

Clinical Value of the N-S-P Scheme for Diagnosing Vulvar Dermatoses (DATRIV Study, Part 2)

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Abstract: The DATRIV study aimed to create a basis for developing standard outcome measures in vulvoscopy to facilitate the diagnosis and treatment of vulvar discomfort. For this purpose, the three rings vulvoscopy (TRIV) was introduced, and the vulvoscopy index and N-S-P scheme were designed as outcome parameters. In this paper, the clinical value of collecting and managing data obtained during TRIV in normal and patients with chronic vulvar distress was carefully examined by introducing the N-S-P scheme. Complex ISSVD vulvodysplasia pattern questionnaire and TRIV form data were methodically performed for data gathering. The collected data were explored using StatSoft (Dell, Austin, Texas), Statistica 12 (TIBCO®, Palo Alto, CA) and SPSS 20 (IBM, Armonk, NY). Ethical permission for the study was acquired from the Institutional Review Board of the Polyclinic Harni, and all patients gave written informed consent. In addition to TRIV, lesions specific to vulvar dermatosis were detected in 82 patients. Histopathology diagnosed vulvar dermatosis at the first biopsy in 72 patients. The resulting difference of ten patients consisted of patients with early vulvar dermatosis. Six of these ten subjects were diagnosed with vulvar dermatosis on a second biopsy during the study period. Statistical tests did not show a significant difference between normal findings or the presence of any type of lesion (nonspecific and specific) concerning the three vulvar rings, except in ten patients with early vulvar dermatoses. The N-S-P scheme accurately recognized the disease in all patients showing 100% sensitivity in detecting vulvar dermatoses. Patients without histopathological verified vulvar dermatosis at the first biopsy were classified as false positives, so the specificity of the test was 96.1%. Overall, the diagnostic accuracy of the N-S-P scheme in detecting vulvar dermatosis was 96.9%. Positive and negative predictive values were 0.88 and 1.00, respectively. The N-S-P scheme and TRIV are convincing clinical tests to detect vulvar dermatoses. Differences between vulvoscopy and histopathological diagnostics imply a lack of specificity of tissue transformations within early forms of vulvar dermatoses sufficient to distinguish them microscopically from normal findings. Consequently, early dermatoses could be a critical area for proposing this test. ClinicalTrials.gov Identifier: NCT02732145.

Keywords: Vulvar Dermatoses, Vulvoscopy, Three Vulvar Rings, Three Rings Vulvoscopy, N-S-P Scheme

1. Introduction

The latest classification of vulvar disorders, published by the International Federation for Cervical Pathology and Colposcopy (IFCPC) and the International Society for the

Study of Vulvovaginal Diseases (ISSVD) in 2011, instructed a comprehensive description of vulvar lesions following dermatological criteria. Although these recommendations are an important step in the classification and interdisciplinary connection in observing this shared area, their implementation

in everyday gynecological practice represents an additional effort to evaluate and organize the therapy of vulvar lesions [1].

To facilitate the diagnostic procedure, simplified, systematic mapping and recognition of the lesion nature concerning the tissue from which it derives, an original technique called three rings vulvoscopy (TRIV) was introduced [2, 3]. A linear or random examination of the vulva has been replaced by systematic, annular observation of the vulva by its rings and determination of lesion specificity. The technique described the outer, middle, and inner ring of the vulva following the anatomy, histological, and embryonic nature of the vulva. Determining and describing the specificity of vulvar lesions required adapting the currently accepted terminology of abnormal findings to simplify their morphological assessment [1, 4]. Lesions with the secondary morphological presentation were gathered into "specific lesions" [1-2, 5], and their localization was defined according to the three vulvar rings concerning vulvar anatomy, histology, and embryology [2, 6-7].

