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Endometrial biopsy in females with abnormal uterine bleeding: Clinical and histopathological patterns

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ABSTRACT

Background: Abnormal uterine bleeding (AUB) is a common presenting symptom in the genecology practice setting all over the world, however the etiology and patterns could vary from one region to another. This study aims to identify the clinical patterns and histopathological different diagnoses encountered in patients of various age groups presenting at a tertiary hospital in one of the biggest countries in the Middle East region. *Materials and Methods*: This is a retrospective study assessing a total number of 210 endometrial biopsies obtained by the gynecologists using three sampling tools; dilation and curettage, endometrial pipelle biopsy, or hysteroscopy endometrial biopsy. The cases were retrieved to identify the different histology patterns of AUB and assess the performed maneuvers endometrial biopsy in the histopathology, genecology, radiology and anesthesia departments. *Results*: The most frequent recorded bleeding type is the menorrhagia which is presented in 40% of the patients, followed by the menometrorrhagia. According to histological patterns; the normal menstrual pattern accounts 25.5% of cases and malignant cases are 13/210 (6.2%). The clinico–histological agreement for diagnosis of the endometrial pathology is 80%. *Conclusion*: Postmenopausal age group carries the higher risk of malignancy, however, malignancy and atypical endometrial carcinoma are also seen in the reproductive age group. Clinical and radiological examination may fail to reach out the final diagnosis, then proper biopsy taking and careful histopathology examination is mandatory.

Keywords: Abnormal uterine bleeding, Endometrial biopsy, General anesthesia, Histological features, Ultrasonogram

1. INTRODUCTION

Abnormal uterine bleeding (AUB) is a very common gynecological problem and one of the most common debilitating menstrual problems affecting all age

groups (Abid et al., 2014; Ely et al., 2006). The uterine bleeding is responsible for more than one-third of all outpatients gynecological visits and considered abnormal when it differs in amount, duration or frequency from the normal menstrual cycles or after menopause (Speroff and Fritz, 2008; Wren, 1998). AUB is associated with functional causes, like abnormal physiological changes of endometrium including inactive endometrium and weakly proliferative endometrium (Longacre et al., 2005) or organic causes where the histopathology examination is the milestone that can specify the nature of the abnormality from the spectrum of those usual and unusual pathologies including endometrial polyp, endometritis, endometrial hyperplasia primary endometrial carcinoma or metastasizing carcinomas (Abdullah and Bondagji, 2011; Hasan et al., 2020[a]; Hasan et al., 2020[b]).

Management of AUB is not complete without tissue diagnosis (Baral and Pudasaini, 2011). Traditionally, endometrial samples for histopathology analysis can be obtained by dilation and curettage (D&C) or hysteroscopy, however, these procedures are not suitable for some cases and other devices like aspiration ones or the pipeline and Tao brush are used (Zhang et al., 2021; Singh et al., 2018). This study aims to identify the clinical patterns and histopathological different diagnoses encountered in patients of various age groups presenting at our tertiary hospital with AUB.

2. MATERIALS AND METHODS

This is a retrospective study performed at Al-Azhar Hospital, Al-Hussein, Cairo and obtained ethical approval from local ethical committee. The study assessed a total number of 210 endometrial biopsies obtained by the gynecologists at our hospital during the period from January 2019 up to December 2019 using three sampling tools; endometrial pipelle biopsy, hysteroscopic endometrial biopsy or D&C under general anesthesia in the operating room by the anesthesiologists including two performed methods; A) dexmedtomidine and fentanyl (DF) received dexmedtomidine loading dose 1 μg/kg over 10 min then followed by 0.5 μg/kg/hr infusion till completion of the surgery. B) Ketamine and fentanyl (KF) received ketamine 0.5 mg/kg slow intravenous Bolus.

Sonohysterogram by the radiologist was done for suspicious patients for uterine mass by the radiologist. All biopsies were sent to the histopathology laboratory for examination and the studied cases were reexamined microscopically by the pathology and histology authors using Hematoxylin and eosin stains (H&E). The clinical data (patient complaint, duration, procedure, clinical diagnosis, and the final diagnosis) were collected from the histopathology reports and requests which are usually providing the relative data (Hasan et al., 2020[c]) and the missing information were collected from the medical files by the authors from the gynecology and anesthesia departments.

