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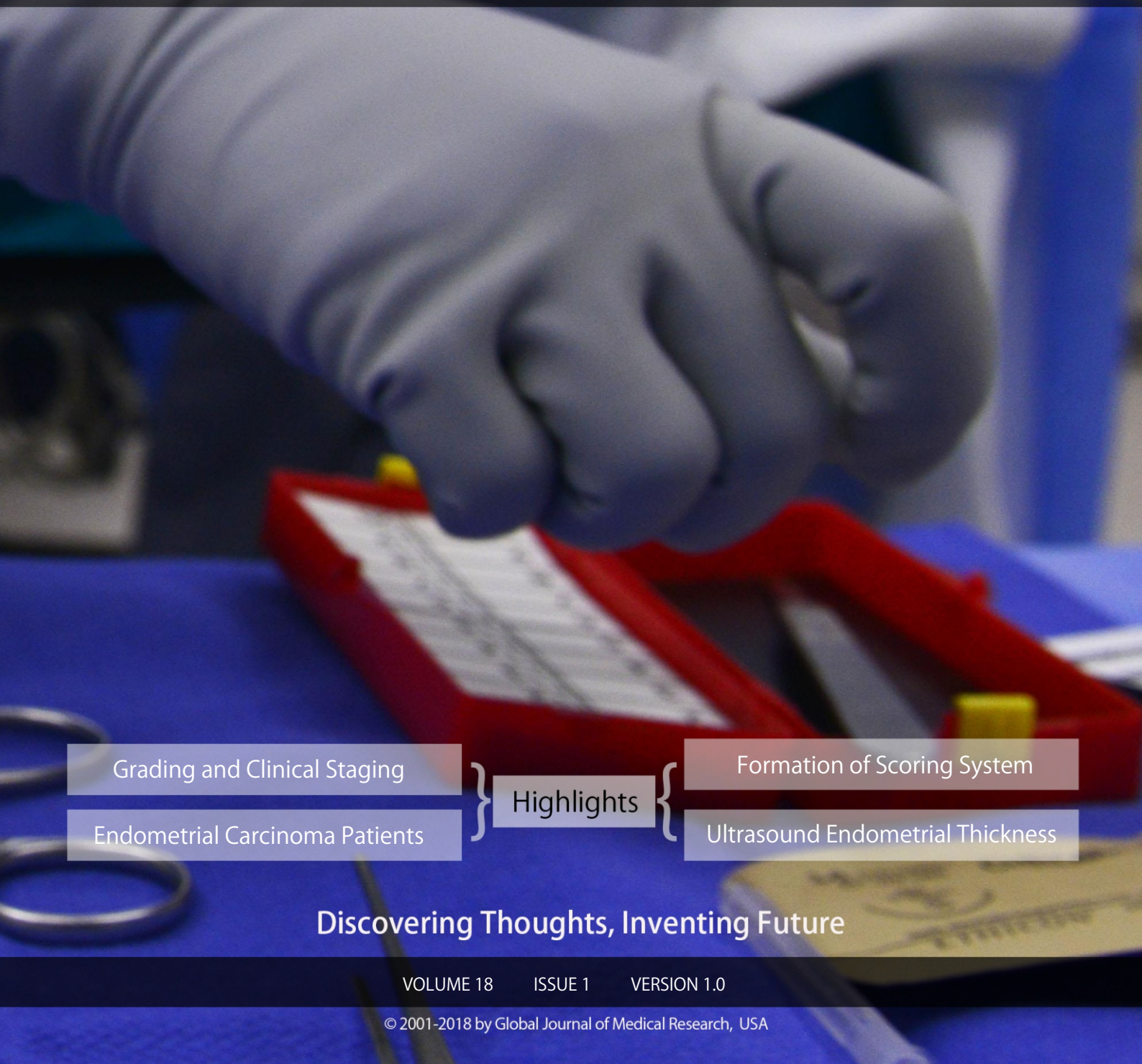

Grading and Clinical Staging

Endometrial Carcinoma Patients

Highlights

Formation of Scoring System

Ultrasound Endometrial Thickness

Discovering Thoughts, Inventing Future

VOLUME 18 ISSUE 1 VERSION 1.0

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The Formation of a Scoring System to Diagnose Endometriosis

By Adibah Ibrahim, Pang Suk Chin & Wan Zahiruddin Wan Mohd
Universiti Sains Malaysia

Abstract- Endometriosis is diagnosed by direct visualization of the lesion, with or without histopathology confirmation, which is often declined by the patients. A non-invasive diagnostic scoring system was formulated to identify patients high likely to have endometriosis, who refused to undergo surgery for diagnosis confirmation.

Objectives: To evaluate the reliability of a non-invasive diagnostic scoring system to diagnose endometriosis.

Results: A non-invasive diagnostic tool named CliEndomet was formulated based on clinical presentation, ultrasound findings and serum Ca125 of patients.

Conclusion: CliEndomet scoring system is a reliable diagnostic tool to diagnose endometriosis in patients who refuse to undergo surgical diagnosis and intervention.

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The Formation of a Scoring System to Diagnose Endometriosis

Adibah Ibrahim [α], Pang Suk Chin [σ] & Wan Zahiruddin Wan Mohd. [ρ]

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Conclusion: CliEndomet scoring system is a reliable diagnostic tool to diagnose endometriosis in patients who refuse to undergo surgical diagnosis and intervention.

I. Introduction

Endometriosis is a common gynecology disorder affecting women of reproductive age. It is a disease characterized by the presence of tissue that is biologically and morphologically similar to the endometrium, containing endometrial glands and stroma, in ectopic locations outside the uterine cavity. The diagnosis of endometriosis cannot be made based on clinical manifestations due to its variable manifestation. Biological markers such as serum Ca125 and IL6 are non-specific and may not reflect the disease well. Ultrasound has limited value to diagnose endometriosis, but it may be helpful to exclude ovarian endometrioma (Moore J, 2002). At present, visualization of the endometriotic lesion, either via laparoscopic or laparotomy, remains the gold-standard to diagnose endometriosis. However, the lack of experience and skill of the surgeon to recognize the lesion limits its accuracy as diagnostic tool (Razvan et al., 2010). Also the fact that there is a high prevalence of women with pelvic pain who refuse to undergo the operation in this region made the accurate diagnosis nearing impossible.

Because of the above reasons, we try to look into a non-invasive method to diagnose endometriosis, by combining the clinical manifestation, ultrasound finding and the level of serum Ca125, and later forming a scoring system to diagnose endometriosis.

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II. Objectives

The objective of this study is to formulate a diagnostic scoring system to diagnose endometriosis, and subsequently test its reliability and validity, to diagnose endometriosis, by comparing it with the gold-standard method by direct visualization of the endometriotic lesion.

III. Methodology

All women who came to the general gynecology and Infertility Clinic of Hospital USM with pelvic pain within the age of 18 to 45 years old were randomized to participate in the study, using the computer-generated block-of-ten randomization. We excluded women who were previously diagnosed to have endometriosis. We obtained written consent from the patients.

The pelvic pain was assessed using the modified version of Andersch and Milsom's multidimensional verbal rating scale. This scale defines pain according to the limitation of ability to work (unaffected = 0, rarely affected = 1, moderately affected = 2, clearly affected = 3), co-existing of systemic symptoms (absent=0, present=1), and the need for analgesia (no=0, yes=1), and rank the total sum in three groups (1-2=mild, 3-4=moderate, 5=severe) (Konincky PR, 1996). The severity of deep dyspareunia and dyschezia was evaluated using a 10-point linear analog scale in which 0 indicated no pain and 10 indicated unbearable pain.

We determined the presence of any pelvic mass by performing the abdominal examination and bimanual vaginal examination. In the presence of a mass, we determined its site, margin, surface, consistency, mobility and tenderness.

Using a transvaginal scan, we further evaluated the features of the mass. We collected the late luteal phase serum Ca125via venipuncture.

All women underwent laparoscopic surgery, where the presence of any endometriotic lesion was documented and staged using the revised American Fertility Society scoring system, and tissue biopsy were performed and sent for histology examination and diagnosis.

The diagnosis of endometriosis was made based on the positive findings of endometriotic lesions during the operation, with or without the confirmation of tissue histology biopsy.

An analysis was made on the data of the women. The simple logistic regression test is used to analyze the clinical symptoms, physical examination findings, ultrasound findings and the level of serum Ca125 of the patients. From this, we selected the significant variables for further analysis using the multiple logistic regression tests to predict the presence of endometriosis. From this, the presence of dysmenorrhoea, pelvic mass and the level of serum Ca125 between 50 to 200u/ml were significantly associated with the presence of endometriosis. Subsequently, a diagnostic scoring system was formulated and tested for its reliability and validity.

IV. Results

A total of 176 women at the age of 35.41 ± 6.90 years, with parity 2.10 ± 2.30, were recruited into the study. 106 women (60.22%) had fertility issues, with the mean duration of subfertility of 4.12 ± 5.41 years. A total of 103 women (58.52%) were diagnosed to have endometriosis during operation, in which 92 of them (89.32%) confirmed by histology examination.

Among the 176 women, 169 women (96.00%) had dysmenorrhea with equal distribution of severity. Out of the 169 women, 100 of them (59.17%) were confirmed to have endometriosis. A total of 26 women had dyspareunia, in which 19 women (73.08%) confirmed to have endometriosis. Only four women had dyschezia and two confirmed to have endometriosis.

158 women were noted to have pelvic masses, confirmed by ultrasound. 75 of them (47.47%) were uniloculated while the rest were multiloculated. 42 women with uniloculated ovarian cyst (56.00%) were noted to have endometriosis, as compared to 57 women with multiloculated cyst (68.67%). Among all ovarian cyst noted 107 of them (67.72%) had the typical feature of endometrioma, which is the ground glass appearance, in which 98 women (91.59%) had endometriosis confirmed.