Despite prior studies, this domain still lacks a relevant criterion for objective evaluation of results as standards in outcome measures are crucial to optimizing patient diagnosis and treatment. [8, 9]. Therefore, the DATRIV study was developed to build the basis for creating standard outcome measures in vulvoscopy. For that objective, two index tests founded on the specificity and localization of the vulvar findings according to the three vulvar rings were developed

as outcome parameters, the vulvoscopy index and the N-S-P scheme [10]. The diagnostic accuracy of both tests was evaluated in concordance with histopathology as a reference test. This paper encompasses clinical data correlated to the N-S-P scheme.

2. Methods

2.1. Study Design

The DATRIV study was intended as a prospective experimental study with diagnostic interventions. TRIV and vulvar biopsy with histopathology as diagnostic interventions were performed in all subjects.

One asymptomatic participant was randomly allocated to each patient with any signs of chronic vulvar discomfort concerning the ISSVD questionnaire. Exclusion criteria were vulvar inflammation, benign tumors, pre-/malignancy, insufficient medical documents, and protocol offenses. The study was conducted at the Polyclinic Harni in Zagreb, Croatia, from December 1, 2011, to December 31, 2016.

The research included a total of 328 consecutive participants (Figure 1). The asymptomatic group without vulvar symptoms (N = 164) and the symptomatic group with chronic vulvar disease (N = 164) were separated considering the patient's history and the ISSVD vulvodynia Pattern Questionnaire [11].

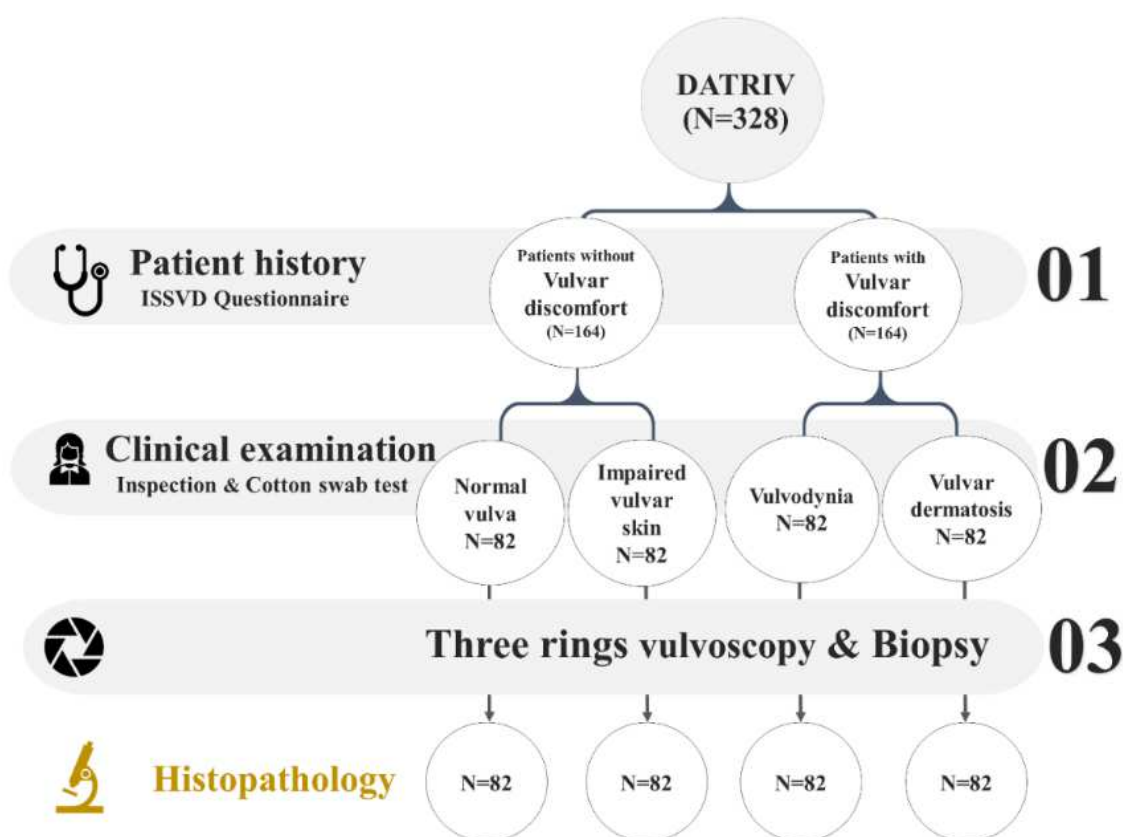


Figure 1. STARD Flow Diagram.