Inclusion criteria: All AUB women from all ages who were histopathologically examined in the hospital laboratory and the studied clinical data are provided on the patient file.

Exclusion criteria: All women missing the clinical data on the medical files and the women who underwent endometrial biopsy for causes other than AUB. Eleven cases with histopathology reporting as (Insufficient/ Unsatisfactory) were excluded. All patients who did not undergo the biopsy taking due to refusal of the anesthesia or procedure, renal insufficient, hepatic insufficient, allergies to drugs, cardiac disease or heart block also excluded.

According to age in years; the patients were grouped, into three main groups as follows: reproductive age (20-39), perimenopausal (40-49), and postmenopausal (>50 yrs) (Figure 1). Data were entered into Excel program (Microsoft Corporation, Redmond, United States of America). Results were presented as the mean ± SD for age, frequencies, and percentages were computed for the descriptive variables. The Interrater reliability between clinical and histopathological final diagnosis was statistically evaluated using kappa test. It is suggested by Cohen that the Kappa value can be interpreted as follows: the value ≤ 0 indicates no agreement, 0.01– 0.20 indicates none to slight, 0.21–0.40 means fair, 0.41– 0.60 indicates moderate, 0.61–0.80 reflects substantial and 0.81–1.00 is almost perfect agreement (McHugh, 2012).

3. RESULTS

The mean age of females with AUB in this study is 46.9 years ±9.5 (25-71 years) and the most common age group is the perimenopausal period which includes (113/210 patients, 53.8%) followed by postmenopausal age group (53/210 patients, 25.2%) and then reproductive age group (44/210 patients, 21%), (Figure 1).

The most frequent AUB type is the menorrhagea which is presented in 40% of the patients, followed by the menometrroragea (Table 1). D & C biopsy was done for 172(82%), Pipelle biopsy for 18 (8.5%) and Hysteroscopic biopsy for 20 (9.5%) patients. The histopathological patterns vary between normal menstrual pattern and malignant behavior (Table 2). All malignant cases were carcinomas with no recorded sarcoma or lymphoma.

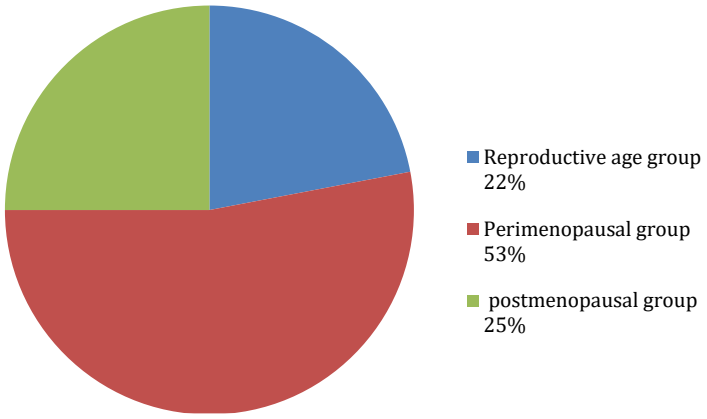

Figure 1 A pie chart showing the percentage of each age group.

Table 1 Patient complaints

Patient complaint	Number (%)	Biopsy procedure; number (%)
Menorrhagia	87 (41.5%)	D&C biopsy; 75 (35.7%) Pipelle biopsy; 5 (2.4%) Hysteroscopic biopsy; 7 (3.4%)
Menometrorrhagia	30 (14.3%)	D&C biopsy; 25 (11.9%) Pipelle biopsy; 2 (1%) Hysteroscopic biopsy; 3 (1.4%)
Metrorrhagia	24 (11.4%)	D&C biopsy; 20 (9.5%) Pipelle biopsy; 3 (1.4%) Hysteroscopic biopsy; 1 (0.5%)
Polymenorrhea	10 (4.8%)	D&C biopsy; 7 (3.4%) Pipelle biopsy; 2 (0.9%) Hysteroscopic biopsy; 1(0.5%)
Oligomenorrhea	6 (2.8%)	D&C biopsy; 5 (2.3%) Pipelle biopsy; 1 (0.5%)
Post menopausal bleeding	53 (25.2)	D&C biopsy; 40 (19.1%) Pipelle biopsy; 5 (2.3%) Hysteroscopic biopsy; 8 (3.8%)
Total	210 (100%)	D&C biopsy; 172 (82%) Pipelle biopsy; 18 (8.5%) Hysteroscopic biopsy; 20 (9.5%)