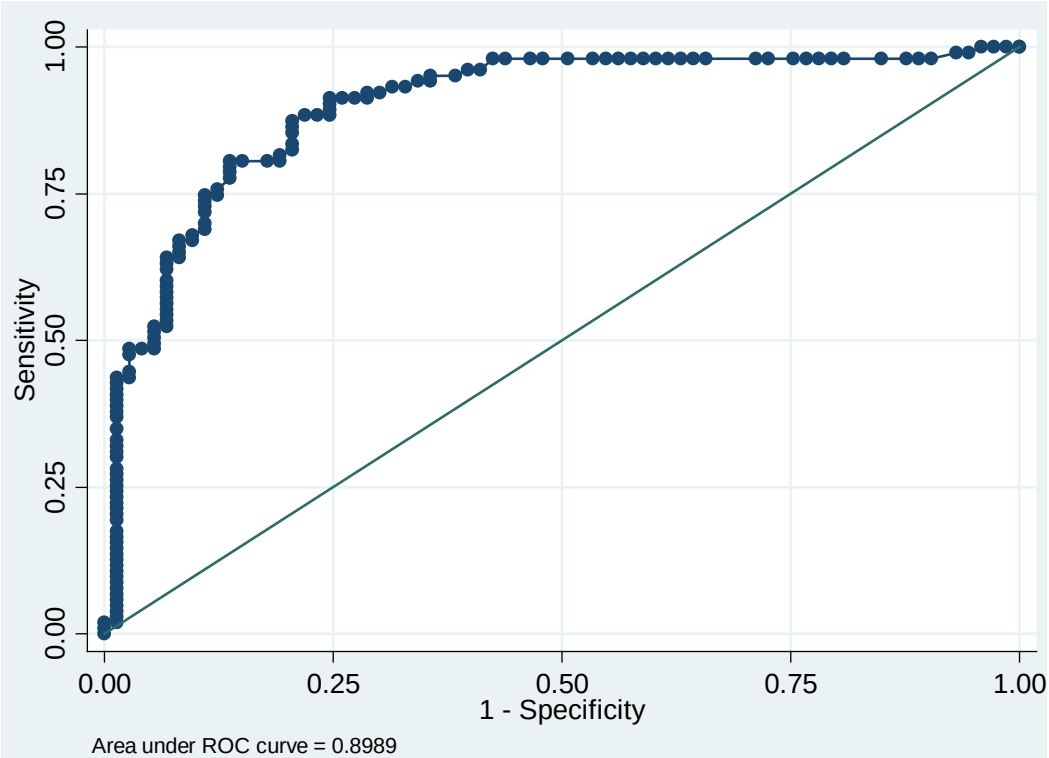

Figure 1: The association between serum Ca125 and the diagnosis of endometriosis

The ROC curve as in Figure 1 shows the association between the level of serum Ca125 and the diagnosis of endometriosis. The AUC was 0.8989, which indicated a good correlation. From the curve, the value of Ca125 equal or more than 50u/ml had a sensitivity of 80% and a specificity of 86%. There is higher likelihood of endometriosis with higher level of Ca125. However, Ca125 level more than 200u/ml had low sensitivity (7.7%) but high specificity at 98.6%.Thus, Ca125 levels were divided into three categories, from 50u/ml to 200u/ml (50–200u/ml) and either less than 50u/ml or more than 200u/ml.

We use the simple logistic regression test to evaluate the association of each clinical feature, ultrasound finding and the serum Ca125 with the diagnosis of endometriosis, as shown in Table 1. From this table, variables with significant association were taken and tested using the multiple logistic regression tests, to predict endometriosis, as shown in Table 2.

Table 1: The association of clinical, biochemical and imaging variables with endometriosis using Simple Logistic Regression test

Variable	b	Crude OR (95% CI)	Wald Statistic (df)	p value
Age (year)	-0.03	0.97 (.93,1.02)	1.49(1)	0.222‡
Parity	-0.23	0.80 (0.69, 0.92)	10.14 (1)	0.001†
Presence of subfertility	0.79	2.20(1.19,4.06)	6.41(1)	0.011‡
Subfertility years	0.05	1.05 90.99,1.11)	2.59(1)	0.108‡
Presence of dysmenorrhoea	1.06	2.90(0.52,16.27)	1.46(2)	0.227‡
Dysmenorrhoea Severity				
Mild	-0.90	0.91 (0.91,4.46)	0.01 (1)	0.912
Moderate	0.62	1.85 (0.39,8.86)	0.59 (1)	0.492
Severe	2.68	14.67 (2.18,98.78)	7,62 (1)	0.006†
Presence of deep dyspareunia	0.48	1.61 (0.68,3.79)	1.18 (1)	0.277
Presence of dyschezia	-0.35	0.70 (0.09,5.11)	0.12 (1)	0.728
Presence of abdominal mass	-0.21	0.81 (0.45,1.49)	0.49 (1)	0.503
Uterus Ligaments				
Thickened			1.00	
Not thickened	-3.19	0.04 (0.01,0.31)	9.56 (1)	0.002†
POD				
Normal			1.00	
Obliterate	1.30	3.68 (1.69,8.02)	10.78 (1)	0.001†
Locule of ovarian mass				
Uniloculated	1.49	4.46 (1.34,14.06)	5.94 (1)	0.015†
Multiloculated	2.04	7.67 (2.30,25.58)	11.00 (1)	0.001†
Content of ovarian mass				
Serous	-2.65	0.07 (0.01,0.68)	5.27 (1)	0.220‡
Thick with sediments	3.64	38.11(10.34,140.42)	29.93 (1)	<0.001†
CA125	0.04	1.04 (1.03, 1.05)	37.24 (1)	<0.001†

Table 2: Association between variables with endometriosis using Multiple Logistic Regression (n=176)

Variable	b	Adjusted OR (95% CI)	LR statistic (df)	p value
CA125	0.03	1.03 (1.02, 1.05)	22.44 (1)	<0.001
Dysmenorrhoea Severity				
No pain		1.00	14.27 (3)	0.003
Mild	0.30	1.35 (0.13, 13.64)	0.06 (1)	0.800
Moderate	2.78	16.04 (4.41, 58.34)	1.34 (1)	0.248
Severe	3.33	27.89 (1.89, 411.95)	5.87 (1)	0.015
Content of ovarian mass				
No cyst		1.00	55.30 (2)	<0.001
Serous	-2.66	0.07 (0.01, 0.68)	5.27 (1)	0.022
Thick with sediments	3.64	38.11 (10.34, 140.42)	29.93 (1)	<0.001

Severe dysmenorrhea was significantly associated with increased likelihood of having endometriosis. Those patients with severe dysmenorrhea will have 27 times higher risk of having endometriosis. Ca125 values and the ultrasound scan findings of thick sediments or ground-glass appearance were highly significant in the diagnosis of endometriosis.

Based on the significant variables in the prediction of endometriosis found in the multiple logistic regression tests, a scoring system, named as CliEndomet, was formulated as shown in Figure 2.

UNIVERSITI SAINS MALAYSIA	**CliEndomet** The Diagnostic Clinical Scoring System for Endometriosis	FERTILITY CENTER

Name: …….. Registration No.: ……

Date: ……

Total Score: …… Recommended treatment: ……

Endometriosis: Yes No ……..

……..

Criteria	Score
Dysmenorrhoea:	
▪ No dysmenorrhea	0
▪ Mild dysmenorrhea	1
▪ Moderate dysmenorrhea	2
▪ Severe dysmenorrhoea	3
Ultrasonograhic findings:	
▪ Solid ovarian mass or cystic ovarian mass with papillary projections	0
▪ Uniloculated, serous ovarian cyst	1
▪ Multiloculated cyst with thick sedimentations (ground glass appearance)	2
Level of serum Ca125:	
▪ <50 u/ml or >200u/ml	0
▪ 50-200u/ml	2
TOTAL	

The CliEndomet formula:

Total score = (Dysmenorrhoea + Ultrasonographic findings + serum Ca125) x 2

Risk of having endometriosis:

Total score	Possibility of endometriosis
Score 0-2	Unlikely
Score 4-6	Low possibility
Score 8-10	Moderate possibility
Score 12-14	High possibility

Figure 2: The CliEndomet Scoring System

The reliability of CliEndomet was tested using kappa, as in Table 3. CliEndomet carried a substantial agreement with direct visualization to diagnose endometriosis.

Table 3: The Agreement between CliEndomet and direct visualization for the diagnosis of endometriosis

Direct Visualisation			
CliEndomet	Endometriosis	No endometriosis	Total
Endometriosis	90	7	97
No endometriosis	13	66	79
Total	103	73	176

Prevalence of endometriosis	= 103/ 176 x 100% = **58.5%**
Observed % agreement	= (90 + 66)/176 x 100% = **88.6%**
Chance-expected % agreement	$= \frac{(97 \times 103)}{176} + \frac{(79 \times 73)}{176} \times \frac{100}{176}$ = **50.87%**
Kappa coefficient (K) = $\frac{\text{(Observed \% agreement) – (chance-expected \% agreement)}}{\text{(Perfect \% agreement) – (chance-expected \% agreement)}}$ $= \frac{(88.6 - 50.87)}{(100 - 50.87)}$ = **0.77**	

V. Discussion

Endometriosis associates with pain and infertility, which causes much distress to the women involved. The gold standard diagnostic tool remains visual inspection of the endometriotic lesion, either by laparoscopy or laparotomy, with the preference of histopathological confirmation. Standing alone, none of the non-invasive tests can accurately diagnose this disease, causing a significant delay of its diagnosis and treatment. However, a combination of various non-invasive tests is yet to be tested.

From this study, among all the non-invasive tests tested for the diagnosis of endometriosis, the presence of dysmenorrhea, ovarian cyst at ultrasound and the level of serum Ca125 between 50 to 200 iu/ml showed a significant association with endometriosis. Based on that, a scoring system was formulated and tested for its reliability. The proposed scoring system (CliEndomet) carried a substantial agreement to diagnose endometriosis in comparison to the standard direct visualization of the disease.

Having able to diagnose endometriosis using a non-invasive or less invasive method could provide an advantage to the patient, especially those who are not suitable or agreeable to undergo surgery. Treatments which include hormones can be administered based on this non-invasive diagnosis, thus reducing the patient's pain agony and morbidity. Neoadjuvant medical treatment can also be administered with certainty before surgery to reduce the intraoperative complication.

Though CliEndomet has been shown to be a reliable diagnostic tool, it requires a proper validation test before its usage.