Asymptomatic participants were allotted to a subgroup of the normal vulva (N = 82) if there were no changes of the vulva or impaired vulvar skin (N = 82) if nonspecific findings of the vulva were observed during clinical assessment with inspection and cotton test. The description of a normal vulva has been accepted from earlier vulvoscopy classifications [2-5]. Nonspecific lesions enclosed nonspecific erythema on any part of the vulva, punctuations and papillae, paleness as a sign of ischemia, smoothness as loss of skin relief, and fissures of the vulvar mucosa. These findings have formerly been depicted as contagious and viral pathology [5].

Participants with chronic vulvar distress were allocated into two subgroups: vulvodynia (N = 82) and vulvar lesions specific for vulvar dermatosis (N = 82). The diagnosis of vulvodynia was made based on Friedrich's criteria as stated by the existing classification [12-14]. Vulvar lesions detected in patients with vulvodynia were nonessential for diagnosing vulvodynia. "Specific lesions" included chronic eczematous inflammation with thickened skin and excoriations (red, flat, and diffuse lesions on the vulvar skin); hypopigmented or white lesions (macule, plaques, and patches); white reticular nets and extensive erosions; erythematous papules with

silver, scaly plaques, agglutination and fusion; resorption of the labia minora and clitoral hood, loss of vulvar architecture, and sclerotic changes [2, 5].

The TRIV data form is developed to compile and manage vulvoscopy data. Vulvar biopsy in patients with vulvar discomfort was conducted as part of standard clinical care. Asymptomatic participants were conscripted from women without vulvar discomfort who underwent planned labiaplasty, and a vulvar biopsy was performed on vulvar samples donated for further investigation.

2.2. N-S-P Scheme

To construct a fundamental database of functional tests to assess the results of vulvoscopy, the vulvoscopy index and the N-S-P scheme were introduced, as the quality measurement of a particular medical technique suggests its significance in the hierarchy of diagnostic procedures. The diagnostic accuracy of both tests was evaluated regarding histopathological diagnosis as the gold standard in diagnosing vulvar dermatoses. This article assesses the diagnostic value of the semiquantitative test called the N-S-P scheme.

