile Tumescence and Rigidity
CDDU	Color Duplex Doppler Ultrasound
AED	Arterial erectile ysfunction
NAED	Non-arterial erectile ysfunction
CCP	Penile corpus cavernosum
ICI	Intracavernous injection
IIEF-5	The abridged five-item version of the International Index of Erectile Function
RDW-CV	Red blood cell distribution width- coefficient of variation
RDW-SD	Red blood cell distribution width-standard deviation
ROC	Receiver-operator characteristic
CVD	Cardiovascular disease
PSV	Peak systolic flow velocity
EDV	End-diastolic flow velocity
RI	Resistance index
kPa	Kilopascals
ANOVA	One-way analysis of variance
AUC	The area under the curve
SMCs	Smooth muscle cells

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Author contributions
QYW: Writing–review and editing, Writing–original draft, Supervision, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. YXG: Writing–review and editing, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. HQZ: Writing–review and editing, Visualization, Supervision, Resources, Project administration. XCQ: Writing–review and editing, Resources, Project administration, Software, Validated.CXZ: Writing–review and editing, Methodology, Investigation, Visualization, Resources.WZ: Writing–review and editing, Writing–original draft, Methodology, Investigation, Data curation, Resources.All authors read and approved the final manuscript.

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

Declarations

Ethics approval and consent to participate
This research involving human data have been performed in accordance with the Declaration of Helsinki and have been approved by an appropriate ethics committee. For this research, informed consent to participate was obtained from participants (or their parent or legal guardian in the case of children under 16).
The name of the ethics committee: The Ethics Committee of Clinical Medicine Research, the First Affiliated Hospital of Anhui Medical University.
The reference number: Quick-PJ 2023-01-28.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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