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Do We Need More than Ultrasound Endometrial Thickness to Predict Malignancy?

By Adly Nanda Al Fattah, Tricia Dewi Anggraeni, Bella Aprilia & Muhammad Ikhsan
Faculty of Medicine Universitas

Abstract- Endometrial thickness (ET) ultrasound measurement has high diagnostic performance for detection of endometrial cancer in symptomatic postmenopausal women. Identified clinical risk factors, Doppler or 3D ultrasound parameters to predict endometrial malignancy had been proposed in several studies. This article is comparing the accuracy of ultrasound endometrial thickness with scoring system/index involving both of clinical and ultrasound parameters to predict endometrial malignancy. Eight eligible diagnostic studies were appraised to assess the accuracy of ultrasound ET and/or ultrasound-based index to predict malignancy. The incidence of endometrial malignancy confirmed by histopathology examination was ranging from 10.5 to 58% from 8 studies. Ultrasound-based index to predict endometrial malignancy had good accuracy (AUC 75%- 98%). The addition of endometrial volume/ uterine corpus volume ratio (EV/UCV) and Doppler to clinical parameters had increased the prediction accuracy of the index. While ultrasound ET alone has also high sensitivity, respectively 90.6% and 96.9% using the cut-off 4 mm and 3 mm with low accuracy.

Keywords: doppler endometrial cancer, ultrasound, clinical.

GJMR-E Classification: NLMC Code: WP 390

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Ultrasound-based index to predict endometrial malignancy had better accuracy compared to ultrasound ET alone. Combination of ultrasound including Doppler parameters and clinical parameters had increased the prediction accuracy of the endometrial malignancy prediction index.

Keywords: doppler endometrial cancer, ultrasound, clinical.

I. Introduction

Endometrial cancer is one of the most common gynecological malignancies. It develops in about 142,000 women worldwide, and lead to approximately 42,000 of mortality [1]. Transvaginal ultrasound followed by endometrial biopsy is the most cost-effective diagnostic approach in the population with post-menopausal bleeding [2]. We therefore consider TVU as the first step in any woman presenting with postmenopausal bleeding [3]. Ultrasonography is a non-invasive method that could assess the morphologic structures of endometrium [4,5]. Sonographically determined endometrial thickness measurement shows high diagnostic performance for detection of endometrial cancer in symptomatic postmenopausal women[6].In addition, there is no universally accepted sonomorphologic criteria to define benign or malignant structure on the endometrium. In order to make the prediction accuracy better, some studies created a scoring system involving clinical and ultrasound parameters [7,8].This article was aimed to appraise studies that assess the accuracy of endometrial malignancy prediction system or index which involving ultrasound as one of the predictors.

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II. Methods

a) Search Strategy

The search was conducted on the Cochrane Library®, PubMed® and EMBASE® with the keywords of "endometrial" AND "malignancy" AND "scoring" OR "prediction" OR "index" on each databases with certain techniques (figure 1). Search focused on articles in diagnostic type showing diagnostic values of the studies. Reference lists of relevant articles were searched for other possibly relevant studies. After obtaining a result, a first selection was done by screening the study titles and abstracts. Eight articles were available as full text, and all of them included in our analysis.

b) Critical Appraisal

Appraisal of 8 diagnostic studies involving 5543 patients underwent clinical and ultrasound for predicting endometrial malignancy confirmed with the histopathology result was conducted finding of the diagnostic values (Se, Sp, PPV, NPV). Review study or study without diagnostic values reported were excluded. We used diagnostic appraisal questions developed by Centre of Evidence-Based Medicine (CEBM), University of Oxford (available at: http://www.cebm.net/critical-appraisal/).

III. Result

Eight eligible studies were appraised to assess the accuracy of ultrasound and/or ultrasound index to predict malignancy. The incidence of endometrial malignancy confirmed by histopathology examination was ranging from 10.5 to 58% from 8 studies. The accuracy of ultrasound-based index to predict endometrial malignancy was ranging from 75% - 98% from eight studies. Opolskiene, et al conducted a consecutive study of 729 post-menopausal bleeding, to evaluate the diagnostic performance of models predicting endometrial cancer. They stated that the

accuracy was increased significantly when endometrial thickness and power Doppler assessment are added to clinical variables. Clinical model including the variables age, use of warfarin and use of hormone replacement therapy had the largest area under the receiver–operating characteristics curve (AUC), with a value of 0.74 (95% confidence interval (CI), 0.67–0.81). A model including age, use of warfarin and endometrial thickness had an AUC of 0.82 (95% CI, 0.76–0.87), and one including age, use of hormone replacement therapy, endometrial thickness and vascularity index had an AUC of 0.91 (95% CI, 0.87 – 0.95)[9].

Dueholm, et al concluded that simple Doppler score (which considered only presence of vascularity and not presence of single/double dominant vessel, multiple vessels, large vessels, color splash or densely packed vessels) had an AUC of 0.83 in the prediction of endometrial cancer. Prediction index including endometrial thickness, Doppler score and interrupted endomyometrial junction on unenhanced TVS predicted endometrial cancer with an AUC of 0.95 (95% CI, 0.92 – 0.99) and, with addition of irregular surface on GIS, the AUC was 0.97 (95% CI, 0.94 – 0.99)[10].

In further study [11] they compare the offline and real time evaluation during scanning to assess efficiency of two-dimensional (2D) and three-dimensional (3D) TVU, power Doppler angiography (PDA) and gel infusion sonography (GIS) to detect endometrial malignancy. Diagnostic efficiency of 3D analysis may be improved by use of risk of endometrial cancer (REC)-scoring systems, without the need for calculation of vascular or endometrial volume. The REC consisted of: (1) body mass index ≥ 30 (+1 point), (2) total endometrial thickness ≥ 10 mm (+1 point), (3) total endometrial thickness ≥ 15 mm (+1 point), (4) interrupted endomyometrial junction (+1 point) and (5) irregular surface at gel instillation sonography (GIS) (+1 point). The first model included BMI, endometrial thickness, presence of an interrupted endomyometrial junction and Doppler score, had AUC of 0.879. Evaluation of 3D-GIS with BMI, an interrupted endomyometrial junction, Doppler score and irregular endometrial surface at 3D-GIS, had the highest diagnostic efficiency on multivariate regression, with an AUC of 0.908. Application of the REC-score system at 3D-PDA or 3D-GIS had comparable efficiency compared with their respective 2D models [11].

Burbos, et al created a model to predict endometrial carcinoma in postmenopausal women called DEFAB (Diabetes, Endometrial thickness, Frequency of bleeding, Age, and BMI). In the DEFAB criteria, presence of diabetes in a patient scores 2; endometrial thickness ≥ 14mm scores 1, recurrent episodes of bleeding scores 4; age ≥64 years scores 1; and BMI ≥31 $\mathrm{kg}\,m^2$ scores 1. The value ≥3 has a positive predictive value (PPV) of 7.78% and negative predictive value (NPV) of 98.2%, whereas a score equal to or greater than 5 has a PPV of 11.9% and NPV of 97.8% [12].

Seek in, et al investigated the accuracy of endometrial thickness in predicting endometrial pathologies in both of symptomatic (group 1) and asymptomatic (group 2) postmenopausal women. The best cut-off point for endometrial thickness in predicting endometrial carcinoma in group 1 was 8.2 mm, which provided 75% sensitivity and 74% specificity; area under the AUC of 0.88; 95% CI, 0.76– 1.00%. In group 2, the AUC was 0.76 (95% CI, 0.46–1.00; p 5 0.114). [6]. In other study, Patel, et al stated that threshold of 4 mm, the sensitivity is 90.6% and increases to 96.9% when decreasing the threshold to 3 mm[13].

Mansour, et al evaluated the role of endometrial/uterine corporeal volume ratio (EV/UCV) assessment in the prediction of endometrial cancer. EV/UCV of a cutoff value 0.017 was predictive of malignancy. Endometrial/uterine volume ratio was more sensitive than endometrial volume and endometrial thickness for prediction of endometrial cancer[7].

Mihajovic, created the transvaginal ultrasound score for endometrial malignancy prediction consisted of: thickness of endometrium (up to five mm = 0, from five to eight mm = 1,> eight mm = 2), echogenicity of the endometrium compared to the myometrium: normal echogenicity = 0, hyperechogenous = 1, hypoechogenous = 2 , the border of the endometrium towards the myometrium - subendometrial hypoechogenous zone (whole = 0. intermittent = 1), homogeneity of the texture of the endometrium (homogenous = 1. inhomogeneous = 2), presence of the colored signals in the endometrium (present = 2. absent = 1), index of resistance in newly-formed blood vessels in the endometrium (> 0.4 = 1. < 0.40 = 2), volume of the endometrium by an ultrasound check-up (< 13 ml = 1. > 13 ml = 2). Score system showed that the value 8 had the best validity for the detection of endometrial malignity, with the sensitivity of 0.857 and specificity of 0.785[4].

IV. Discussion

In our study, the incidence of endometrial malignancy was varied among studies. It could possibly explain by the variation of the population. In some studies, they included women with a complaint of postmenopausal bleeding who has endometrial thickness ≥ 4.5 mm[9], while other studies included subjects without considering the ET.[12,14] We found the incidence of endometrial malignancy from 5 to 58%. It was similar with the finding from The Gynecologic Oncology Group (GOG) that found 42.6% of endometrial malignancy, 123 of 289 specimens [14].

Sorosky in their review stated that the positive predictive value and negative predictive value of an

office biopsy are greater than 90% [14].TVS screening for endometrial cancer has good sensitivity in postmenopausal women [15]. In addition, in certain conditions in which the cervical canal could not be accessed by curettage, the role of ultrasound will be useful to predict malignancy.

Monsour had the highest appraisal score, because they show all the diagnostic parameters of their result. Transvaginal 3D render mode ultrasound was used to assess the volume of the uterus in the coronal plane using manual lining technique. Volumes were manually calculated in the coronal plane with 30° rotation steps. They found that EV/UCV had the best in prediction of malignancy compared to endometrial thickness and endometrial volume; AUC (area under the curve) for endometrial thickness, volume and EV/UCV was respectively 75, 92 and 100%. However, further studies should be conducted with a larger number of subjects to support these findings.[7] The interobserver and intraobserver reproducibility of 3D ultrasound for assessment of endometrial volume measurements in patients with postmenopausal bleeding was well proved, showing better reproducibility than 2D measurement of endometrial thickness [7].

