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Original Research

The Accuracy of Endometrial Sampling and Clinical Affecting Factors as a Predictor of Final Surgical Pathology in Endometrial Cancer

Lukkana Promwattanaphan[1], Sikarn Satitniramai[1,*]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 10400 Bangkok, Thailand
*Correspondence: sikarn.sat@mahidol.ac.th (Sikarn Satitniramai)

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Abstract

Background: We conducted a retrospective study to evaluate the correlation between preoperative and final histologic diagnoses of endometrial cancer and to identify clinicopathologic factors associated with the concordance between initial and final hysterectomy specimens. **Methods**: Patients who underwent primary surgical treatment for endometrial cancer at our institute from January 2016 through December 2020 were enrolled. The International Federation of Gynecology and Obstetrics (FIGO) grade and histologic subtype in the pathologic reports were recorded. The level of agreement of tumor grade and histologic type were analyzed. **Results**: A total of 425 cases were recruited. The overall level of agreement between preoperative grading was moderate according to kappa statistics (κ = 0.469, 95% confidence interval [CI]: 0.385, 0.553). Furthermore, agreement related to the histologic subtype was substantial (κ = 0.778, 95% CI: 0.682, 0.874). The most frequently used endometrial sampling methods were the office endometrial sampling and endometrial curettage (49.2% and 32%, respectively). Among each diagnostic method, manual vacuum aspiration and endometrial curettage had high tumor grade correlation between the preoperative sampling and final pathology (κ = 0.743, 95% CI: 0.549, 0.937 and κ = 0.624, 95% CI: 0.512, 0.736, respectively). Negative peritoneal cytology was was the significant factor associated with concordance between preoperative endometrial sampling and final surgical pathology, with an adjusted odds ratio (OR) of 2.01 (95% CI: 1.03, 3.92; p = 0.040). **Conclusions**: Regardless of the different diagnostic methods, preoperative endometrial biopsy has limitations in predicting tumor grade compared with final hysterectomy specimens in women with endometrial cancer.

Keywords: endometrial cancer; endometrial sampling; endometrial curettage; office biopsy; tumor grade

1. Introduction

Endometrial cancer is becoming more prevalent among several gynecological malignancies; it is the second ranking gynecological cancer in Thailand, with a 5-year prevalence of 39.64 per 100,000 [1]. Most patients with endometrial cancer present at the early stage of the disease, when it is limited to the uterus, because of abnormal uterine bleeding [2]. Although most cases are associated with excellent outcomes and prognoses, some have a higher risk for dissemination or recurrence. The recommended standard treatment consists of hysterectomy and bilateral adnexectomy with or without regional lymph node dissection [3] because there is no benefit of systematic lymphadenectomy for patients with clinically early stage endometrial cancer at low risk for lymph node metastasis [4,5], and such overtreatment may cause drawbacks such as lymphedema of lower extremities,lymphocele and prolong hospitalization. In contrast, high-grade endometrial cancers are at higher risk of lymph node involvement and require full staging surgery.

The histologic subtype and the grade of endometrial cancer are key features affecting the potential for disease spread and recurrence, in addition to other uterine histopathological factors, such as myometrial invasion, cervical stromal involvement, and lymphovascular space invasion (LVSI) [6–14]. Therefore, the accuracy of preoperative assessment is crucial to determine the optimal extent of surgical management of this disease.

Although some evidence has demonstrated a fair to moderate correlation [15,16] between preoperative endometrial sampling and final surgical pathology in endometrial cancer, there are controversial issues in terms of accuracy related to different methods (office endometrial sampling, sharp curettage, manual vacuum aspiration [MVA], and hysteroscopy) and other clinicopathological factors that might be useful for prediction of final surgical pathology in endometrial cancer. The main objective of this study was to assess the correlation between the histologic subtype and tumor grade from the preoperative endometrial biopsy and final surgical specimen in women with endometrial cancer. In addition, we aimed to clarify clinicopathological factors associated with the concordance between initial and final hysterectomy specimens. The secondary objective was to demonstrate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rates for each tumor grade.