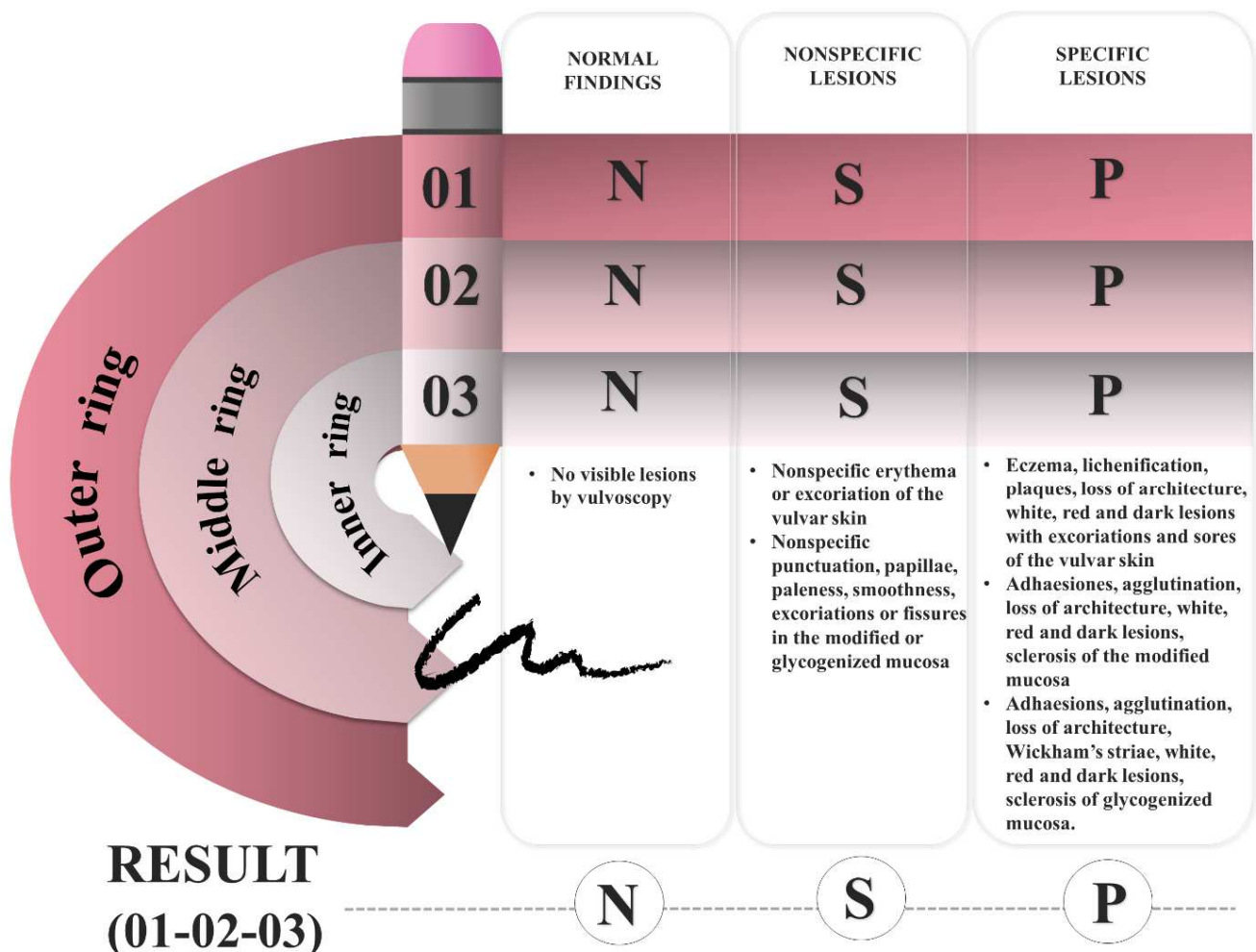


Figure 2. N-S-P Scheme.

