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Coll. Antropol. **30** (2006) 1: 137–142
Original scientific paper

Interobserver Variability in Cytologic Subclassification of Squamous Intraepithelial Lesions – The Bethesda System *vs.* World Health Organization Classification

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A B S T R A C T

The aim of the study was to compare interobserver variability for The Bethesda System (TBS) and World Health Organization (WHO) classification of cervical squamous intraepithelial lesions. A total of 1,000 conventional Papanicolaou smears (156 positive and 884 negative) were examined »blindly« by three cytologists and one cytotechnician. The degree of observer agreement was expressed by kappa statistics using a program for the calculation of interobserver variation and association »Agree« (Svanholm and Jergensen, 1989). Kappa (κ) was determined for each cytologic diagnosis within a particular classification and total for either classification. The association with and separation from other diagnoses was determined for each cytologic diagnosis in the form of conditional probability (P_j). In WHO classification, the diagnoses of dysplasia media and dysplasia gravis showed poor reproducibility (κ=0.114 and κ= 0.259, respectively), the diagnosis of dysplasia levis good reproducibility (κ=0.639), and the diagnosis of carcinoma in situ excellent reproducibility (κ=0.762). WHO classification yielded pool κ of 0.741. In TBS classification, the diagnosis of LSIL showed good, and HSIL excellent reproducibility (κ=0.542 and κ=0.763, respectively). TBS classification yielded pool κ of 0.699. Dysplasia media (P_j=0.121) and dysplasia gravis (P_j=0.274) were found to be morphologically poorly defined, and carcinoma in situ (P_j=0.777) and dysplasia levis (P_j=0.651) well defined diagnoses. LSIL was morphologically moderately defined (P_j=0.587) and HSIL well defined (P_j=0.789) diagnosis. Accordingly, TBS does not substantially improve diagnostic reproducibility of the cytologic diagnoses of squamous intraepithelial lesions, while providing considerably less information to the clinician than the four-grade dysplasia/CIS terminology, thus eliminating the opportunity of choosing a different procedure for the diagnosis of dysplasia media, which is of utmost importance in the population of young nulliparae.

***Key words**: observer variability, cervical cytology, intraepithelial lesions, TBS classification, WHO classification*

Introduction

Grading of the intraepithelial lesion severity by semiquantitative criteria such as »mild«, »moderate«, »severe«, »low« or »high« is a matter of the subjective judgment of the cytologist and pathohistologist, which entails considerable intra- and interobserver variability that increases with the number of options among which the morphologist may choose. Therefore, the classification of intraepithelial lesions has over time shown a continuous tendency to reduce the number of diagnoses from the initial three grades of dysplasia and carcinoma *in situ*[1] through four and three grades of cervical intraepithelial neoplasia[2,3] to only two grades of squamous intraepithelial lesions[4,5].

The Bethesda System (TBS)[4,5] uses a two-grade terminology for SIL, i.e. LSIL (low-grade) and HSIL (high-grade), based on the main virology, molecular and clinical evidence that LSIL mostly is a transient human papilloma virus (HPV) infection, whereas HSIL is more

Received for publication May 24, 2004

commonly associated with viral persistence and higher risk of progression[6–9]. This type of classification has been supported by the results of the National Cancer Institute (NCI) ALTS study[10], which demonstrated good reproducibility for LSIL and HSIL, but poor reproducibility for further HSIL subclassification into moderate and severe dysplasia or CIN2 and CIN3.

The question is whether the reproducibility of the two intraepithelial diagnoses in TBS classification is significantly better than the reproducibility of the four intraepithelial diagnoses in WHO classification, and is it of any practical value? The aim of the present study was to answer this question.

Materials and Methods

Study population included 1,000 selected conventional Papanicolaou smears obtained in daily routine by wooden spatula and cotton swab. The findings were classified according to 1988 TBS classification, while previous terms (three stages of dysplasia and carcinoma *in situ*, and three CIN stages) were used in parallel for squamous epithelial lesions, as recommended by the authors of TBS[4]. According to the initial cytologic evaluation, there were 844 negative findings (within normal limits, reactive and repair alterations) and 156 positive findings (intraepithelial or invasive lesions). The smears containing koilocytes alone and free from changes indicative of intraepithelial lesion, and those with atypical squamous cells of undetermined significance (ASCUS) were excluded from the study.

