

Descriptive Analysis Of Cervical Cytology By Bethesda System With Histological Correlation In A Tertiary Centre In Jabalpur- A Study Of 800 Cases

Pathology

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Abstract:

Background: Cervical cancer is a unique malignancy that can be prevented, as the process typically starts from the cervical epithelium and the cervix is readily amenable organ for examination. The Gold standard in the the diagnosis of cervical intraepithelial neoplasia (CIN) is morphological assessment. A diagnosis of CIN is based primarily on the presence of nuclear atypia and loss of normal squamous maturation (polarity).

Aims: To assess the prevalence of surface epithelial lesions among all Pap smears and to study the cyto-histological correlation, in cases where biopsies are available.

Material and Methods: The patients selected for study included those presenting with various complaints like discharge, bleeding per vaginum, low backache, pain in abdomen, irregular menstrual cycles and contact bleeding etc. In all patients cervico-vaginal smear were analyzed based on 2001 Bethesda system. Coloposcopic and cervical biopsies were taken when possible with patient concurrence and stained using Haematoxylin & Eosin. Cytohistological correlation was done in these cases to assess the sensitivity and specificity of the cytological method of diagnosis.

Results: The maximum incidence of surface intraepithelial lesion i.e. LSIL and HSIL belonged to the age group of 30-39 years. The maximum number of cases squamous cell carcinoma was in 40-59 years of age group. 71% of patients of the study group belong to low socioeconomic status. Incidence of ASC-US, ASC-H, HSIL and Squamous cell carcinoma were also maximum in low socioeconomic group. An increased percentage of LSIL (35%) was seen in middle socio-economic group.

The maximum number of cases of surface intraepithelial lesion and squamous cell carcinoma was present in which the age of marriage was < 16 or 16-17 years.

Conclusion: All high risk groups which include women with early marriage, early age at first intercourse, multiple sexual partners, young age at first pregnancy – poor socio-economic status, poor nutrition, poor hygiene with mutiparity and closely spaced pregnancies. The high risk groups also include erosion, cervicitis, HPV infection and STD, immuno-suppressed patients, patients on high risk dose oral contraceptive pills and follow-up cases of dysplasias even after treatment to detect recurrence.

Keywords: Descriptive analysis, cervical cytology, Bethesda system, tertiary centre.

Introduction:

Cervical cancer is a unique malignancy that can be prevented, as the process typically starts from the cervical epithelium and the cervix is readily amenable organ for examination.¹ Thus, screening of the cervix can prevent development of cancer and even if it has developed, can be diagnosed and treated in early stage.² The basis for any screening programme include: A long latent period in which premalignant change or

occult cancer can be detected and effective treatment for premalignant change and for cancer.

Therefore, all high risk groups which include women with early marriage, early age at first intercourse, multiple sexual partners, young age at first pregnancy – poor socio-economic status, poor nutrition, poor hygiene with multiparity and closely spaced pregnancies.^{3,4,5} The high risk groups also include erosion, cervicitis, HPV infection and STD, immuno-suppressed patients, patients on high risk dose oral contraceptive pills and follow-up cases of dysplasias even after treatment to detect recurrence.⁶ The Gold standard in the diagnosis of cervical intraepithelial neoplasia (CIN) is morphological assessment. A diagnosis of CIN is based primarily on the presence of nuclear atypia and loss of normal squamous maturation (polarity).⁷

Material and Methods:

The patients selected for study included those presenting with various complaints like discharge, bleeding per vaginum, low backache, pain in abdomen, irregular menstrual cycles and contact bleeding etc. In all patients cervico-vaginal smear were made by means of Ayres-spatula and cotton swab stick. The smears were immediately fixed in 95% alcohol for ½ minutes and then stained by Papanicolaou method and analyzed based on 2001 Bethesda system. Colposcopic and cervical biopsies were taken when possible with patient concurrence and stained using Haematoxylin & Eosin. Cytological correlation was done in these cases to assess the sensitivity and specificity of the cytological method of diagnosis.