Using ultrasound parameter, the accuracy of prediction index was higher compared to the non-ultrasound based index. In our study, the accuracy of prediction index involving ultrasound parameters was ranging from 0,75 to 0.98. It was higher compared to the clinical-based prediction index. Burbos, et al created a clinical predictive model called FAD 31 (F for the frequency of bleeding episodes, A for the age of the patient, D for diabetes, and number 31 represents the BMI cut-off value). The AUC was 0.73. Among 14 recognized indexes in our appraisal study, only 3 indexes had the AUC below 0.8 [8].

V. Conclusion

Ultrasound-based index to predict endometrial malignancy had good accuracy. Addition of endometrial thickness and power Doppler to clinical parameters had increased the prediction accuracy. EV/UCV had the best in prediction of malignancy compared to endometrial thickness and endometrial volume. Further larger study should be conducted to assess the effectivity and eligibility of several ultrasound parameters.

Conflict of Interest

None to declare.

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Table 1: Eight Eligible Studies

Reference	Eligible for analysis	Design	Required parameters	Endometrial malignancy rate (%)	Result (accuracy for endometrial malignancy)
Opolskiene (2011)	729	Cross-sectional	- Age, use of warfarin and endometrial thickness. - Age, use of hormone replacement therapy, endometrial thickness and vascularity index.	24%	AUC 0.82 Sens 84%, Spec 66%, LR+ 2,49, LR 0,24 AUC 0, 91. Sens 90%, Spec 77%, + LR 3.14, - LR 0.13.
Dueholm (2014)	432	Cross-sectional	- Presence of vascularity and not presence of single/double dominant vessel, multiple vessels, large vessels, color splash or densely packed vessels - Endometrial thickness, Doppler score and interrupted endomyometrial junction on unenhanced TVS - Endometrial thickness, Doppler score and interrupted endomyometrial junction on unenhanced TVS with addition of irregular surface on GIS	41%	AUC 0.83 AUC 0.95 AUC 0.97
Burbos, et al (2010)	3047	Cross-sectional	Norwich DEFAB prediction: - Diabetes - Endometrial thickness (ET) - Age - Frequency of bleeding - BMI	58%	AUC 0.77 ET Cut-off ≥3 mm PPV 7.78% NPV: 98.2% ET Cutoff ≥ 5 mm PPV 11.9% NPV: 97.8%
Dueholm (2015)	169	Prospective cohort	- BMI, interrupted endomyometrial junction, Doppler score, irregular endometrial surface at 3D-GIS (Model 4) - REC score 3D-PDA (BMI≥30, ET≥10mm, ET≥15mm, interrupted endomyometrial junction, Doppler score) - REC score 3D-GIS (BMI≥30, ET≥10mm, ET≥15mm, interrupted endomyometrial junction, Doppler score, irregular surface at 3D-GIS)	40,8%	AUC: 0.908, Sens 85.3% Spec 89.3% AUC: 0.88, Sens 86.9%, Spec 81% AUC: 0.894, Sens: 85.3% Spec: 86.9%
Mihajlovic (2015),	100	Cross-sectional	- Thickness of endometrium - Echogenicity of the endometrium compared to the myometrium - The border of the endometrium towards the myometrium - subendometrial hypoechogenous zone - Presence of the coloured signals in the endometrium - Index of resistance in newly-formed blood vessels of the endometrium - Volume of the endometrium by an ultrasound check-up	21%	Cutoff: 8 Sens 85.7%, Spec 78,5%

Mansour (2012)	160	Cross-sectional	An endometrial/ uterine volume (EV/UCV) ratio Endometrial thickness Endometrial volume in cc	16,87%	Cutoff: 0.017, Accuracy: 98%, Sens: 99%, Spec: 98%, PPV: 98%, NPV: 99% Cutoff: 5mm, Accuracy: 75%, Sens: 68%, Spc: e 82%, PPV: 77%, NPV: 74% Cutoff: 1.4 cc, Accuracy: 86%, Sens: 81%, Spec: 90%, PPV: 88%, NPV: 84%
Seekin, (2015)	602	Cross-sectional	Endometrial thickness	Symptomatic group: 2,9% Asymptomatic group: 0,9%	Cutoff ≥ 8.2 mm Sens 75%, Spec 74%, AUC: 0.88 Cutoff ≥ 5 mm AUC: 0.76
Patel et al (2017)	304	Cross-sectional	Endometrial thickness	10,5%	Cutoff 4 mm, Sens: 90.6% Cut off 3 mm, Sens: 96.9%

BMI, body mass index; ET, endometrial thickness; TVS, trans-vaginal ultrasound; GIS, gel infusion sonography; PDA, power Doppler Angiography; EV/UCV, endometrial volume/uterine corporeal volume; REC score, risk of endometrial cancer score; Sens., sensitivity; Spec., specificity; LR+, positive likelihood ratio; LR–, negative likelihood ratio; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

Table 2: Appraisal Table

No.	Study	Population	Validity			Result					Applicability	Total Score
			1	2	3	4 (Sn)	5 (Sp)	6 (PPV)	7 (NPV)	8 AUC	9	
1.	Opolskiene (2011) Clinical parameters, ET Clinical parameters, ET and vascularity index	729	+	+	+	84 % 90%	66 % 77%	- -	- -	0.82 0.91	+	7/9 7/9
2.	Dueholm (2014) Presence of vascualrity ET, Doppler, TVS parameter ET, Doppler, TVS parameter + irregular surface on GIS	432	+	+	+	-	-	-	-	0.83 0.95 0.97	+	4/9 4/9 4/9
3.	Burbos, et al (2010) Cutoff ≥3 mm Cutoff ≥ 5 mm	3047	+	+	+	- -	- -	7.78% 11.9%	98.25% 97.8%	0.76	+	4/9 4/9
4.	Seekin, (2015) Cutoff ≥ 8.2 mm Cutoff ≥ 5 mm	602	+	+	+	75%	74%	-	-	0.88 0.76	+	4/9 4/9
5.	Dueholm (2015) Moedl 4 REC score 3D-PDA REC score 3D-GIS	169	+	+	+	85.3% 86.9% 85.3%	89.3% 81% 86.9%	- - -	- - -	0.90 0.88 0.89	-	6/9 6/9 6/9
6.	Mansour (2012) EV/UCV Endometrial thickness Endometrial volume in cc	160	+	+	+	99% 68% 81%	98% 82% 90%	98% 77% 88%	99% 74% 84%	0.98 0.75 0.86	+	9/9 5/9 9/9
7	Mihajovic (2015)	100	+	+	+	85.7%	78.5%	-	-	-	+	5/9
8.	Patel et al (2017) Cutoff 4 mm Cutoff 3 mm	304	+	+	+	90.6% 96.9%	- -	- -	- -	- -	+	5/9 5/9

1, representative patients; 2 reference standard; 3, blind & independent; 4, sensitivity; 5, specificity; 6, positive predictive value; 7, negative predictive value; 8,area under the curve; 9 detail methods to permit replication;US, ultrasound; +, adequate; −, inadequate; ?, unknown, no information given'. Every item was scored based on diagnostic study appraisal questions developed by CEBM (available at: http://www.cebm.net/critical-appraisal/)

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Didelphys Uterus and Cervical Cancer: A Case Report and Review of Literature

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Abstract- Congenital malformations of the female genital tract are defined as deviations from normal anatomy resulting from embryological maldevelopment of the Müllerian or paramesonephric ducts. This condition represents a rather common benign condition with a prevalence of 4–7%. Cervical cancer and didelphys uterus is an infrequent condition in clinical practice. Association between cervical cancer and Müllerian malformation is limited to medical references. We present a surgical treatment with a result IB1, with systematic pelvic and paraaortic nodal dissection, with poor prognostic factors, she is chemoradiotherapy treatment. She is a patient 55 years old, with no symptoms in young adulthood or teenager in relation to didelphys uterus.

Always it is possible we encourage the primary surgical treatment, we can get prognostic factors and is possible scan other congenital malformation, also the point A is not constant for planned a radiotherapy treatment finally lymphatic channels in anatomical distortion could be evaluated and measure the nodal affection, and improve and personalize radiotherapy treatment. This case is an absolutely infrequent in the clinical practice.

GJMR-E Classification: *NLMC Code: WP 400*

Strictly as per the compliance and regulations of:

Didelphys Uterus and Cervical Cancer: A Case Report and Review of Literature

Dr. Victor E. Valdespino [α], Dra. Hilda Mendoza Ramon [σ], Dr. German Maytorena Cordova [ρ], Dr. Victor Valdespino Gomez [ω], Dra. Paola Ferrer Torres [¥] & Dr. Pedro Blas Hernandez [§]

Abstract- Congenital malformations of the female genital tract are defined as deviations from normal anatomy resulting from embryological maldevelopment of the Müllerian or paramesonephric ducts. This condition represents a rather common benign condition with a prevalence of 4–7%. Cervical cancer and didelphys uterus is an infrequent condition in clinical practice. Association between cervical cancer and Müllerian malformation is limited to medical references. We present a surgical treatment with a result IB1, with systematic pelvic and paraaortic nodal dissection, with poor prognostic factors, she is chemoradiotherapy treatment. She is a patient 55 years old, with no symptoms in young adulthood or teenager in relation to didelphys uterus.

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I. Introduction

Cervical cancer is typically preventable if pre-cancerous lesions are detected and treated early. Cervical cancer screening by means of cytology, or the Papanicolaou smear, seeks to detect precancerous or cancerous cervical lesions prior to symptom on set. Research has consistently observed that cervical cytology screening is highly efficacious against invasive cervical cancer incidence and death among women of reproductive age 1. Therefore, regular cervical cancer screening and follow-up are critical.