2. Materials and Methods

A retrospective cross-sectional study was carried out on women with endometrial cancer who underwent primary

surgical treatment at Department of Obstetrics & Gynecology, Faculty of Medicine, Ramathibodi Hospital, Bangkok, from January 2016 through December 2020. The inclusion criteria in the study were as follows: patients undergoing primary surgical treatment for endometrial cancer at our faculty after having been diagnosed by preoperative endometrial sampling; patient age $\geq$18 years; and cancer stage I to IVB with any grade of differentiation and histologic subtype according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification. In addition, the preoperative endometrial pathology had to be reviewed by non-specific pathologists of total 20 staff from Pathology unit at Ramathibodi Hospital in case of the patients had undergone endometrial biopsy from other hospitals. Nevertheless, the results of initial pathology were not blinded under the re-evaluation process. The majority of the specimens were assessed by morphologic features but there were a few specimens which inconclusive result need to be analyzed further by immunohistochemistry.We excluded cases with incomplete medical records, inconclusive histologic subtypes or tumor grading, undiagnosed endometrial cancer preoperatively, and cases with radiation or chemotherapy before surgical treatment. The study protocol was reviewed and approved by our ethical committee.

The data were extracted from the medical records, including age, menopausal status, underlying disease, parity, serum cancer antigen 125 level (CA 125), method of preoperative endometrial biopsy, histologic type and tumor grade from preoperative endometrial sampling, histologic type and tumor grade from final pathological exams, tumor diameter, depth of myometrial invasion, cervical involvement, lymphovascular space invasion and cervical stromal involvement, peritoneal cytology, FIGO stage, surgical treatment, residual disease, and postoperative adjuvant treatment.

Continuous data were determined with a *t*-test or Mann-Whitney U test, according to the data distribution. Categorical data were determined with the Chi-square test or Fisher's exact test when appropriate. Multivariate logistic regression analysis was applied. A *p*-value of less than 0.05 was considered statistically significant. The sensitivity, specificity, PPV, NPV, and accuracy rates were calculated for all preoperatively assessed tumor grades. The kappa correlation evaluated the agreement between preoperative and final pathologies of hysterectomy specimens. The strength of agreement by kappa statistics was used in the evaluation as follows: less than 0, no agreement; 0 to 0.19, poor; 0.2 to 0.39, fair; 0.4 to 0.59, moderate; 0.6 to 0.79, substantial; and 0.8 to 1, excellent [17]. All statistical analyses were performed using STATA, version 16 (StataCorp. 2019. College Station, TX, USA).

3. Results

In all, 612 patients with endometrial cancer were diagnosed from our cancer registry. Patients who were excluded from this analysis involved those with previously surgical treatment at other hospitals (n = 54), no pathologic review of preoperative biopsy at Ramathibodi Hospital (n = 41), unknown tumor grading and histologic type on preoperative biopsy (n = 40), preoperatively undiagnosed endometrial cancer (n = 26), receiving radiation or chemotherapy before surgical treatment (n = 18), and incomplete medical records (n = 8). A total of 425 patients met the inclusion criteria. The mean age at diagnosis was 58.6 years (standard deviation (SD) 11.6). Most patients were postmenopause (n = 314, 73.9%); the mean age at menopause at 50.9 years. The demographic and clinicopathologic of patients are summarized in Table 1. The FIGO stages were as follows: Stage I in 303 patients (71.3%), stage II in 30 patients (7.1%), stage III in 64 (15.1%), and stage IV in 28 patients (6.6%). The endometrial biopsy was obtained by endometrial curettage in 136 patients (32.0%); office endometrial biopsy in 209 (49.2%); hysteroscopy in 21 (4.9%); MVA in 46 (10.8%); and other methods, such as cervical biopsy, in 13 (3.1%). Based on the preoperative pathology, 165 patients had endometrioid carcinoma grade 1, 125 patients had endometrioid carcinoma grade 2, and 20 patients had endometrioid carcinoma grade 3. Among non-endometrioid carcinomas, serous carcinoma, clear cell carcinoma, carcinosarcoma, and mixed histology were identified in 63, 12, 21, and 19 cases, respectively. The final surgical pathological report from hysterectomy specimen, endometrioid carcinoma, and non-endometrioid carcinoma were confirmed in 302 patients and 123 patients, respectively.