Method of Collection:

Patients were advised to avoid coitus, vaginal douche or any other local medication 48 hrs prior to sample collection. Examination was done in lithotomy position, Cusco's self retaining speculum was placed, without any lubricant and prior to per-vaginum examination, to visualize vagina and cervix for any abnormality. Endocervical brush was placed inside endocervix and rolled firmly. Then Ayre's spatula was placed against cervix with its longer limb within the endocervical canal and firmly rotated 3600 to scrape the entire transformation zone, Sample obtained was immediately smeared on glass slides and wet fixed. The smears were stained with Papanicolaou technique after at least 30 minutes of wet fixation in 95% ethanol.

Results:

TABLE – 1:
Distribution of the Studied Cases According to Various Cytological Findings (N=750)

S . No.	Cytological Categorization	No. of Cases	Percentage
1.	Specimen Adequacy		
I	Unsatisfactory for evaluation	50	6.3
II	Satisfactory for evaluation	750	93.8
2.	General Categorization (n=750)		
I	<u>Negative for intra epithelial Lesion /malignancy</u>	650	81.3
	NILM (NOS)	355	47.3
(a)	Organisms	63	8.4
	Trichomonas	22	2.9
	Candida albicans	2	0.26
	Gardenella vaginalis	37	4.936
	Herpes simplex virus	1	0.13
	Tuberculosis	1	0.13
(b)	Reactive cellular changes associated with inflammation and Repair	215	28.6
(c)	Atrophic	17	2.26
II	Squamous cell abnormalities	100	13.3
a	Atypical Squamous cells of undetermined significance (ASC-US)	26	3.46
b	Atypical Squamous cells can not exclude HSIL (ASC-H)	10	1.3
C	LSIL	31	4.13
D	HSIL	20	2.66
e	Invasive carcinoma cervix	13	1.73
		750	100

Table 1 shows that majority of cases 86.6% were Negative for intraepithelial lesion/malignancy. In this group organism could be cytologically identified in 63 (8.04%) cases. The most common was Gardenella vaginalis in 37 (5%) cases followed by trichomonas vaginalis 22 (3%) cases. Fungal spores (Candida albicans) could be identified in only 2(0.6%) cases while there was a single patient each showing herpes simplex and tuberculosis infection. There were 215 (28.6%) cases showing reactive cellular changes associated with inflammation and repair, while atrophic smears were seen in 17 (2.2%) cases.

Squamous cell abnormalities were observed in 100 (13.3%) cases among these LSIL was the commonest constituting 4.13% followed by ASC-US which was observed in 26

(3.46%) cases. HSIL was found in 20 (2.66%) cases. In 10 (1.13%) cases atypical squamous cells were seen in which HSIL could not be excluded (ASC-H). There were 13 cases (1.73%) of invasive carcinoma of cervix.

Table – 2:
Correlation between Age and Cervical Cytology (n = 750)

Age (In years)	NILM	ASC-US	ASC-H	LSIL	HSIL	SCC	Total (%)
<20	9 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.2)
20-29	153 (23.5)	4 (15.4)	3 (30)	6 (19.4)	1 (5)	1 (7.7)	168 (22.4)
30-39	266 (40.9)	11 (42.3)	2 (20)	14 (45.2)	7 (35)	2 (15.4)	302 (40.26)
40-49	150 (23.1)	7 (26.9)	2 (20)	5 (16.1)	4 (20)	4 (30.8)	172 (22.9)
50-59	45 (6.9)	2 (7.7)	3 (30)	4 (12.9)	4 (20)	5 (38.5)	63 (8.4)
60-69	24 (3.7)	1 (5)	0 (0.0)	2 (6.5)	3 (15)	1 (7.7)	31 (4.1)
70+	3 (0.5)	1 (5)	0 (0.0)	0 (0.0)	1 (5)	0 (0.0)	5 (0.6)
Total	650 (100)	26 (100)	10 (100)	31 (100)	20 (100)	13 (100)	750 (100)
Mean ±SD Median	35.81 ±10.39 35.0	38.12 ±11.53 36.50	38.80 ±11.29 38.50	37.87 ±10.23 36.0	45.95 ±14.65 45.0	45.69 ±10.29 47.0	36.46 ±10.75 35.0