Cytological screening will most likely decline in favor of HPV-based screening because of its superiority over cytology in the 2 characteristics that influence test efficacy; HPV DNA testing can detect invasive cervical cancer risk for a longer period than cytology (2, 3), and its sensitivity is an absolute 40% higher than that of cytology (4, 5). Thus, the relationship between these screening modalities efficacies is knowable-the efficacy of HPV-based screening is expected to exceed that of cytology, all things being equal. Analysis of extant data on cytology screening, therefore, may offer a minimum estimate of HPV-based screening efficacy among older women. However, screening by cytology alone remains acceptable under all current guidelines, and Papanicolaou smears continue to be widely used. Further, a study to evaluate the efficacy of HPV DNA testing among women will not be possible for years after an HPV DNA–based screening program is implemented until a sufficient number of deaths have occurred to make meaningful comparisons on the basis of prior HPV DNA screening history.6, 7.

Mullerian duct anomalies are congenital defects of the female genital system that arise from abnormal embryological development of the Mullerian ducts. These abnormalities can include failure of development, fusion, canalization, or reabsorption, which normally occurs between 6 and 22 weeks in utero. Most sources estimate an incidence of these abnormalities to be from 0.5 to 5.0% in the general population 8,9

Septate uterus is the commonest uterine anomaly with a mean incidence of 35% followed by bicornuate uterus (25%) and arcuate uterus (20%) 9

Unicornuate and didelphys uterus have term delivery rates of 45%, and the pregnancy outcome of patients with untreated bicornuate and septate uterus is also poor with term delivery rates of only 40%. 9

Most women with a didelphys uterus are asymptomatic, but some present with dyspareunia or dysmenorrhea in the presence of a varying degree of longitudinal vaginal septum. Rarely, genital neoplasms, hematocolpos hematometrocolpos, and renal anomalies are reported in association with didelphys uterus. Despite some of these complications, there are many cases of women with a didelphys uterus that did not exhibit any reproductive or gestational challenges.

The VCUAM classification (Vagina, Cervix, Uterus Adnex Associated Malformation) is anatomical. Organs are classified as separated similar to TNM classification, (tumor, nodal, metastases). This manner allows a categorization, is precise, detail, and very representative. Different anatomical anomalies could be

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described and the practitioner has a good idea of each organ is affected in a single manner.10.

Lee reports a case of a congenital abnormality of uterus didelyphys in a patient who developed invasive carcinoma of the cervix. The patient received radical radiotherapy by a combination of external beam pelvic radiotherapy and high dose rate brachytherapy by insertion of afterloading catheters into both uterine canals. A newly defined prescription point was used midway between the two catheters and 2 cm above the mean cervical position. The classical point A was regarded as inappropriate in this patient with a rare condition. Acute toxicity was minor and the patient is tumor free with no significant normal tissue late effects after follow-up of nearly 3 years.

Depends on main cervical tumor is localized, the classical point A, could change, in position, in consequence, the radiotherapy treatment should be personalized and very precise for a better response on the tumor. 11

In addition, we can consider cervical cancer in a patient with Mullerian anomalies, we must offer the best treatment option, it is possible to get the nodal status, by lymphadenectomy or radical surgery by laparoscopic surgery or traditional surgery, when the stage allow it, or chemoradiotherapy.

When the cervical cancer is treated with surgery, we choose a specific surgery with a Quelow - Morrow hysterectomy, the patient does not need more morbidity with the greatest surgery, in our clinical practice when we performed a hysterectomy control, we always practice standing nodal affection pelvic and paraaortic lymphadenectomy, and we can get specific information about the nodal tumoral invasion, it is necessary specific adjuvant treatment.

II. Case Report

The present case is a women 55 years old, with hypertension 12 years of history, cholecystectomy at 32 years old, no more familiar background, gynecological antecedent menarche 12 years old, 28 x 5 days, 4 pregnancies, 1 labour, 3 caesarean, menopause 50 year old. In a yearly control cervicovaginal cytology reported an epithelial neoplasia grade II, in the medical first level unit, the patient was sent to colposcopy in a third level medical unit, in this evaluation (colposcopy) they notice two cervices, one of them with cervical cancer (right) and left cervix without tumoral damage. A curettage endocervical was performed in both cervix, squamous invasive cancer was reported on the right cervix, endocervical glands without alterations on the left cervix. Colposcopy service, operate a conization on right cervix with definitive report squamous cell carcinoma measure 0.8 x 0.5 cm margin was positive an invasive tumor. An ultrasound was made, cervix reported 32 x 26 x 30 mm no tumor was obvious, uterine corpus 46 x 48 x 20 mm and we performed a hysterectomy Querlow - Morrow B2 on right side and Querlow - Morrow A on left side, we carry on a systematic lymphadenectomy pelvic and paraaortic with 17 nodes without tumor in pelvis and 24 nodes without metastases in retroperitoneal area. 12. The final tumoral measure was 27 mm, tumoral get involvement all right cervix, with lymph-vascular infiltration, and tumor comprises lower uterine segment. Surgical stage final was IB1 epidermoid cervical right cancer. The left cervix does not expose a tumoral injury, including no cervical dysplasia. At the moment of transoperative, we found a double uterine body, in a relationship with double cervix we achievement, a didelphys uterus and cervical cancer. The patient suffers a ureteral leak, it was resolved with a catheter JJ, she was sent to radiotherapy and chemotherapy, she is on concomitant treatment right now with good tolerance.

In the current clinical practice, this association between uterus didelphys and cancer are very rare, we performed a surgery a Querlow-Morroe B2 in right side and a Querlow-Morroe A in the left side also pelvic and paraaortic lymphadenectomy.12

As Chiappa and coworkers, we improve our clinical point of view with a cervical ultrasound this value measure, is extraordinarily helpful because improve our clinical diagnosis, and we performed this as a routine in our service when a patient will be programmed for a surgery or chemoradiotherapy by cervical cancer.13

In addition cervical cancer in a didelphys uterus is absolutely infrequent even in historical technical literature do not is mentioned technical change performing a hysterectomy, just is refer briefly to get free neoplastic margin.14

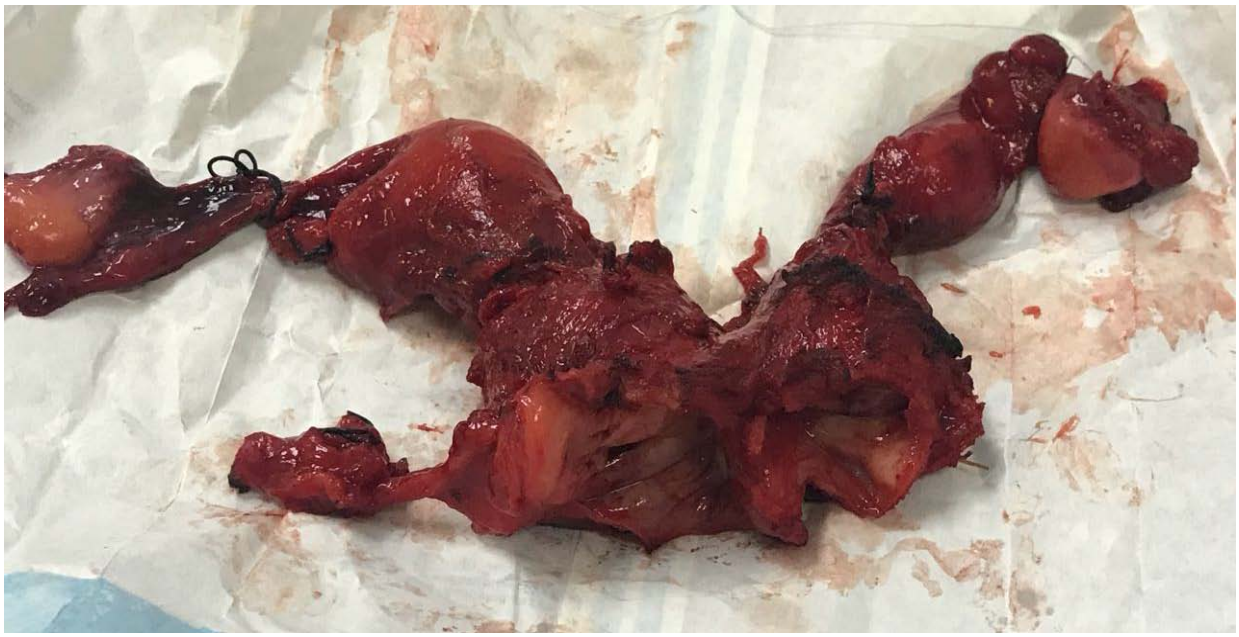

Fig.1: Cervical uterine cancer in the right cervix, with the scar of the cone, and parametrial resection. Atrophied uterine corpus left, cervix and vagina without tumor