Table 2 summarizes the correlation between preoperative endometrial biopsy and final surgical pathology. The concordance rates were 68.5% for grade 1, 68.8% for grade 2, 60% for grade 3, and 86.9% for non-endometrioid adenocarcinoma. In total, 114 (26.8%) had discordance between preoperative and final surgical pathology. Forty-six patients (10.8%) were upgraded from preoperative endometrioid grade 1 to grade 2, 2 were upgraded to grade 3, and 4 were recategorized as non-endometrioid carcinoma. Eleven patients (2.6%) were upgraded from grade 2 to grade 3 endometrioid carcinoma and 15 were recategorized as having non-endometrioid carcinoma. Downgrading occurred in 17 patients (4%); 13 patients were downgraded from preoperative grade 2 to grade 1 and 4 patients from grade 3 to grade 2. Furthermore, 15 patients were allocated from non-endometrioid carcinoma to endometrioid carcinoma. The accuracy rates were 83.5% for grade 1, 77.6% for grade 2, 93.4% for grade 3, and 90.3% for non-endometrioid tumors. The sensitivity, specificity, PPV, NPV, and accuracy rate of preoperative grade prediction are summarized in Table 3. Among preoperative histologic grading, endometrioid carcinoma grade 1 had the highest sensitivity; however, the specificity was lower compared with grades 2 and 3.

The overall level of agreement between preoperative grading was moderate according to the kappa statistics (κ

Table 1. Demographic and clinicopathologic of patients.

Variables	Endometrioid carcinoma	Non-endometrioid carcinoma
	n = 302	n = 123
Age, years, mean (SD)	56.8 (12.2)	63.0 (8.8)
BMI, kg/m^2, mean (SD)	27.4 (5.4)	26.2 (4.6)
Hypertension, n (%)		
Yes	144 (47.7)	76 (61.8)
No	158 (52.3)	47 (38.2)
Diabetes Mellitus, n (%)		
Yes	72 (23.8)	30 (24.4)
No	230 (76.2)	93 (75.6)
Dyslipidemia, n (%)		
Yes	113 (37.4)	54 (43.9)
No	189 (62.6)	69 (56.1)
Menopause status, n (%)		
Premenopause	98 (32.5)	13 (10.6)
Postmenopause	204 (67.5)	110 (89.4)
Age menopause, years, mean (SD)	50.9 (3.4)	50.7 (3.9)
Cervical cytology, n (%)		
Negative	213 (71.7)	64 (55.7)
Atypical glandular cell	53 (17.8)	20 (17.4)
Adenocarcinoma	22 (7.4)	26 (22.6)
Others	9 (3.0)	5 (4.3)
Parity, n (%)		
0	139 (46.2)	32 (26.0)
1–2	107 (35.5)	64 (52.0)
3–4	47 (15.6)	23 (18.7)
>4	8 (2.7)	4 (3.3)
Diagnostic method, n (%)		
Endometrial curettage	96 (31.8)	40 (32.5)
Office biopsy	149 (49.3)	60 (48.8)
Hysteroscopy	15 (5.0)	6 (4.9)
Manual vacuum aspiration	35 (11.6)	11 (8.9)
Others	7 (2.3)	6 (4.9)
FIGO Stage, n (%)		
I	236 (78.1)	67 (54.5)
II	19 (6.3)	11 (8.9)
III	38 (12.6)	26 (21.1)
IV	9 (3.0)	19 (15.4)
Surgical treatment, n (%)		
Hysterectomy ± BSO	6 (2.0)	11 (8.9)
Surgical staging	296 (98.0)	112 (91.1)
Residual tumor, n (%)		
No	296 (98.0)	112 (91.1)
≤2 cm	2 (0.7)	2 (1.6)
>2 cm	4 (1.3)	9 (7.3)
Adjuvant, n (%)		
No	161 (54.0)	9 (7.4)
Radiation	89 (29.9)	8 (6.6)
Chemotherapy	7 (2.3)	29 (24.0)
Radiation + Chemotherapy	41 (13.8)	75 (62)

Table 1. Continued.