Table 2 shows on various cytological findings according to different age groups. The mean age of overall cases was found to be 36.46 (±10.75) years. The mean age of cases observed with NILM was found 35.81 (± 10.39) years, for cases with ASCUS it was 38.12 (± 11.53) years for cases with ASCUS-H 38.80 (± 11.29) for LSIL it was 37.87 (± 10.23) while the mean age of HSIL and SCC was observed at 45.95 (± 14.65) years and 45.69 (± 10.29) respectively. The mean age of the cases observed with HSIL and SCC was significantly higher ($P < 0.001$) compared with the mean age of other categories

Table – 3: Correlation between Age at Marriage and cervical cytology. (n = 750)

Age at Marriage (In years)	NILM	ASC-US	ASC-H	LSIL	HSIL	SCC	Total (%)
<16	3 (0.46)	0 (0.0)	2 (20)	0 (0.0)	5 (25)	3 (23.1)	13 (1.7)
16-17	112 (17.2)	21 (80.8)	5 (50)	8 (25.8)	12 (60)	7 (53.8)	165 (22.0)
18-19	445 (68.5)	3 (11.5)	3 (30)	18 (58.1)	2 (10)	3 (23.1)	474 (63.2)
20-21	78 (12)	2 (7.7)	0 (0.0)	5 (16.1)	1 (5)	0 (0.0)	86 (11.5)
22-23	11 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (1.5)
> 23	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Total	650 (100)	26 (100)	10 (100)	31 (100)	20 (100)	13 (100)	750 (100)
Mean ±SD Median	18.26 ±1.14 18.00	17.00 ±1.35 17.00	16.90 ±1.28 17.00	18.16 ±1.12 18.00	16.35 ±1.42 16.00	16.38 ±1.12 16.00	18.11 ±1.24 18.00

Table 3 shows that correlation between age at marriage and cytological findings. The results showed that the age at marriage of cases with SCC was 16.38 (± 1.12) years and with HSIL it was 16.35 (± 1.42) years and this was considerably lower than those who were diagnosed with LSIL (18.16 ± 1.12) years, ASCUS (17.00 ± 1.35) years and NILM (18.26 ± 1.14). The Median age of marriage of the cases diagnosed with SCC and HSIL was 16 years as compared to median age of NILM cases which was 18 years.

Table – 4:
Correlation between Locality and cervical Cytology.
(n = 750)

Locality	NILM	ASC-US	ASC-H	LSIL	HSIL	SCC	Total
Rural	263 (40.5)	10 (38.5)	4 (40.0)	11 (35.5)	10 (50.0)	7 (53.8)	305 (40.7)
Urban	387 (59.5)	16 (61.5)	6 (60.0)	20 (64.5)	10 (50.0)	6 (46.2)	445 (59.3)
Total	650	26	10	31	20	13	750

Table 4 shows that correlation between locality and cytological findings. NILM category was more common in urban cases (59.5%) where as squamous cell carcinoma was more in rural class (53.8%). Cases of LSIL were seen twice in urban group.

Table – 5:
Correlation between cervical cytology and Complains. (n = 750)

Cytology Report	Complains						Total
	Discharge	PCB	PMB	IMB	Pain in Abd	Other	
NILM	482 (89.3)	11 (57.9)	18 (60)	50 (86.2)	61 (81.3)	28 (100)	650 (86.7)
ASC-US	16 (3.0)	1 (5.3)	2 (6.7)	2 (3.4)	5 (6.7)	0 (0.0)	26 (3.5)
ASC-H	6 (1.1)	1 (5.3)	1 (3.3)	0 (0.0)	2 (2.7)	0 (0.0)	10 (1.3)
LSIL	20 (3.7)	2 (10.5)	2 (6.7)	1 (1.7)	6 (8.0)	0 (0.0)	31 (4.1)
HSIL	10 (1.9)	4 (21.1)	2 (6.7)	4 (6.9)	0 (0.0)	0 (0.0)	20 (2.7)
SCC	6 (1.1)	0 (0.0)	5 (16.7)	1 (1.79)	1 (1.3)	0 (0.0)	13 (1.7)
Total	540 (100)	19 (100)	30 (100)	58 (100)	75 (100)	28 (100)	750 (100)

PCB - Post coital bleeding; PMB-Post menopausal bleeding; IMB- Intermenstrual bleeding

In table 5, Vaginal discharge was the most common complaint observed in all cases including SCC, HSIL & LSIL. PCB (17.4%), IMB (6.8%) & PMB (6.5%) with discharge observed in HSIL cases. In 85% of SCC cases discharge & post menopausal bleeding were the most common complaint.