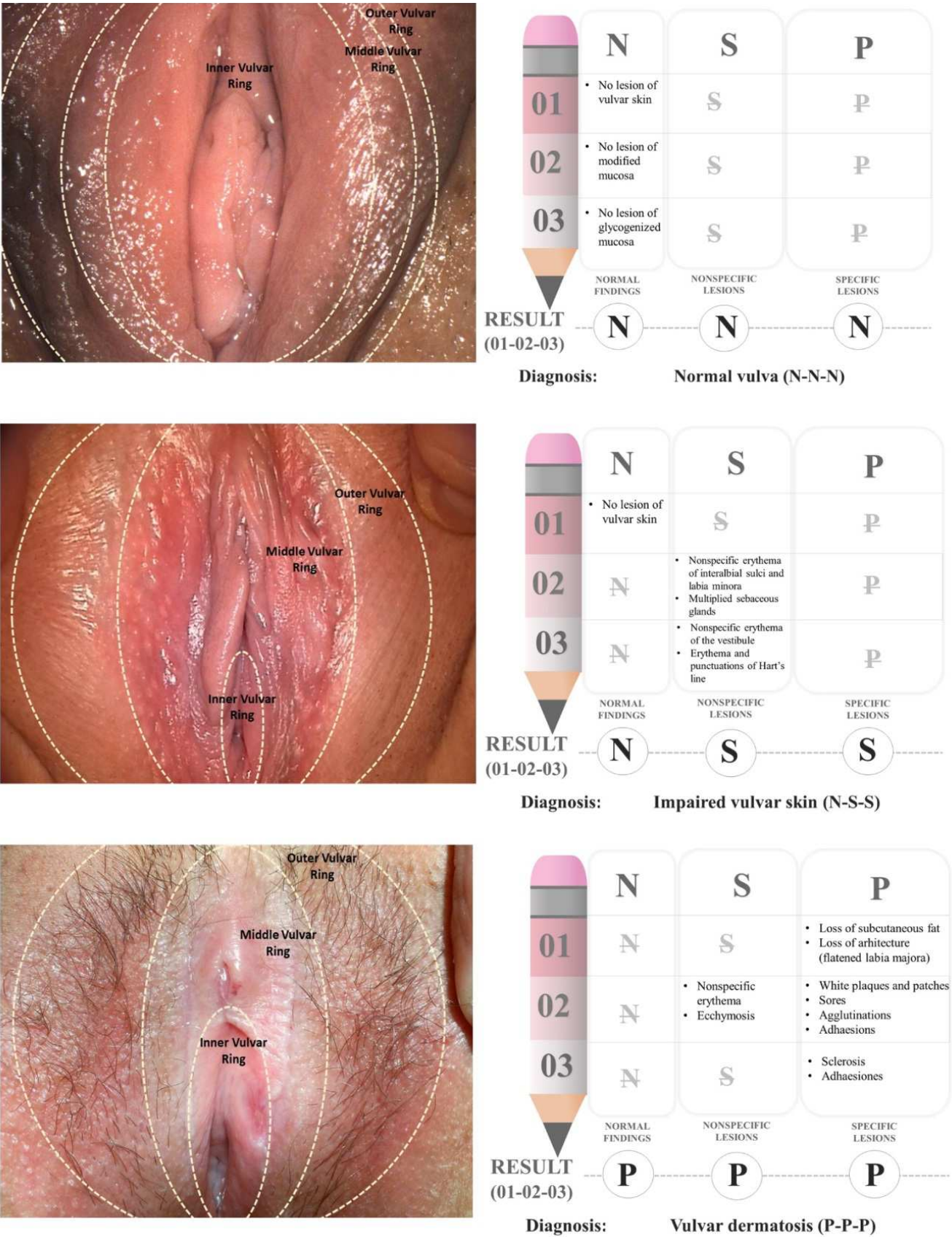


Figure 3. Evaluation of vulvar lesions according to N-S-P Scheme.

The N–S–P scheme is a double-cross classification. The result of vulvoscopy is described with three simple symbols (N, S, or P), one symbol for each individual vulvar ring, the order and type of symbols being crucial (Figure 2). Symbol "N" (normal)

represents a vulvar ring without any lesion, "S" (suspect) marks the presence of nonspecific lesions, and "P" (pathological) is a label for lesions specific to dermatosis. If nonspecific and specific lesions have been attending in the identical ring, the conclusive appraisal is the pathological result.

Each of the three vulvar rings is tagged with one of these

symbols according to the lesions found, and the definitive result is marked as a simple three-symbol scheme. The first symbol (01) reveals the result in the outer vulvar ring. The middle character (02) demonstrates the result in the middle vulvar ring, and the last component (03) symbolizes the result of the inner vulvar ring.

Table 1. Vulvar findings concerning N-S-P scheme in patients with and without vulvar dermatosis diagnosed by vulvoscopy and histopathology.