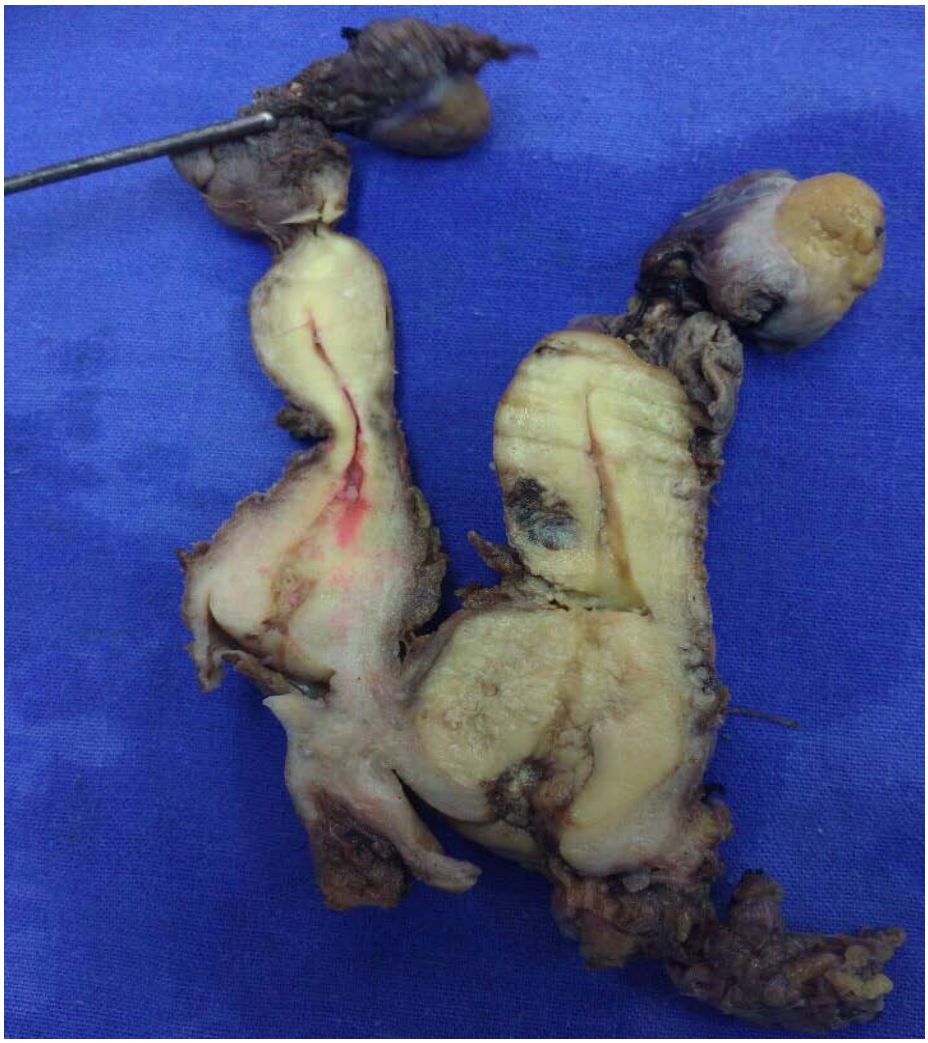

Fig. 2: This photo is sagittal cut-off, we can notice an atrophic uterus and cervix on the left and cervical cancer in almost all cervix (right image) and parametrial resection

III. Discussion

Rarely, cervical cancer and endometrial carcinoma are reported in association with cases of didelphys uterus 15.16

Most women with a didelphys uterus are asymptomatic but may present with dyspareunia or dysmenorrhea in the presence of a thick, sometimes obstructing vaginal septum. This obstructing vaginal septum can lead to hematocolpos/hematometrocolpos and thus present as chronic abdominal pain as well. Or some problems if the patient desire a pregnant.

In the present report, the patient has no knowledgment about dydelphys uterus because she has no problems at reproductive age and develops 4 pregnancies with successful evolution. Previously at his childhood and teenager, she does not refer chronic pelvic pain or sexual discomfort in early adulthood. This does not agree with medical reports.

It is generally accepted that having a uterine anomaly is associated with poorer pregnancy outcomes such as increased chances of spontaneous abortion, premature labor, cesarean delivery due to breech presentation, and decreased live births, compared to a normal uterus. However in the present report could get 4 pregnant, with 1 labours delivery and 3 cesarian.8

The modalities for correct diagnosis frequently used include highly invasive methods such as hysteroscopy, hysterosalpingography, and laparoscopy/ laparotomy, also ultrasound. 3D ultrasound is becoming more commonly used for diagnosis as it is not only noninvasive, this analytic tool gives all the information needed for morphological classification 10,17. Magnetic resonance imaging is also just as accurate and valuable in diagnosing müllerian abnormalities, as hysterosalpingograms, hysteroscopy, and laparoscopy are, even more so as it is noninvasive and can diagnose associated urinary tract abnormalities at the same time 13. Nonetheless, it is still difficult to distinguish between these different anomalies on imaging modalities due to subjectivity; differences in morphology are often subtle and changing classification systems. 17

In opposition to the medical reports, this patient was diagnosed until medical assistance on cancer standing; colposcopy and ultrasonography evaluation. 18

Other malignant tumors have been reported in Muellerian anomalies, as Iavazzo, reported a case on didelphys uterus an uterine carcinosarcoma. 19

Present case report presents an IB1 cervical cancer with nodal evaluation pelvic and retroperitoneal negative, why a cervix develops cervical cancer and others do not develop any malignant or premalignant injury we can not answer this question, maybe by epigenetic changes because the viral exposition was positive on both cervix.

Sugimori, reported two cases of cervical cancer in uterus didelphys. One was extensive adenocarcinoma and one was squamous cell carcinoma in situ. 20

IV. Conclusion

If a patient has a Müllerian duct anomalies and cervical cancer, clinical staging can be ambiguous, the natural history may be altered, also common association with renal agenesis, or other anatomical variation. Some treatments which could influence the use of potentially nephrotoxic agents, like cisplatin, then are a part of standard chemoradiotherapy, must be considered at moment on select a therapy.

Treatment decision making needs to be precise and personalized, in view of the minimal amount of prior literature on the topic.

Applicator placement for intracavitary brachytherapy may be fraught with this patients. Because inability to define a point A in patients with anomalies featuring double cervix and uterus is a challenge. Is very useful the surgical approach because we can get prognostic factors, and real pathology stage and another abnormal anatomical variation could be evident and to be evaluated. 21

That's why always it is possible the patients must be treated with surgery the local (pelvic) disease and lymphatic nodes and retroperitoneal, because no available literature to describe the lymphatics of the various Müllerian ducts anomalies. In fact, we recommend performing a lymphatic node dissection pelvic and retroperitoneal in stage IIB or advanced, and know the specific node pathological of the disease and improve radiotherapy field treatment. 22

Among patient with cervical cancer who have Mullerian anomalies, radical surgery should be selected over radiotherapy in the early operable stages. Surgery provides a real stage for nodal metastases pelvic and retroperitoneal, and personalities treatment could be given with more success and less morbidity.

When the surgery is not indicated concurrent chemoradiotherapy must be used.

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Preoperative Histopathological Grading and Clinical Staging versus Surgico-Pathological Grading and Surgical Staging in Endometrial Carcinoma Patients: A Single Centre Retrospective Study

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Materials and Methods: A retrospective analysis of 81 patients who were diagnosed with endometrial carcinoma and underwent hysterectomy at the 1st Affiliated Hospital of Chongqing Medical University from January 2015 to December 2016.

Results: Endometrioid adenocarcinoma was the most common histological subtype with an agreement of 75.3% (61/81) on final pathology. The overall concordance rate between pre- and postoperative histological grade was 65.4% (53/81). 25.9% (21/81) patients had been upgraded while 8.6% (7/81) had been downgraded. The accuracy of clinical and surgical staging was 64.2% (52/81) with 22.2% (18/81) patients had been upstaged and 13.6% (11/81) down-staged.

Conclusion: Tumor histology and grade, as well as the clinical staging, are only moderate predictors of the final surgical pathological outcome and surgical staging.

Keywords: endometrioid adenocarcinoma, serous carcinoma, clear cell carcinoma, histological grade and staging.

GJMR-E Classification: NLMC Code: WP 390

Strictly as per the compliance and regulations of:

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Conclusion: **Tumor histology and grade, as well as the clinical staging, are only moderate predictors of the final surgical pathological outcome and surgical staging. The highly aggressive serous and clear cell carcinomas have been missed on endometrial samplings. Preoperative grade 1 and clinical stage II tumors had the lowest agreement when compared postoperatively. Cautious planning and patient counseling must be required regarding the surgical approach to endometrial cancer.**

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I. Introduction

Endometrial cancer tops the list among tumors of the female genital tract in developed countries (1). In China, endometrial cancer ranks in second place behind cervical cancer as the most prevalent gynecological malignancy. It has been associated with reproductive factors, late menopause and high usage of exogenous hormone (2). Based on clinical and histopathologic features, endometrial carcinoma is classified as Types I (mainly endometrioid) and II (non-endometrioid). Type I endometrial carcinomas are generally endometrioid adenocarcinomas making 80-90% of all cases. Type II cancers comprise the remaining 10-20% and include uterine papillary serous carcinoma and clear cell carcinoma (3, 4).

Tumor grade and subtype are crucial parameters that dictate the extent of surgery, adjuvant therapy and prognosis (5). These have been determined by histological examination of an endometrial sample obtained by dilation and curettage (D & C) or Pipelle endometrial biopsy or hysteroscopic biopsy (6). The tumor is graded according to the percentage of solid non-squamous growth as follows: Grade 1 ≤ 5%; Grade 2: 6-50%; Grade 3: ≥ 50% solid growth (7).

From its introduction in 1958 until 1988 endometrial carcinoma had been clinically staged by the International Federation of Gynecology and Obstetrics (FIGO) (8). Inaccuracies in clinical staging (9) and results of Gynecologic Oncology Group (GOG) 33 contributed its alteration to surgical staging in 1988 (10). The latter has been lastly revised in 2009 (11). Endometrial carcinoma is distinct from other gynecologic cancers in that it has a double staging system: clinical and surgical staging (12) which are shown below in tables 1 and 2 (13, 14). Clinical staging has been based on pelvic examination, endometrial biopsy and imaging studies (12). Surgical staging-either by laparotomy or minimally invasive techniques (15)-involves inspection of the abdomen and pelvis, the collection of pelvic washings, hysterectomy, bilateral salpingo-oophorectomy (BSO) and pelvic and para-aortic lymphadenectomy (16). It has to be noted that pelvic washings no longer form part of FIGO 2009 surgical staging but are still collected at the time of hysterectomy (17).

Comprehensive surgical staging allows precise diagnosis of the disease and its extent, identification of high-risk patients for recurrence, tailoring of patients for adjuvant therapy to decrease the relapse risk and

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determination of the prognosis (18, 19). Despite these advantages, surgical staging has, clinical staging still holds significant importance in several instances. Firstly, it is valuable for patients who are not candidates for a hysterectomy due to morbid obesity or cardiopulmonary dysfunction that render surgery or anesthesia too risky (20). Adjuvant therapy has to be prescribed based solely on clinical staging and potential risk. This treatment plan adds to cost of medical care and increased morbidity for the patients (21). Secondly, clinical staging is applicable for young women desiring complete preservation of fertility. The endometrial lesions need to be excised and hormone therapy initiated (22). Thirdly, patients with clinical stage II disease who cannot undergo a radical hysterectomy due to associated co-morbidities may have to be treated by neoadjuvant radiotherapy followed by simple hysterectomy (23).

The study aims to compare the accuracy of the tumor cell type and grade in the endometrial sampling with that of the hysterectomy specimen. Clinical and surgical staging were also analyzed to determine the reliability of the pretreatment clinical assessment.