Variables	Endometrioid carcinoma	Non-endometrioid carcinoma
	n = 302	n = 123
LVSI, n (%)		
Negative	210 (69.5)	51 (43.2)
Positive	92 (30.5)	67 (56.8)
Myometrial invasion, n (%)		
No	52 (17.2)	15 (12.6)
<50%	164 (54.3)	49 (41.2)
≥50%	86 (28.5)	55 (46.2)
Cervical stromal involvement, n (%)		
No	266 (88.1)	90 (75.0)
Yes	36 (11.9)	30 (25.0)
Peritoneal cytology, n (%)		
Negative	266 (88.1)	95 (77.2)
Positive	23 (7.6)	23 (18.7)
CA125, median (IQR)	18.0 (12.1, 36.3)	22.9 (12.0, 54.0)
Tumor diameter, median (IQR)	2.5 (1.5, 4.2)	4.0 (2.0, 5.0)

BMI, body mass index; BSO, bilateral salpingo-oophorectomy; LVSI, lymphovascular space invasion; IQR, interquartile range.

Table 2. Correlation between preoperative endometrial biopsy and final surgical pathology.

	Final surgical pathology				
Preoperative biopsy	Grade 1	Grade 2	Grade 3	NE	Total
Grade 1	113	46	2	4	165
Grade 2	13	86	11	15	125
Grade 3	0	4	12	4	20
NE	2	6	7	100	115
Total	128	142	32	123	425

NE, non-endometrioid carcinoma.

= 0.469, 95% confidence interval [CI]: 0.385, 0.553). Furthermore, agreement on histologic subtype was substantial (κ = 0.778, 95% CI: 0.682, 0.874). According to each diagnosis method of endometrial sampling, MVA, and endometrial curettage, the κ values were highest in the tumor grade correlation between preoperative sampling and final pathology (κ = 0.743, 95% CI: 0.549, 0.937 and 0.624, 95% CI: 0.512, 0.736, respectively) compared with office endometrial biopsy (κ = 0.604, 95% CI; 0.520, 0.688) and hysteroscopy (κ = 0.546, 95% CI: 0.297, 0.795).

The factors associated with the correlation between preoperative and final pathological diagnosis are demonstrated in Table 4. In univariate analysis, peritoneal washing cytology was significantly associated with concordance between pre-and postoperative pathological diagnosis with *p*-values of 0.038. However, myometrial invasion had a trend to associate with concordance between pre- and postoperative pathological diagnosis without significant *p*-value (0.069). Therefore, the negative peritoneal cytology was the significant factor associated with concordance between preoperative endometrial sampling and final surgical pathology with an adjusted odds ratio (OR) of 2.01 (95% CI: 1.03, 3.92; p = 0.040) in multivariate analysis.

4. Discussion

The updated international guideline [18]and pathological features, such as histopathologic type, grade, myometrial invasion, and LVSI, are crucial in assessing prognosis and further management of endometrial cancer. In addition, endometrial biopsy assessed using the WHO Classification of Tumors (5th edition) [19] and FIGO grading of endometrial carcinoma is required for adequate planning of therapy, including extension and the necessity of lymph node dissection in early stage endometrial cancer. The histologic subtype along with the histological tumor grading are crucial in case of the low-risk endometrioid subtype histology grade 1, 2 without myometrial invasion, thus the lymph node dissection can be omitted regarding the benefit outweigh the risk. In addition, molecular classification of endometrioid carcinoma, such as POLE-mutations, microsatellite instability, low-copy-number alteration, tu-

Table 3. Sensitivity, Specificity, PPV and NPV for prediction of tumor grading and non-endometrioid histology.

	Grade 1	Grade 2	Grade 3	NE
Sensitivity, % (95% CI)	88.0 (81.0, 93.1)	60.6 (52.0, 68.7)	37.5 (21.1, 56.3)	79.4 (71.2, 86.1)
Specificity, % (95% CI)	81.7 (76.8, 85.9)	86.2 (81.6, 90.0)	98.0 (96.0, 99.1)	95.0 (91.9, 97.2)
PPV, % (95% CI)	66.7 (58.9, 73.8)	68.8 (59.9, 76.8)	60.0 (36.1, 80.9)	87.0 (79.4, 92.5)
NPV, % (95% CI)	94.2 (90.7,96.7)	81.3 (76.5, 85.6)	95.1 (92.5, 97.0)	91.6 (88.0, 94.4)
Accuracy, %	83.5	77.6	93.4	90.3

mor protein 53 (TP53) mutations is also recommended for demonstrating clinical outcomes and valuable prognostic. Integration of microscopic and molecular features is the best approach to classified patients to predict prognosis in available resource settings [18].