Table – 6 Correlation Between Parity and cervical cytology. (n = 750)

Parity	NILM	ASC-US	ASC-H	LSIL	HSIL	SCC	Total
Nulli	132 (20.3)	4 (15.4)	1 (10.0)	5 (16.1)	2 (10.0)	2 (15.4)	146 (19.5)
Multi	518 (79.7)	22 (84.6)	9 (90.0)	26 (80.6)	18 (90.0)	11 (84.6)	604 (80.5)
Total	650	26	10	31	20	13	750

Table 6 shows correlation between parity & cytological findings. Multiparous female contributed 80% of all cases, and increased no. of cases of ASC-US, ASC-H, HSIL & SCC were seen in multiparous women.

Table – 7:
Correlation between Effective marital duration and cervical cytology (n = 750)

EMD (in years)	NILM	ASC-US	ASC-H	LSIL	HSIL	SCC	Total
<5 yrs	82 (12.6)	1 (3.8)	0 (0.0)	3 (9.7)	0 (0.0)	0 (0.0)	86 (11.5)
5-10	84 (12.9)	3 (11.5)	3 (30.0)	3 (9.7)	1 (5.0)	1 (7.7)	95 (12.7)
10-15	145 (22.3)	5 (19.2)	0 (0.0)	4 (12.9)	4 (20.0)	0 (0.0)	158 (21.1)
15-20	111 (17.1)	6 (23.1)	2 (20.0)	10 (32.3)	2 (10.0)	2 (15.4)	133 (17.7)
20-25	97 (14.9)	5 (19.2)	1 (10.0)	4 (12.9)	2 (10.0)	2 (15.4)	111 (14.8)
25+	131 (20.1)	6 (23.0)	4 (40)	7 (22.5)	11 (55)	8 (61.5)	167 (22.2)
Total	650 (100)	26 (100)	10 (100)	31 (100)	20 (100)	13 (100)	750 (100)

Table 7 shows , effective marital duration >25 years shows greater number of cases of ASC-H, HSIL & SCC. Forty five percent with EMD between 10-25 years were NILM all cases of which EMD <10 years, 2 of 192 shows HSIL & SCC.

Cases with EMD of > 25 years showed maximum number of SCC (61.5%). HSIL (55%), category showed similar preponderance. Findings of NILM were distributed evenly in all EMD groups.

Table 8 -
Correlation between cervical cytology and Histopathological findings (n = 98)

PAP	Benign	CIN I	CIN II	CIN III	Invasive	Total
NILM	53 (81.5)	7 (10.88)	4 (6.2)	1 (1.5)	0 (0)	65 (100)
ASC-US	4 (66.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	6 (100)
ASC-H	2 (33.33)	2 (33.33)	0 (0.0)	0 (0.0)	2 (33.33)	6 (100)
LSIL	3 (60)	2 (40)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)
HSIL	2 (22.22)	1 (11.11)	0 (0.0)	2 (22.22)	4 (44.5)	9 (100)
SCC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100)	7 (100)
Total	64	12	5	4	13	98

Table 8 shows the Correlation between Cervical cytology and Histopathological findings. Out of 65 cases diagnosed cytologically as NILM, the histology (benign) matched cytological diagnosis in 53 (81.5%) cases. In others 7 (10.88%) were CIN I, 4 (6.2%) were CIN II, 1 (1.5%) were CIN III by histology.

There were 6 cases of ASCUS out of which 4 (66.7%) confirmed to be benign by histology. Among the remaining CIN I and CIN II was seen histologically in 1 (16.7%) case each.

Among 6 cases of ASC-H 2 showed CIN I and 2 could be confirmed as invasive carcinoma 2 (33.33%). However 2 (33.33%) showed benign changes on histology. There were 5 cases of LSIL by cytology, while diagnosis would be histologically confirmed in only 2 (40 %) cases. The remaining 3 (60%) cases were histologically benign.