N-S-P scheme	Vulvar dermatosis			Absent vulvar dermatosis		
	Vulvoscopy n=82 (%)	Histopathology n=72 (%)	t-test proportion	Vulvoscopy n=246 (%)	Histopathology n=256 (%)	t-test proportion
<i>Outer vulvar ring</i>						
N	6 (7.3%)	5 (6.9%)	NS	227 (92.3%)	228 (89.1%)	NS
S	24 (29.3%)	22 (30.6%)	NS	18 (7.3%)	20 (7.8%)	NS
P	73 (89.0%)	64 (88.9%)	NS	0 (0%)	9 (3.5%) [▲]	p=0.002**
<i>Middle vulvar ring</i>						
N	0 (0%)	0 (0%)	NS	131 (53.3%)	131 (51.2%)	NS
S	41 (50.0%)	35 (48.6%)	NS	115 (46.8%)	121 (47.3%)	NS
P	73 (89.0%)	65 (90.3%)	NS	0 (0%)	8 (3.1%) [▲]	p=0.006**
<i>Inner vulvar ring</i>						
N	9 (11.0%)	5 (6.9%)	NS	89 (36.2%)	93 (36.3%)	NS
S	55 (67.1%)	51 (70.8%)	NS	157 (63.8%)	161 (62.9%)	NS
P	49 (59.8%)	46 (63.9%)	NS	0 (0%)	3 (1.2%)	NS
Absent vulvar lesions in all three vulvar rings	0 (0%)	0 (0%)	NS	83 (33.7%)	83 (32.4%)	NS
Nonspecific lesions in any vulvar ring	67 (81.7%)	60 (83.3%)	NS	163 (66.3%)	170 (66.4%)	NS
Specific lesions in any of vulvar ring	82 (100%)	72 (100%)	NS	0 (0%)	10 (3.9%) [▲]	p=0.002**

N, normal (absent lesion); S, suspect (nonspecific lesion); P, pathological (specific lesion); NS, not significant; * p<0.05; ** p<0.001

Normal vulvoscopy is characterized by the result "N-N-N." That suggests no lesions visible by vulvoscopy in any vulvar rings (Figure 3). The finding of nonspecific lesions (S) in any vulvar rings implies impaired vulvar skin or vulvodynia. If nonspecific lesions (S) are present in any vulvar rings, the vulvoscopy result is suspect.

The diagnosis of vulvar dermatosis is assembled by finding a specific lesion (P) in any of the vulvar rings, whereby the result of TRIV is marked as pathological. It is crucial to emphasize that patients with inflammatory changes, benign tumors, and pre-/malignant lesions were excluded from the study, so the concept of pathological outcome and specific lesions in this approach always refers to vulvar dermatosis. This classification was called the "N-S-P" scheme.

The diagnosis of vulvodynia is made according to Friedrich's criteria, which include the patient's history (dyspareunia) and a cotton swab test, so it cannot be made solely based on vulvoscopy or the N-S-P scheme.

2.3. Data Analysis

Statistical analysis was conducted using software packages StatSoft (Dell, Austin, Texas), Statistica 12 (TIBCO®, Palo Alto, CA), and SPSS 20 (IBM, Armonk, NY). Fundamental statistics were conducted, including computing the mean (the arithmetic mean, quartiles, mode) and measures of dispersion (variance, standard deviation).

A hypothesis that there would be discrepancies among the distributions was also scrutinized. When the allocation of random variables was theoretically known, the appropriate parametric tests were used, and when the allotment was

theoretically unknown, the proper nonparametric tests were utilized. The chi-square and Fisher's exact tests were used to calculate the data on a nominal or ordinal scale. The t-test as a parametric test or the Mann-Whitney U test as a nonparametric test were used to test the difference in the distribution of the two continuous random variables.

2.4. Ethical Approval

All participants were informed that their participation was voluntary and reserved the right to deny accomplishing the questionnaire. Patients delivered written informed permission for vulvoscopy and vulvar sampling. No incentive was proposed for involvement.

Ethical approval for this study was obtained from the Institutional Review Board of Polyclinic Harni, Ethical Approval Number 20111201001, as of December 1, 2011. The DATRIV study was documented at ClinicalTrials.gov Identifier: NCT02732145).