Table 1: FIGO Clinical Staging (1971)

Stage	Characteristics
Stage I	The carcinoma is confined to the corpus uteri
Stage IA	The length of the uterine cavity is ≤ 8 cm
Stage IB	The length of the uterine cavity is> 8 cm
Stage II	The carcinoma has involved the corpus and the cervix but has not extended outside the uterus
Stage III	The carcinoma has extended outside the uterus but not outside the true pelvis
Stage IV	The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allocated to stage IV
Stage IVA	Spread of the growth to adjacent organs
Stage IVB	Spread of distant organs

Table 2: FIGO surgical staging system for endometrial cancer (2009)

Stage	Characteristics
I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastasis to pelvic and/or paraaortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive paraaortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intraabdominal metastases and/or inguinal lymph nodes

II. Materials and Methods

Following approval by the Institutional Review Board, a retrospective review had been conducted in the tumor registry of the 1st Affiliated Hospital of Chongqing Medical University to identify all patients who underwent surgery for endometrial carcinoma during January 2015 throughout December 2016.

Inclusion criteria were as follows:

1. Patients who had been adequately investigated,
2. Patients with a preoperative histopathological report suggesting endometrial cancer which had been confirmed after hysterectomy,
3. Patients who underwent both clinical and surgical staging.

Exclusion criteria included:

1. Patients in whom endometrial carcinoma was not the primary disease,
2. Patients who received neoadjuvant therapy: chemotherapy, radiation therapy, hormone therapy,
3. Patients who had been diagnosed with endometrial carcinoma postoperatively and thus had an absent initial histological grade, cell type, and clinical staging,
4. Patients who were inoperable and hence had no surgical staging.

The electronic medical records of these patients had been examined, and clinicopathological data including age, body mass index, parity, clinical staging, tumor grade and histology preoperatively and postoperatively as well as surgical staging had been extracted. Preoperative investigations were: complete blood count, fasting blood sugar, liver function tests, blood urea, creatinine, electrolytes, thyroid function tests, tumor markers and chest X-ray. All the patients underwent a sonographic examination at first, followed by dilation and curettage and lastly either abdominopelvic CT scan or MR imaging. In patients in whom endometrial cancer was being suspected, but the histopathological report was inconclusive hysteroscopy has been performed. The surgical approach for hysterectomy was either laparotomy or laparoscopy depending on the surgeon's skills and experience. Upon entering the abdomen 100ml of sterile saline were poured in the pelvis and the peritoneal washings had been collected. Then, followed a thorough intra abdominal and pelvic exploration and any suspicious areas were biopsied or excised. Next hysterectomy with bilateral salpingo - oophorectomy, pelvic lymphadenectomy, and selective para - aortic lymphadenectomy were carried out.

The statistical workouts have been performed using SPSS software version 20.

III. Results

From January 2015 to December 2016, 97 endometrial carcinoma patients had been identified. 16 of them had been excluded from the study as:

1. Four patients received neoadjuvant chemotherapy.
2. Five patients received radiation therapy preoperatively.
3. One patient - histological report revealed no cancer cell from the hysterectomy specimen.
4. Four patients-endometrial tissue sampling identified adenocarcinoma, but the hysterectomy specimens have been reported as severe endometrial hyperplasia.
5. Two patients-endometrial carcinoma was diagnosed postoperatively. These patients lacked preoperative tumor histology, grading, and clinical staging.

The final sample constituted of 81 patients. The characteristics of the study group have been summarized in Table 3.

Table 3: Demographic characteristics of the patients in the study group

Characteristics		(N= 81, 100%)
Age	< 50 years	31 (38.3%)
	≥ 50	50 (61.7%)
Gravida	Nulligravida	4 (4.9%)
	Primigravida	11 (13.6%)
	Multigravida	66 (81.5%)
Parity	Nulliparous	6 (7.4%)
	P1	42 (51.9%)
	P2	26 (32.1%)
	P≥3	7 (8.6%)
BMI	< 18.5	3 (3.7%)
	18.5-24.9	36 (44.4%)
	25.0-29.9	37 (45.7%)
	≥30	5 (6.2%)

These women had a mean age of 53.6 years (range 35-76 years). 81.5% of the cohort were multigravida (range G0-G10), and 51.9% were primipara (range P0-P5). The median body mass index (BMI) was 25.1 kg/m^2 (range 17.7-37.2 kg/m^2).

Table 4: Comparison of the histologic types at dilation and curettage and hysterectomy

		Hysterectomy Specimen					Total
		Endometrioid carcinoma	Serous carcinoma	Clear cell carcinoma	Mucinous carcinoma	Mixed carcinoma	
Dilation and curettage	Endometrioid carcinoma	56	3	2	0	0	61
	Serous carcinoma	1	2	0	0	0	3
	Clear cell carcinoma	0	0	1	0	0	1
	Mucinous carcinoma	0	0	0	1	0	1
	Mixed carcinoma	0	0	0	0	1	1
	Adenocarcinoma	12	0	0	1	1	14
	Total	69	5	3	2	2	81

Table 4 shows the results of histological analysis of the preoperative curettage samples and the hysterectomy specimens.

a) Preoperative Cell Type

According to the histologic examination of the endometrial tissue samplings, endometrioid carcinoma was the most common pathology (61/81 = 75.3%) followed by adenocarcinoma (14/81 = 17.3%). The remaining 6 cases (7.4%) have been read as follows: Three serous carcinoma, one clear cell carcinoma, one mucinous carcinoma and one mixed carcinoma.

b) Postoperative Cell Type

From the postoperative specimens, the adenocarcinoma subtype has been ultimately assigned as endometrioid carcinoma (12/14 = 85.7%), mucinous carcinoma (1/14 = 7.1%), mixed carcinoma (1/14 = 7.1%).

8.2% (5/61) of endometrioid carcinoma have been reviewed to serous carcinoma (3 cases) and clear cell carcinoma (2 cases) in the final histological report.

1 patient with serous carcinoma has been diagnosed as endometrioid carcinoma on the final histology.

As a result, the tumors were finally distributed as endometrioid (69/81= 85.2%), serous (5/81= 6.2%), clear cell (3/81=3.7%), mucinous (2/81=2.5%) and mixed carcinoma (2/81=2.5%).

c) Overall Agreement

The overall concordance between the preoperative and postoperative subtypes was 75.3% (61/81). Diagnoses of fifty six endometrioid carcinomas, two serous carcinomas, one mucinous carcinoma, one clear cell carcinoma and one mixed carcinoma corresponded with their original subtypes.

Table 5: Comparison between preoperative and postoperative histologic grade

		Postoperative			Total
		Grade 1	Grade 2	Grade 3	
Preoperative	Grade 1	10 (45.5%)	9 (40.9%)	3 (13.6%)	22 (27.2%)
	Grade2	4 (9.3%)	30 (69.8%)	9 (20.9%)	43 (53.1%)
	Grade 3	1 (6.2%)	2 (12.5%)	13 (81.3%)	16(19.7%)
Total		15 (18.5%)	41 (50.6%)	25 (30.9%)	81 (100%)

Table 5 summarizes the comparison of the histologic grades between the preoperative samplings and the surgical specimens.

d) Preoperative Tumor Grade

Based on initial pathological analysis of endometrial curettage, 43/81 (53.1%) cases of endometrial carcinoma have been mostly read as Grade 2 tumors, 22/81 (27.2%) as Grade 1 tumors and 16/81 (19.7%) as Grade 3 tumors.

e) Postoperative Tumor Grade

However, in the postoperative specimens Grade 2 tumors were still the most common diagnosis but in lesser amount 41/81 (50.6%). This decline also mirrored Grade 1 tumors 15/81 (18.5%). Compared with the initial grading, Grade 3 tumors have been increased to 25/81 (30.9%) in the final pathology report.

f) Overall Agreement

The accuracy between the different preoperative and postoperative tumor grades has been highlighted in light green in table 5. As the tumor grades were increasing, the discrepancy between the endometrial tissue samplings and the hysterectomy specimens decreased. The results show the highest concordance of 81.3% (13/16) in Grade 3 tumors and lowest concordance in Grade 1 tumors, 45.5% (10/22). In Grade 2 tumors 30/81 (69.8%) of the preoperative grading coincided with the final one. Therefore the overall concordance rate was 53/81 (65.4%)

g) Upgrading and Downgrading

34.6% (28/81) of the patients had a revision in their tumor grade. 21/81(25.9%) had been upgraded while only 7/81 (8.6%) had been downgraded.

12/22 (54.5%) of Grade 1 tumors were upgraded: 9/22 (40.9%) to Grade 2 and 3/22 (13.6%) to Grade 3.

Out of the 43 Grade 2 tumors, 9/43 (20.9%) were upgraded to Grade 3 while 4/43 (9.3%) had been downgraded to Grade 1.

Of the 16 Grade 3 tumors, 2/16 (12.5%) were being downgraded to Grade 2, and 1/16 (6.2%) had been downgraded to Grade 1.

Table 6: Comparison between clinical staging and surgical staging

	Surgical Staging			
	Stage I	Stage II	Stage III	Total
Clinical Stage I	44 (78.6%)	7 (12.5%)	5 (8.9%)	56 (69.1%)
Stage II	11 (47.8%)	6 (26.1%)	6 (26.1%)	23 (23.4%)
Stage III	0	0	2 (100%)	2 (2.5%)
Total	55 (67.9%)	13 (16.05%)	13 (16.05%)	81 (100%)

Table 6 shows the outcome of clinical and surgical staging in the study cohort.

h) Clinical Staging

Regarding clinical staging, 69.1 % (56/81) were stage I, 23.4% (23/81) were stage II and 2.5% (2/81) were stage III.

i) Surgical Staging

According to FIGO 2009 classification, 67.9% (55/81) had been surgically diagnosed as stage 1, 16.05% (13/81) as stage II and 16.05% (13/81) as stage III.

j) Discordances

The discrepancy between clinical stage I and surgical stage I was 21.4% (12/56). 7 cases (12.5%) had been upstaged to surgical stage II and 5 cases (8.9%) to surgical stage III.