Depending on clinical and pathologic risk, additional imaging modalities can be considered. Abdominal MRI or ultrasound has clinical utility to evaluate deep myometrial and cervical stromal invasion, moreover abdominal computerized tomography scan, positron emission tomography scan can assess metastatic disease. Consequently, preoperative histology, tumor grading and imaging help tailor an adequate surgical plan. Nevertheless, the resources of these investigation tools are still limited in our institute and the majority of the hospitals in Thailand whether the availability of time or funding.

In line with a previous report [20], the present study revealed a moderate correlation between preoperative tumor grading and final surgical hysterectomy specimens in women with endometrial cancer. Nevertheless, agreement on histologic subtype was higher between endometrioid and non-endometrioid carcinomas. The concordance rates between preoperative endometrial sampling and hysterectomy specimens were approximately 60%–68% for endometrioid carcinoma and 86.5% for non-endometrioid carcinoma; these results are comparable to the findings of previous studies [21–23]. Among endometrioid carcinomas, grade 3 tumors had the highest accuracy rate to predict postoperative tumor grading (93.4%), which was a similar result to results reported by other authors [16,22,24–27]. Thus, prediction of final tumor grade is unreliable, especially in the upgrading rate of 10.8% in endometrioid carcinomas of grades 1,2. Possible factors were clarified as causes of the discordance between pre- and postoperative surgical pathology, such as the quality and quantity of biopsy specimens. One factor is that the amount of limited tissue obtained by endometrial biopsy or abundant hemorrhagic material can hinder the diagnosis. Another factor, related to FIGO grading, is that there may be a low volume of solid growth tumor in the initial biopsy compared with the total tumor volume after hysterectomy, as demonstrated by Lago *et al*. [28]; a large tumor (>3 cm) is more likely to have discordant tumor grade. In addition, our results showed several factors that could affect intra-tumor diversity, leading to discordant grading between initial and final specimens. LVSI, myometrial invasion, cervical stromal involvement, tumor diameter, serum CA 125, and peritoneal washing cytology were all analyzed as possible factors. Consequently, negative cytology were only significant factors associated with concordant pathology. However, we could not accurately predict this factor during preoperative and intraoperative timing.

The upgrading and downgrading rates in endometrioid carcinoma were 20.6% and 5.5%, respectively. Focusing on downgrading, this most frequently occurred in preoperative diagnosis of endometrioid carcinoma grade 2 and final diagnosis of endometrioid grade 1. Nevertheless, the adjuvant treatment did not alter between preoperative and postoperative diagnoses. The second most frequent downgrade discrepancies were preoperative diagnosis of non-endometrioid and postoperative diagnosis of endometrioid carcinoma grade 1, 2, or 3. A lower grade of the final specimen could be difficult to interpret and require adjuvant treatment. To our knowledge, there is no clear evidence for choosing adjuvant treatment in these situations. For those patients whose adjuvant treatment was judged based on postoperative final diagnosis (seven patients), no patient showed recurrence of disease at the last follow-up.

Comparing each diagnostic method, office endometrial biopsy remained the most common evaluation method for women with suspected endometrial cancer in our study. Leitao *et al*. [22] showed that dilation and curettage (D&C) was more accurate in determining the real tumor grade in the endometrioid subtype compared with office endometrial sampling, with rates of upgrading of 8.7% and 17.4% (p = 0.007), respectively. Nevertheless, our data support a different point of view: MVA was found to have an upgrade rate of 6.3%, endometrial curettage had an upgrade rate of 21.7%, and office endometrial biopsy had an upgrade rate of 23.8%. Consequently, the best agreement was found in MVA (κ = 0.743) but the number of MVA sampling was too limited to evaluate superiority. The correlations of both sharp curettage and office endometrial biopsy were comparable, at κ = 0.623 and κ = 0.603, respectively. Additionally, the advantages of office endometrial biopsy are known to be less invasion, minimizing patient discomfort, and cost effectiveness in diagnosis of endometrial cancer [29]. The office endometrial sampling should be considered for the preoperative planning in general cases, although patients considering uterine preservation, especially those who need fertility-preserving treatment, the recommended method for achieving adequate specimen and sampling accuracy is endometrial curettage or MVA.