In all 9 cases of HSIL, 4 (44.5%) cases were invasive, 2 (22.22%) were CIN III and 1 (11.11%) cases were CIN I on histology. However 2 turned out to be benign by histology.

Lastly all 7 cases of squamous cell carcinoma were confirmed histologically.

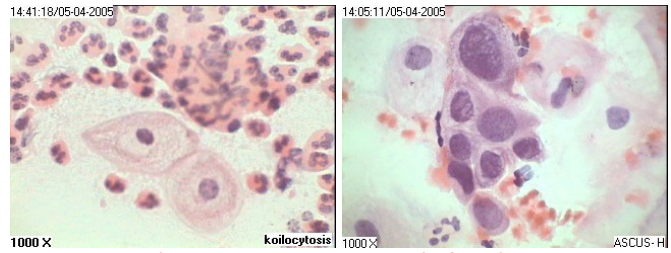


Fig 5:
LSIL (HPV Infection) -
Perinuclear halo

Fig6: High grade
squamous intraepithelial
lesion

Discussion:

Table 1 shows that majority of cases 86.6% were Negative for intraepithelial lesion/ malignancy. In this group organism could be cytologically identified in 63 (8.04%) cases. The most common was *Gardenerella vaginalis* (Fig 2) in 37 (5%) cases followed by *trichomonas vaginalis* (Fig 3) 22 (3%) cases. Fungal spores (*Candida albicans*) could be identified in only 2(0.6%) cases while there was a single patient each showing herpes simplex (Fig 1) and tuberculosis infection. There were 215 (28.6%) cases showing reactive cellular changes associated with inflammation and repair, while atrophic smears were seen in 17 (2.2%) cases. Squamous cell abnormalities were observed in 100 (13.3%) cases among these LSIL (Fig 5) was the commonest constituting 4.13% followed by ASC-US which was observed in 26 (3.46%) cases. HSIL (Fig 6) was found in 20 (2.66%) cases. In 10 (1.13%) cases atypical squamous cells were seen in which HSIL could not be excluded (ASC-H). There were 13 cases (1.73%) of invasive carcinoma of cervix.

Table 2 shows on various cytological findings according to different age groups. The mean age of overall cases was found to be 36.46 (± 10.75) years. The mean age of cases observed with NILM was found 35.81 (± 10.39) years, for cases with ASCUS it was 38.12 (± 11.53) years for cases with ASCUS-H 38.80 (± 11.29) for LSIL it was 37.87 (± 10.23) while the mean age of HSIL and SCC was observed at 45.95 (± 14.65) years and 45.69 (± 10.29) respectively. The mean age of the cases observed with HSIL and SCC was significantly higher ($P < 0.001$) compared with the mean age of other categories

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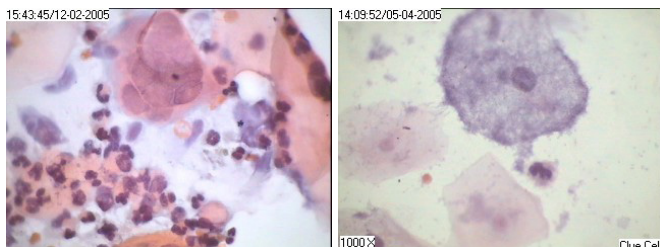


Fig 1:
Herpes Genitalis Infection
(Multinucleated Cell) X 400

Fig 2:
Gardenerella Vaginalis
Infection

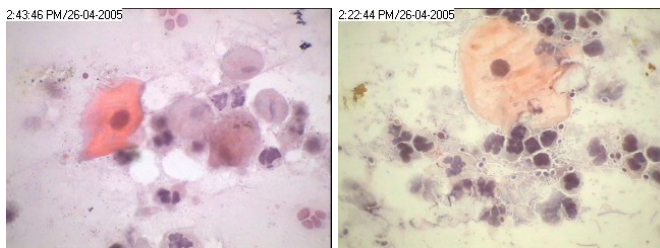


Fig 3:
Trichomonas vaginalis
infection X 1000

fig 4:
Candida Infection
(Conidias) X 400

and NILM (18.26 ± 1.14). The Median age of marriage of the cases diagnosed with SCC and HSIL was 16 years as compared to median age of NILM cases which was 18 years.