Three cytologists and one cytotechnician, following the mode of classification used in daily routine, examined these 1,000 smears »blindly«. All three terms (SIL, CIN, and dysplasia/CIS) were recorded for squamous intraepithelial lesions, thus making the classifications directly comparable upon single examination.

The degree of agreement (kappa values), association and separation of diagnoses (conditional probability) were determined by use of the »Agree« statistical software to calculate interobserver variation and association, developed in 1989 by Svanholm and Jergensen[11,12].

Data on WHO classification were entered first, where the four observers classified the cytologic findings of 1,000 smears into one of the eight diagnoses: negative finding (within normal limits, reactive and repair changes), dysplasia levis, dysplasia media, dysplasia gravis, carcinoma *in situ*, squamous cell carcinoma, atypical cylindrical cells of undetermined significance (AGCUS) – endocervical and adenocarcinoma – endocervical. These were followed by entering data on TBS classification, where the four observers classified the cytologic findings of 1,000 smears into one of the six findings: negative finding (within normal limits, reactive and repair changes), LSIL (dysplasia levis), HSIL (dysplasia media, dysplasia gravis and carcinoma *in situ)*, squamous cell carcinoma, atypical cylindrical cells of undetermined significance (AGCUS) – endocervical and adenocarcinoma – endocervical.

The degree of agreement between the results thus obtained was expressed by kappa statistics introduced by Cohen[13]. Kappa is a coefficient of observer agreement, which takes into account that part of the observed agreement between observers is due to chance. Kappa is defined as the observed agreement (P_o) adjusted for chance agreement (P_s), divided by the maximum possible agreement also corrected for the chance agreement ($\kappa = P_o–P_s/1–P_s$). Kappa values range from –1 to +1, with 0 representing only chance agreement.

Borderline kappa values (κ) set by Landis and Koch[14] and Fleiss[15] were used on interpretation of the results. According to these borderline values, kappa values greater than 0.75 are taken to represent excellent agreement beyond chance; values below 0.40 indicate agreement that is a little better than chance agreement; and values between 0.40 and 0.74 represent fair-to-good agreement beyond chance.

The association or separation of diagnoses was expressed as conditional probability (P_j) and presented in table of conditional probability. If a randomly chosen observer makes a diagnosis on a random sample, the table shows the probability for other randomly chosen observers to make the same or another diagnosis on the same sample. The sum of each row is 1.

Finally, the results referring to the diagnosis of squamous intraepithelial lesions were compared between the two classifications of cytologic findings employed in the study.

Results

According to WHO classification, all cytologic diagnoses had $\kappa>0$, indicating that interobserver agreement significantly exceeded chance agreement ($p<0.05$, Table 1). The κ values obtained for squamous intraepithelial lesions indicated low reproducibility for the diagnoses of dysplasia media ($\kappa=0.114$) and dysplasia gravis ($\kappa= 0.259$), fairly good reproducibility for the diagnosis of dysplasia levis ($\kappa=0.639$), and excellent reproducibility for the diagnosis of carcinoma *in situ* ($\kappa=0.762$). WHO classification yielded pool κ of 0.741 for the eight diagnoses observed.

According to TBS classification, both diagnoses also yielded $\kappa>0$, indicating that interobserver agreement significantly exceeded chance agreement ($p<0.05$, Table 2). The κ values showed fairly good reproducibility for the diagnosis of LSIL ($\kappa=0.542$) and excellent reproducibility for the diagnosis of HSIL ($\kappa=0.763$). TBS classification yielded pool κ of 0.699 for the six diagnoses observed.