The normal menstrual pattern includes secretory phase (in 5.7 %) and proliferative phase (in 3.8 %). Disordered proliferative endometrium (16.2). The other histological patterns come as follows; benign endometrial polyp (24.3%) (Figure 2), chronic endometritis (1.9%), leiomyoma (1.9%), non-atypical endometrial hyperplasia (22.8 %) (Figure 3), atypical endometrial hyperplasia (17.2%), and endometrial carcinoma; endometrioid adenocarcinoma and serous adenocarcinoma (6.2%) (Figure 4). The endometrial carcinoma cases were 13 cases distributes in all age groups as follows: 2 patients in reproductive age group, 4 patients in perimenopausal age, and 7 patients in postmenopausal age. Unexplained cervical tissue fragments are seen microscopically in 24/210 of the endometrial specimens (11.4%). The clinical–histological agreement percentage for diagnosis of the endometrial pathology was 85.4 %. The applied Interrater reliability Cohen's kappa coefficient (κ) showed moderate agreement (5.1).

Table 2 Histopathology patterns

Histology pattern	Number
Secretory phase	12 (5.7%)
Proliferative phase	8 (3.8%)
Endometrial polyp,	51 (24.3%)
Disordered proliferative endometrium,	34 (16.2%)
Chronic endometritis	4 (1.9%)
Leiomyoma	4 (1.9%)
Endometrial hyperplasia	48 (22.8)
Atypical endometrial hyperplasia	36 (17.2%)
Endometrial carcinoma; endometrioid type Serous type	13 (6.2%) 10 (4.8) 3 (1.4%
Total	210 (100%)