Among 23 cases which were assigned clinical stage II, the inaccuracy in their diagnoses was 74.9% (17/23) after surgical staging. 11 cases (47.8%) were down-staged to the surgical stage I and 6 cases (26.1%) had been upstaged to surgical stage III.

2 cases (100%) with clinical stage III had been confirmed as surgical stage III.

Based on these results, the highest discrepancy rate has been noted in clinical stage II. i.e., 74.9%. The light blue values in table 6 indicate concordance rate between clinical and surgical staging.

k) Upstaging and Down-Staging

The above modifications led to an overall change in staging in 29/81 cases (35.8%). 18 cases (22.2%) had been upstaged while the remaining 11 (13.6%) were down-staged. Highest upstaging and down-staging rate have been observed in clinical stage II.

IV. Discussion

Endometrial cancer is of multifactorial etiology. In all, increasing body mass index and obesity is a well-established risk factor for endometrial cancer incidence, both in premenopausal and postmenopausal women (24, 25).Before menopause estrogen is primarily derived from the ovaries. However, after menopause adipose tissue becomes the principal source of estrogen. In response to advancing age and excess adiposity, the level of aromatase enzyme increases. Aromatase causes peripheral aromatization of and rostenedione to estrone and estradiol. Simultaneously overweight/ obesity decreases the level of sex hormone binding globulin (SHBG) that binds estrogens (24). This biologic model is especially evident in postmenopausal women (26). The net result is an increased level of unopposed estrogens that stimulate endometrial proliferation, a prerequisite for endometrial tumorigenesis (27). Other well-known risk factors include low parity, early menarche, late menopause, use of tamoxifen or exogenous estrogens without progestins, physical inactivity, diabetes, hypertension, and Lynch syndrome (28-32).

Grading indicates the degree of tumor aggressiveness (33). Histotype, grade, and stage are fundamental pathological elements that constitute an integral part of different risk predictive clinical models used to guide treatment (34). Preoperative grading and histologic subtype are among parameters used to determine lymphadenectomy during a hysterectomy (35). However, tumor grade following hysterectomy is frequently different from the initial endometrial sampling (36).

In a meta-analysis which included 16 previous studies that were published between 1997 and 2016 and assessed the accuracy of endometrial sampling in endometrial carcinoma, Visser et al. reported a magnitude of 67% agreement between preoperative tumor grading and final diagnosis (6). Several previous kinds of literature have shown that the rate of concordance increases with tumor grade, discrepancy being pronounced in grade 1 tumor (12, 37-40). Wang et al. compared the histological grades between curettage and hysterectomy specimen and concluded an upgrading of 50% in grade 1 tumors (41). Furthermore, Petersen et al. deduced the poorest correlation in grade 1 tumors and expressed the need for comprehensive surgical staging during hysterectomy regardless of the grade (38). These findings are consistent with those in this study. On the contrary results of analysis by Wang et al show an accuracy of 70.2%, 67.2%, and 84.4% for grades 1, 2 and 3 respectively (42). All of these studies demonstrate highest concordance rate in grade 3 tumors but figures shuffling between grades 1 and 2. A plausible

explanation for the difficulty in the distinction between grades 1 and 2 tumors has been attributed to an inter-observer agreement. Tumor grading has been based on nuclear features, and the amount of non-squamous solid tumor distinguished from the glands. It becomes very challenging for pathologists to accurately determine the 5% and 6% cutoff values in Grades 1 and 2 tumors. The overall kappa statistics for FIGO grade assignment between pathologists is 0.41-0.68 which signifies only moderate levels of inter-observer agreement. Also, when keratinization is unidentifiable, some squamous areas may be read together with the solid tumor (34, 43).

Overall the reasons for changes in tumor grade are numerous. Firstly, more tissue is available for histological analysis following hysterectomy than during curettage. Stock et al. concluded that D & C blindly scrapes less than 50% of the uterine wall in 60% of patients (44). Secondly, in the final specimen, the tumor is examined in a complete form. As a result, tissue sampling from an intact uterus for morphology increases the accuracy of the postoperative diagnosis. Thirdly, there may be a change in tumor grade from the time of D&C to hysterectomy be there a long gap for surgery. This time span is not applicable to this study as surgery has been performed within weeks after initial diagnosis. Finally, the discrepancy between grades may not be an erroneous diagnosis. In the hysterectomy specimen, there are variations in histologic type, areas of marked cellular and nuclear pleomorphism, high mitotic activity and lack of glandular differentiation. As a result, there is a heterogeneous population of cells and grade ranging from grades 1 to 3 (37). Hence, it is unlikely that the area which has been scrapped during D & C has been analyzed in the final hysterectomy specimen.

Concerning tumor histology, a concordance rate of 75.3% between prehysterectomy sample and final pathology has been found. This figure corroborates with several previous studies. Cowles et al. reported that the change between pre- and postoperative histologic subtype was 27.4% (36). Suwannee Buranawattana-choke et al. found a 25.5% change in histotype which was lower than that of Cowles et al. and Campbell et al.(40). Vorgias et al. and Filip Kisielewski et al. revealed that 67.3% and 83.75% respectively of the final histologic subtypes were similar to those found in the initial report (45, 46).

A discrepancy rate of 8.2% was seen among the endometrioid adenocarcinomas as they have been finally diagnosed as the high grade serous and clear cell carcinoma. M.H. Baek et al. reviewed 817 patients, of which 672 (82.3%) were of endometrioid cell type, with a discordance rate of 6.8% (47). Uterine papillary serous carcinoma and clear cell carcinoma are aggressive histologic subtypes with the propensity of extrauterine metastasis and have been associated with more than 50% of relapses and deaths from endometrial carcinoma (48, 49). Initial management involves a hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and omentectomy (50). On the other hand, the primary treatment of patients with early–staged endometrial carcinoma is hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy (51). In a study of 349 patients with clinical stage 1, grade 1 endometrioid tumors (low-risk) Ben-Shachar et al. found that 2.5% of these patients had been ultimately diagnosed as the serous or clear cell carcinoma on final pathology (52). Based on misdiagnoses from the curettage samples in this study, five patients (8.2%) would have undergone suboptimal surgical staging which would have resulted in deleterious outcomes on overall survival of these patients. In his study, A. Di Cello et al. showed that preoperatively patients who had been positively identified as serous carcinoma erroneously diagnosed as grade 3 endometrioid adenocarcinoma is not as harmful to the patients as the reverse (53).

In this study cohort, 61.7% of patients were above 50 years. The discrepancy between initial and final histology has been explained by the fact that postmenopausal women usually have an atrophic endometrium and obtaining an adequate amount of tissue for histological diagnosis is often challenging (54). A large volume of tissue may permit more accurate evaluation of mixed endometrioid and non-endometrioid tumors (55). Lack of technical skills while performing curettage and low reproducibility between pathologists can also explain a magnitude of discrepancy between initial and final histologic subtypes (56, 57).

The tumor stage has been recognized as the chief prognostic factor for endometrial carcinoma, irrespective of histology and grade (58).Accurate preoperative staging is of clinical value to guide the surgical approach to avoid over - or under-treatment of patients, especially the elderly ones due to associated comorbidities (33). In the present study, a discordance of 35.8% between the clinical and surgical stage was found. This value coincides with other previous studies, occurring in 26.9%- 51% of patients (36, 40, 59, 60). In this study, 21.4% of patients with clinical stage 1 were upstaged following surgery. A similar outcome between 19.7% - 30.4% was reported (36, 40, 59-62). However, the highest inaccuracy had been observed in clinical stage II where 73.9% of patients were assigned a different stage postoperatively. Several authors have also evoked this in their literature with a discrepancy rate ranging between 49% - 80.5% (36, 59, 60, 62, 63). This change in staging might have been accounted by the fact that at the time of dilation and curettage lesions of an involved cervix might be omitted or an uninvolved cervix might have been wrongly diagnosed as having tumor cells (62). In this study, 8.9% and 26.1% of clinical stage I and II patients were upstaged to surgical stage III. Relying on the clinical staging these patients would have been undertreated had lymphadenectomy been

skipped. Intraoperative neurovascular injury, pelvic lymphocyst formation, and leg edema are complications of lymphadenectomy that are a serious concern to surgeons (64). Orr et al. reported that the long-term risks of lymphocyst formation were 1.3% and that of lymphedema was 0.7% (65). The benefits of lymphadenectomy outweigh the harms of the complications and provide valuable information regarding adjuvant therapy and recurrence.

Our study is limited firstly by its retrospective nature as well as a small number of patients. Secondly, hysterectomy has been performed by a team of multiple surgeons who have different levels of expertise. Thirdly, the number of lymph nodes removed at the time of hysterectomy varies. Finally, the preoperative samplings and final hysterectomy specimens have not been examined by the same pathologists. This alteration may have included bias in the reading of the histological slides. However, all the patients selected for the study were from a single center, and surgical specimens had been analyzed at that same institution which allowed a detailed discussion with the pathologists regarding the intraoperative findings. Another strength of our study is that all the preoperative specimen were obtained by D & C rather than by Pipelle endometrial biopsy as the latter has low sensitivity in the atrophic endometrium.

V. Conclusion

In short, tumor grade was similar in 65.4% of patients. 25.9% had been upgraded, and 8.6% downgraded. While 75.3% of preoperative histology corresponded with the final report, 8.3% of aggressive tumors had been missed. Concordance between clinical and surgical staging was 64.2%. 22.2% had been upstaged whereas 13.6% were down-staged. The surgeon should diligently interpret preoperative reports to plan hysterectomy and the extent of lymphadenectomy or adopt fertility-sparing surgery in endometrial cancer as the final histopathological findings and staging might change.

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Disclosures

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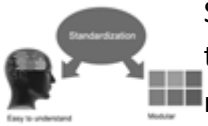

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- • This individual has learned the basic methods of applying those concepts and techniques to common challenging situations. This individual has further demonstrated an in–depth understanding of the application of suitable techniques to a particular area of research practice.

Note :

"

- In future, if the board feels the necessity to change any board member, the same can be done with the consent of the chairperson along with anyone board member without our approval.
- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of "Difference of Opinion [if any]" among the Board members, our decision will be final and binding to everyone.

"

Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

Before and during Submission

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct,* along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

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1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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