Dysplasia media ($P_j=0.121$) and dysplasia gravis ($P_j=0.274$) were found to be morphologically poorly defined diagnoses that showed overlapping with all other intraepithelial diagnoses, even with negative findings. Carcinoma *in situ* ($P_j=0.777$) proved to be a well defined diagnosis marginally overlapping with the diagnosis of dysplasia gravis, however, a minimal probability for all

TABLE 1
STATISTICS FOR AGREEMENT FOR PARTICULAR SQUAMOUS INTRAEPITHELIAL CYTOLOGIC DIAGNOSES (WHO CLASSIFICATION)

Cytologic diagnosis	Statistical parameters					
	$\sum(n_{i,j})^2$	p_j	P_j	$Kappa_j$	Variance ($Kappa_j$)	$Kappa_j$/SE
DL	369	0.031	0.651	0.639	0.0002	49.53
DM	45	0.008	0.121	0.114	0.0002	8.82
DG	142	0.020	0.274	0.259	0.0002	20.27
CIS	883	0.066	0.777	0.762	0.0002	58.99

$\sum(n_{i,j})^2$ – sum of the squares of the number of observers who placed the i^{th} case in the j^{th} diagnosis, p_j – proportion of the j^{th} diagnosis, P_j – conditional probability that the second assignment is to j, given that the first was j, $Kappa_j$ – agreement beyond chance, Variance ($Kappa_j$), $Kappa_j$/SE – t-test for statistical significance to the normal distribution, DL – dysplasia levis, DM – dysplasia media, DG – dysplasia gravis, CIS – carcinoma *in situ*

TABLE 2
STATISTICS FOR AGREEMENT FOR PARTICULAR SQUAMOUS INTRAEPITHELIAL CYTOLOGIC DIAGNOSES (TBS CLASSIFICATION)

Cytologic diagnosis	Statistical parameters					
	$\sum(n_{i,j})^2$	p_j	P_j	$Kappa_j$	Variance ($Kappa_j$)	$Kappa_j$/SE
LSIL	1082	0.098	0.587	0.542	0.0002	41.97
HSIL	1488	0.111	0.789	0.763	0.0002	59.07

$\sum(n_{i,j})^2$ – sum of the squares of the number of observers who placed the ith case in the j^{th} diagnosis, p_j – proportion of the j^{th} diagnosis, P_j – conditional probability that the second assignment is to j, given that the first was j, $Kappa_j$ – agreement beyond chance, Variance ($Kappa_j$), $Kappa_j$/SE – t-test for statistical significance to the normal distribution, LSIL – low-grade squamous intraepithelial lesion, HSIL – high-grade squamous intraepithelial lesion

TABLE 3
ASSOCIATIONS BETWEEN CYTOLOGIC DIAGNOSES EXPRESSED AS CONDITIONAL PROBABILITY P_J (WHO CLASSIFICATION)*

Assignment by first observer	Probability assignment by second observer							
	NEG	DL	DM	DG	CIS	SCC	AGCUS	AC
DL	0.168	0.651	0.067	0.069	0.045	0.000	0.000	0.000
DM	0.121	0.254	0.121	0.273	0.222	0.000	0.000	0.010
DG	0.128	0.111	0.115	0.274	0.368	0.000	0.004	0.000
CIS	0.026	0.021	0.028	0.108	0.778	0.021	0.003	0.015

*Read the table horizontally: If an observer has allocated an object to one category, the table calculated the probability that another randomly selected observer will place the same case in the same or in another category. The sum of each row is 1 (total probability). NEG – negative, DL – dysplasia levis, DM – dysplasia media, DG – dysplasia gravis, CIS – carcinoma *in situ,* SCC – squamous cell carcinoma, AGCUS – atypical endocervical cylindric cells of undetermined significance, AC – adenocarcinoma

other diagnoses was recorded. Dysplasia levis (P_j= 0.651) was also found to be a fairly well defined diagnosis showing marginal overlapping with negative findings and minimal probability for other intraepithelial diagnoses (Table 3).

LSIL (P_j=0.587) proved to be a morphologically moderately defined diagnosis overlapping with negative findings and HSIL, whereas HSIL (P_j=0.789) was found to be a well-defined diagnosis with minimal probability for all other diagnoses (Table 4).

Comparison of the two classifications revealed a comparable degree of reproducibility for the diagnoses of LSIL and dysplasia levis (κ=0.542 and κ=0.639, respectively), and for those of HSIL and carcinoma *in situ* (κ=0.763 and κ=0.762, respectively), whereby additional information on the possible presence of dysplasia media and dysplasia gravis are unavailable on TBS.