3. Results

Histopathological criteria for impaired vulvar skin and vulvodynia are not determined, but the benchmarks for interpreting vulvar dermatosis are well described. Consequently, the study participants were categorized into two classes for statistical research. The first class was marked as vulvar dermatosis. The second grouping, documented as absent vulvar dermatosis, was assembled from subjects diagnosed with the normal vulva, impaired vulvar skin, and vulvodynia. The clinical value of the N-S-P scheme was determined by comparing these two groups of participants.

To estimate the concordance between the diagnosis of vulvar dermatoses guided by the N-S-P scheme and histopathological diagnosis, the frequency and relative frequency of separate entities of the N-S-P scheme in both test groupings were approximated, as indicated in *Table 1*.

There was no statistically significant discrepancy between the frequency and relative frequency of vulvar lesions within the individual items of the N-S-P scheme and histopathology,

excluding the data marked with ▲, where the lesions specific for vulvar dermatosis were observed in the outer and middle vulvar ring by vulvoscopy. Nonetheless, histopathology did not prove the diagnosis of vulvar dermatosis in these patients at the first biopsy. The diagnosis of vulvar dermatosis was histologically verified in six of these participants during the investigation time.

Table 2. Diagnostic accuracy of the N-S-P scheme in detecting vulvar dermatosis.

Histopathological diagnosis	Vulvoscopy diagnosis according to the N-S-P scheme	
	Vulvar dermatosis	Absent vulvar dermatosis
Vulvar dermatosis	72	0
Absent vulvar dermatosis	10	246
Diagnostic value		95% Confidence interval
Sensitivity	1.0000	1.0000 – 1.0000
Specificity	0.9609	0.5794 – 1.0000
Accuracy	0.9695	0.6313 – 1.0000
Positive predictive value (PPV)	0.8780	0.2270 – 1.0000
Negative predictive value (NPV)	1.0000	1.0000 – 1.0000

The N-S-P scheme accurately recognized vulvar dermatosis in all patients with this histopathological diagnosis, showing 100% sensitivity of the N-S-P scheme to detect vulvar dermatosis. Patients without a histopathological verified vulvar dermatosis at the first biopsy were enclosed in false-positive cases, reflecting a lower test specificity value of 96.1%. Overall, the diagnostic accuracy of the N-S-P scheme in detecting vulvar dermatosis was 96.9%. The positive and negative predictive values were 0.88 and 1.00, respectively (*Table 2*).

4. Discussion

The submitted data are the conclusive part of a 10-year engagement and questioning opportunities to improve the clinical process of recognizing, diagnosing and treating vulvar dermatoses. Concerns about the lack of fundamental indicators of the clinical value of the tests used in the diagnostic approach to the vulva have led to the identification of this problem in routine gynecological care in its full spectrum.

The problem of aging in the general population, with a predominance of older women in whom vulvar dermatosis is most often revealed, is another remarkable issue [15-16]. This condition is responsible for chronic vulvar discomfort that further degrades the life quality, and progression to differentiated vulvar intraepithelial neoplasia may pose a risk of developing vulvar cancer [10].

The most influential prior observations that seemingly identical lesions in various regions of the vulva have different importance required deeper immersion in the histological and embryological characteristics of individual anatomical parts of the vulva [1, 17-20]. By modifying the viewing point and using an annular instead of a linear approach, the qualities of each of the three types of vulvar tissue were recognized and correlated, and three separate rings were identified as the ground for vulvar observation [2-3].

The appearance and texture of lesions in the four most common vulvar dermatoses and the possibility of simplifying all vulvar changes into two classes were observed [21]. By introducing the concepts of nonspecific and specific lesions in a new light, the conditions for using TRIV in the clinical diagnosis of vulvar dermatoses have been met. The magnification applied in vulvoscopy makes it possible to distinguish altered epithelial structure and even changes in subepithelial elements, particularly the presentation of blood vessels in the inner vulvar ring. With this stage, the technique fulfilled the principal doctrines of vulvoscopy.