Table 4. Clinicopathologic factors associated with concordance of tumor grade and histologic type.

	Discordance	Concordance	Univariate analysis	Multivariate analysis	*p*-value
	n = 114 (%)	n = 311 (%)	*p*-value	OR (95% CI)	
Age, years, mean (SD)	59 (12.3)	58.4 (11.4)	0.427		
BMI, kg/m^2, mean (SD)	27.2 (4.8)	27.0 (5.4)	0.841		
Menopause status			0.658		
Premenopause	28 (24.6)	83 (26.7)			
Postmenopause	86 (75.4)	228 (73.3)			
Age menopause, years mean (SD)	51 (2.9)	50.8 (3.8)	0.598		
Cervical cytology			0.882		
Negative	74 (66.7)	203 (67.4)			
Abnormal	37(33.3)	98 (32.6)			
FIGO Stage			0.582		
I	79 (69.3)	224 (72)			
II–IV	35 (30.7)	87 (28)			
LVSI			0.102		
Negative	63 (55.7)	198 (64.5)			
Positive	50 (44.3)	109 (35.5)			
Myometrial invasion			0.069		
≤50%	68 (59.6)	212 (69.1)		1.50 (0.96, 2.35)	0.070
>50%	46 (40.4)	95 (30.9)		1	
Cervical stromal involvement			0.83		
No	95 (83.3)	261 (84.7)			
Yes	19 (16.7)	47 (15.3)			
Tumor size			0.488		
≤2 cm	41(36.3)	124 (40)			
>2 cm	72 (63.7)	186 (60)			
Peritoneal cytology			0.038		
Neg	89 (83.2)	272 (90.7)		2.01 (1.03, 3.92)	0.040*
Positive	18 (16.8)	28 (9.3)		1	
CA125			0.312		
≤20	53 (50)	166 (55.7)			
>20	53 (50)	132 (44.3)			

BMI, Body mass index; LVSI, Lymphovascular space invasion; **p*-value, statistical significance.

In a previous study [28], hysteroscopy-guided endometrial sampling was the most reliable technique for predicting the final tumor grade (κ = 0.551). However, the researchers found no difference in correlations among other methods (D&C, Pipelle). Despite the lower agreement of hysteroscopy in the present study, the kappa coefficient still exhibited a moderate strength of agreement (κ = 0.546). Few cases were initially diagnosed by hysteroscopy-assisted endometrial sampling (n = 21) owing to our institute's concern about higher expenses and more complex operations. Moreover, hysteroscopy is still controversial in terms of disseminating malignant cells in the peritoneal cavity [30].

The more reliable classification of molecular features in endometrial carcinoma had been applied to diagnostic endometrial biopsy. Excellent level of concordance was observed between biopsy and final hysterectomy specimens for mismatch repair-loss (MMR-loss), microsatellite instability-high (MSI-high), P53-wild and abnormal types, especially in p53 abnormal (κ = 1.0) comparing with moderate agreement of histologic subtype and tumor grading (κ = 0.5) [31]. Through more reproducibility of molecular systems in initial diagnostic specimen, implementation of the molecular classifier is pragmatic options in clinical decision to guide surgery, adjuvant treatments and surveillance.

Some limitations of this study are its retrospective nature, which can be associated with missing data. The main strength of the study is the substantial sample sizes of endometrioid and non-endometrioid carcinomas in the context of endometrial cancer. Another strength is that we included only cases where the pathological reports were reviewed from our university hospital.

5. Conclusions

The present study confirmed that regardless of the diagnostic method used, preoperative endometrial sampling

restricts the prediction of grading similarity with final surgical specimens. However, in terms of the histologic subtype, it showed substantial agreement between the initial biopsy and postoperative pathology. Although MVA is associated with the highest kappa value of correlation for forecasting final surgical histology, all available information should be considered when it comes to establishing treatment planning.

Author Contributions

LP and SS designed the reseach study, performed the research. SS analyzed the data and wrote the manuscipts. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University: COA. MURA2021/625. Informed consents were unable to be obtained due to retrospective nature of this study.

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Conflict of Interest

The authors declare no conflict of interest.

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