Discussion

A certain degree of observer variability is characteristic of all diagnostic tests involving individual interpretation, including cytological as well as histological interpretation of intraepithelial findings, which are the reference standard for deciding on treatment options for cervical disease. There are many studies of inter- and intra-

TABLE 4
ASSOCIATIONS BETWEEN CYTOLOGIC DIAGNOSES EXPRESSED AS CONDITIONAL PROBABILITY P_J (TBS CLASSIFICATION)*

Assignment by first observer	Probability assignment by second observer					
	NEG	LSIL	HSIL	SCC	AGCUS	AC
LSIL	0.298	0.587	0.111	0.000	0.004	0.000
HSIL	0.072	0.099	0.789	0.019	0.008	0.013

*Read the table horizontally: If an observer has allocated an object to one category, the table calculated the probability that another randomly selected observer will place the same case in the same or in another category. The sum of each row is 1 (total probability). NEG – negative; DL – dysplasia levis, DM – dysplasia media, DG – dysplasia gravis, CIS – carcinoma *in situ*, SCC – squamous cell carcinoma, AGCUS – atypical endocervical cylindric cells of undetermined significance, AC – adenocarcinoma

observer variability[16–37], however, few have reported results in a standardized format of kappa, i.e. agreement adjusted for chance. A kappa varying between 0.22 and 0.69 has been reported for interobserver variability in the cytologic and histological grading of cervical lesions[16,22–24].

On histology, the diagnosis of CIN1 showed low reproducibility (κ=0.120–0.329) and that of CIN3 good reproducibility (κ=410–0.794)[16,17,25,26]. The introduction of TBS classification has resulted in higher reproducibility; however, it still suffers from the low reproducibility of the diagnosis of LSIL[27,28]. Analyzing the two classifications in parallel, McCluggage *et al.*[29] found both to yield a low level of reproducibility (κ=0.360).

Cytologic diagnoses are almost as reproducible as histological ones, only the cytological diagnosis of LSIL shows a higher degree of reproducibility than the histological diagnosis of these lesions[30–35]. In a large sample, Stoler and Schiffman[27] demonstrated the pool reproducibility of LBC (liquid based cytology), colposcopy biopsy and LEEP biopsy to be moderate and comparable (κ= 0.460 for cytology and colposcopy biopsy, and κ=0.490 for LEEP biopsy). The low reproducibility of histology was most evident for LSIL, which showed higher reproducibility on cytology than on histology.

Taking in consideration the etiologic association of HPV infection and cervical carcinoma, the fact that most low risk HPV types were associated with condylomata and CIN1 lesions and most high risk HPV types with CIN2/CIN3 lesions, and poor diagnostic reproducibility of the differentiation of mild, moderate and severe dysplasia/CIS, the Bethesda conference participants defined only two clinically relevant categories, i.e. low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). The classification of LSIL included HPV, mild dysplasia, or CIN1, and that of HSIL moderate dysplasia, severe dysplasia, CIS, or CIN2 and CIN3[4–9].

However, the results of the present study showed the two-grade TBS classification to have provided no substantial improvement of the diagnostic reproducibility of cytology, at the same time offering considerably less information than the four-grade dysplasia/CIS terminology[38]. The more so, pool reproducibility was even lower (κ=0.699) than for the three grades of dysplasia and carcinoma *in situ* (κ=0.741). LSIL showed comparably moderate reproducibility as dysplasia levis (κ=0.542 and κ=0.639, respectively), whereas HSIL showed identical reproducibility as the diagnosis of carcinoma *in situ* (κ=0.763 and κ=0.762, respectively).

The diagnosis of dysplasia media or CIN2 remains dubious, its natural course being closer to CIN1 than CIN3 according to the rate of progression. According to literature data, 43% of CIN2 lesions show spontaneous regression, whereas 35% are persistent. To compare it with other types of lesions, spontaneous regression has been reported in 57% and 32%, and persistence in 32% and 56% of CIN1 and CIN3 lesions, respectively[39]. In line with these rates, the clinical approach may be quite different in patients with CIN2 and those with CIN3 lesions, which is of paramount importance for the population of young nulliparae.