An essential segment of the present work is to heighten consideration regarding developing suitable implements for evaluating test outcomes, as formerly advised [20]. The DATRIV study assessed the clinical value of the vulvoscopy index and the N-S-P scheme as parameters of the TRIV outcome to facilitate data management and gain the possibility of measurability and comparison of vulvoscopy results.

The vulvoscopy index considers the patient's medical history, clinical examination, and cotton swab test, as well as the specificity and localization of lesions towards the three vulvar rings according to TRIV. The work so far has shown the immense potential of the vulvoscopy index in the detection of vulvar dermatoses with a diagnostic accuracy of 96.9% [10]. Since the test result is a sum of points, a feasible option is to monitor the failing and improvement of treatment and compare the findings by corresponding to the outcome. That should be investigated by future research.

Additionally, the vulvoscopy index recognized two groups of patients with the same spectrum of nonspecific lesions. Still, one group had no symptoms (impaired vulvar skin), while the other patients were clinically diagnosed with vulvodynia. These unexpected results raise many questions. One question is whether the patients with impaired vulvar skin potential candidates for vulvodynia are.

Unlike the vulvoscopy index, the N-S-P scheme is founded

solely on examination of the vulva under colposcopy magnification and light to assess the specificity and localization of the vulvar lesions according to the vulvar rings. Thus, the N-S-P scheme is an explicit measure of the clinical value of TRIV. In addition, the result of this semiquantitative test has been straightforwardly expressed as pathological in the presence of vulvar dermatosis and normal or suspect if there is a lack of dermatosis.

Despite the considerable differences in the conception of these two tests, the DATRIV study showed their equal clinical value in detecting vulvar dermatosis. Paradoxically, it has been established that the diagnosis of vulvar dermatosis can be founded only on TRIV (N-S-P scheme). A patient history or clinical examination is not necessary to assemble that diagnosis. However, these are fundamental segments of a gynecological exam, and they should always be carried out to exclude other causes of chronic vulvar discomfort, primarily vulvodynia.

The N-S-P scheme uses fewer diagnostic steps in recognizing vulvar dermatosis than the vulvoscopy index; hence this test is simpler and a faster onset of use and more significant penetration of this test among clinicians is to be expected, especially in gynecological settings. It remains to be investigated whether the examination time is shorter by using this test.

The DATRIV study provided medical evidence to change the way of the observation and examination of the vulva and vulvar lesions. A simplified division of the vulvar changes into normal findings, nonspecific lesions, and specific lesions is appropriate in diagnosing vulvar dermatoses. A more comprehensive application of the tests in different conditions and under other circumstances will show the true clinical value of these tests and their applications in vulvology. The introduction of TRIV could mark a turning point for this clinically important aspect of the vulvar examination.

Furthermore, early dermatoses could be a critical area for applying this test due to the incapability of histopathology to recognize early forms of vulvar dermatoses, as shown in Tables 1 and 2. Histopathological changes in early dermatosis are absent or nonspecific; however, they have been described [22]. If other authors see this potential, the gold standard in diagnosing early forms of vulvar dermatosis could be reconsidered and redefined.

5. Conclusion and Recommendations

The DATRIV study offered a new concept of vulvoscopy based on the nature and location of vulvar lesions and added two diagnostic tests for the detection of vulvar dermatoses to medical evidence: the vulvoscopy index and the N-S-P scheme. Both tests showed a sensitivity, specificity, and diagnostic accuracy of 100%, 96.1%, and 96.9%, respectively, for detecting vulvar dermatosis, compelling new clinical tests in diagnosing vulvar dermatosis.

As the N-S-P scheme is founded solely on TRIV, this test represents an explicit outcome measure of the clinical value of TRIV.

Further research is needed to verify the value of TRIV and described tests in uncontrolled conditions, inter- and intraobserver variability, and the impact of additional education in vulvoscopy, dermatology and pathology on the implementation and duration of examinations. It is equally important to investigate the possibility of tests application to monitor improving and worsening of vulvar dermatoses and the ability to recognize early forms of vulvar dermatoses.

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