Table 4 shows that correlation between locality and cytological findings. NILM category was more common in urban cases (59.5%) where as squamous cell carcinoma was more in rural class (53.8%). Cases of LSIL were seen twice in urban group.

Table 5 shows Vaginal discharge was the most common complaint observed in all cases including SCC, HSIL & LSIL. PCB (17.4%), IMB (6.8%) & PMB (6.5%) with discharge observed in HSIL cases. In 85% of SCC cases discharge & post menopausal bleeding were the most common complaint.

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2 turned out to be benign by histology. Lastly all 7 cases of squamous cell carcinoma were confirmed histologically.

Conclusion:

1. The maximum incidence of surface intraepithelial lesion i.e. LSIL and HSIL belonged to the age group of 30-39 years. The maximum number of cases squamous cell carcinoma was in 40-59 years of age group. 71% of patients of the study group belong to low socioeconomic status. Incidence of ASC-US, ASC-H, HSIL and Squamous cell carcinoma were also maximum in low socioeconomic group. An increased percentage of LSIL (35%) was seen in middle socio-economic group.
2. The maximum number of cases of surface intraepithelial lesion and squamous cell carcinoma was present in which the age of marriage was < 16 or 16-17 years.
3. The maximum incidence of surface intraepithelial lesion i.e. LSIL and HSIL belonged to the age group of 30-39 years. The maximum number of cases squamous cell carcinoma was in 40-59 years of age group. 71% of patients of the study group belong to low socioeconomic status. Incidence of ASC-US, ASC-H, HSIL and Squamous cell carcinoma were also maximum in low socioeconomic group. An increased percentage of LSIL (35%) was seen in middle socio-economic group.
4. The maximum number of cases of surface intraepithelial lesion and squamous cell carcinoma was present in which the age of marriage was < 16 or 16-17 years.
5. In 650 NILM cases different organism 63 (8.4%) cases were found. out of 63 cases gardenerella vaginalis 5%, trichomonas vaginalis 3%, candida (0.6%) and single case of tuberculosis and herpes simplex was found.
6. Pap smear of 215 cases showed reactive cellular changes associated with inflammation and repair. These patients were advised repeat pap smear after the control of inflammation. Seventeen cases had atrophic smears.

7. In 26 cases were diagnosed as having atypical squamous cells of undetermined significance (ASC-US) 6 of these 26 cases biopsy was done and histological diagnosis came out to be CIN II in 1 case CIN III in 1 case and chronic cervicitis in 4 cases. Atypical squamous cell cannot exclude high grade lesion (ASC-H) was the diagnosis in 10 cases and 6 of them underwent colposcopic biopsy. The histological findings in these were CIN I in 2 cases, 2 cases invasive and chronic cervicitis in 2 cases.
8. Fifty one cases were diagnosed with various grades of squamous intraepithelial lesion: Low grade squamous intraepithelial lesion (LSIL) – 31 cases and High grade SIL (HSIL) – 20.
9. Thirteen cases of frank invasive carcinoma were diagnosed. All of them of squamous cell type. Large cell nonkeratinizing type- 9 cases, large cell keratinizing type – 3 cases, small cell type – 1 case.
10. Histology co-related with cytology in 98 cases having various grades of SIL and invasive carcinoma. Hundred percent correlation was found in invasive carcinoma, while there is lack of correlation of milder grade of atypia i.e. LSIL and HSIL. 12 cases were diagnosed as false negative. The most common cause of false negative was sample failure where there were no abnormal cells on the slide. This could have been due to non-optimal preparation or non optimal collection.
11. False positivity was noted in 7 cases. Cervicovaginal smears having atypical metaplastic cells and atrophic smears were the frequent cause of false positivity.
12. The sensitivity of Pap smear in detecting squamous intraepithelial lesions and invasive carcinoma of cervix was found to be 62.5%, specificity was 88.3%, positive predictive value was 74.1% and negative predictive value was 81.5%.

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