Accordingly, it appears quite justifiable to single out CIN2 (dysplasia media) from the HSIL group and differentiate it as a separate diagnostic entity. However, as it has been demonstrated to be morphologically most poorly defined diagnosis (P_j=0.121), it may be more suitable to consider it together with CIN1 due to their comparable natural course and identical treatment. In Croatia, we followed such a practice until 1990, with the cytologic finding IIIA including CIN1 and CIN2[40]. Having subsequently accepted TBS classification, we have continued using the previous dysplasia/CIS, and. CIN terminology for SIL, thus having left the possibility for a different treatment.

Either the level of reproducibility, association with HPV types, or biologic behavior[42] has not support the current classification into LSIL and HSIL.

Conclusion

TBS does not substantially improve diagnostic reproducibility of the cytologic diagnoses of SIL, at the same time providing considerably less data to the clinician than the four-grade dysplasia/CIS terminology. Pooled reproducibility was even lower for the three degrees of dysplasia and carcinoma *in situ*. LSIL was found to be as moderately reproducible as dysplasia levis, whereas HSIL showed excellent reproducibility, just as the diagnosis of carcinoma *in situ*.

CIN2 (dysplasia media) should be singled out from HSIL because of its different natural course and thus different treatment required, and should be differentiated as a separate diagnostic entity. However, as it is morphologically the most poorly defined diagnosis, it may prove more useful to classify it together with CIN1.

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INTEROBSERVER VARIJABILNOST U CITOLOŠKOJ SUBKLASIFIKACIJI SKVAMOZNIH INTRAEPITELNIH LEZIJA – BETHESDA SYSTEM (TBS) *VS.* WORLD HEALTH ORGANIZATION (WHO)

SAŽETAK

Cilj rada je bio usporediti interobserver varijabilnost za The Bethesda System (TBS) i World Health Organization (WHO) klasifikaciju skvamoznih intraepitelnih lezija cerviksa uterusa. Set od 1000 konvencionalnih Papa razmaza (156 pozitivnih i 884 negativnih) »na slijepo« su pregledala 3 citologa i jedan citotehničar. Stupanj slaganja je izražen kappa statistikom pomoću programa za računanje interobserver varijacija i asocijacija »Agree« (Svanholm i Jergensen, 1989.). Weighted κ je određen za svaku citološku dijagnozu unutar klasifikacije, kao i za klasifikacije u cijelosti. Za svaku citološku dijagnozu je određena povezanost, odnosno razgraničenost s drugim dijagnozama u obliku uvjetne vjerojatnosti (P_j). Kod WHO klasifikacije su slabo reproducibilne dijagnoze dysplasia media (κ=0,114) i dysplasia gravis (κ=0,259), prilično dobro je reproducibilna dijagnoza dysplasia levis (κ=0,639), a odlično je reproducibilna dijagnoza carcinoma in situ (κ=0,762). Za klasifikaciju u cijelosti κ je 0,741. Kod TBS klasifikacije LSIL je prilično dobro rep-

roducibilna dijagnoza (κ=0,542), dok je HSIL odlično reproducibilna dijagnoza (κ=0,763). Za klasifikaciju u cijelosti κ je 0,699. Dysplasia media (P=0,121) i dysplasia gravis (P_j=0,274) su morfološki slabo definirane dijagnoze, carcinoma in situ (P_j=0,777) i dysplasia levis (P_j=0,651) su dobro definirane dijagnoze. LSIL (P_j=0,587) je morfološki srednje definirana dijagnoza, dok je HSIL (P_j=0,789) dobro definirana dijagnoza.TBS ne popravlja bitno dijagnostičku reproducibilnost citoloških dijagnoza za skvamozne intraepitelne lezije, a kliničaru daje znatno manje informacija nego četverodijelna dysplasia / CIS terminologija i time oduzima mogućnost različitog postupka za dijagnozu dysplasia media što je osobito važno za populaciju mladih nulipara i trudnica.