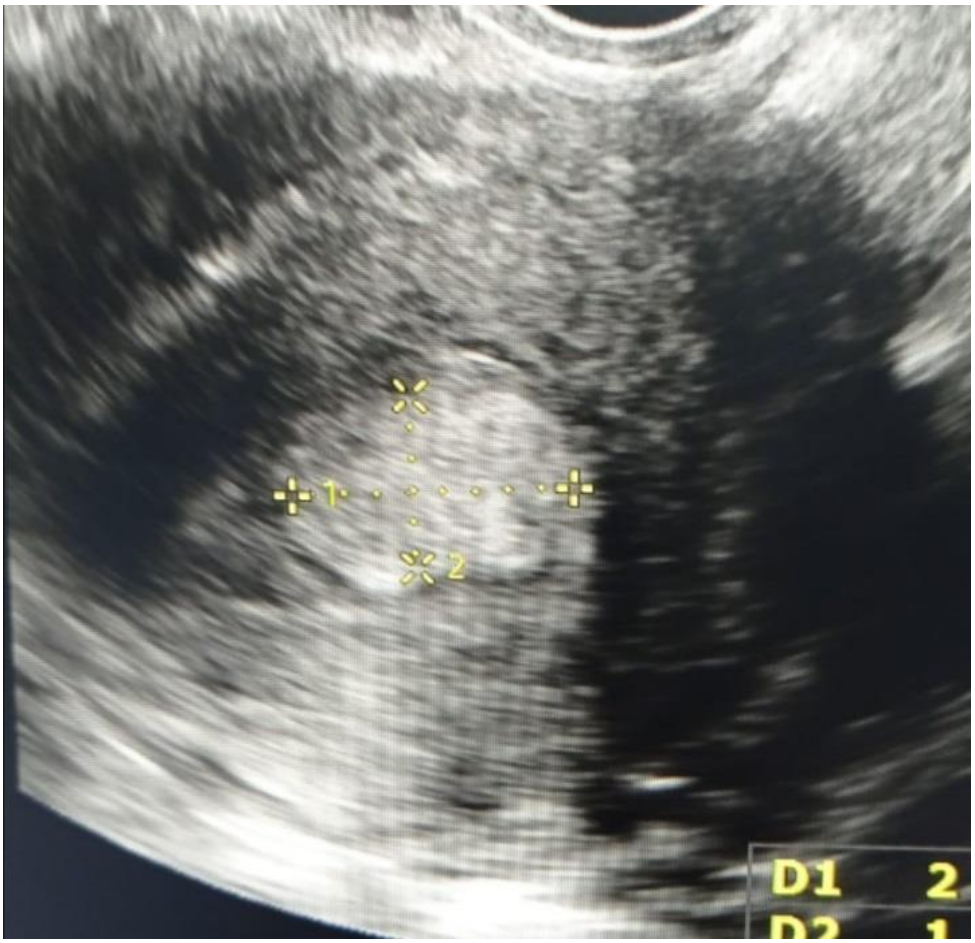

Figure 2 Songogram picture of endometrial polyp showing echogenic focal lesion with feeding vessels.

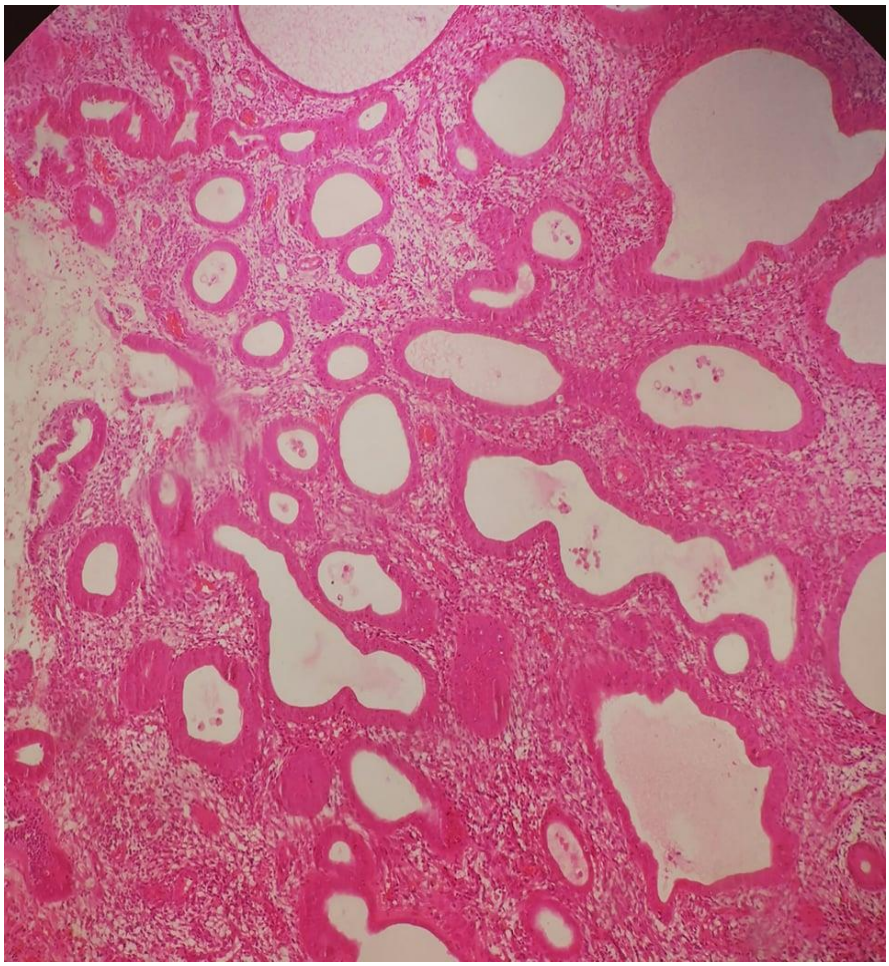

Figure 3 A histopathological picture of a case of endometrial hyperplasia with no atypia (H&E, 200x)

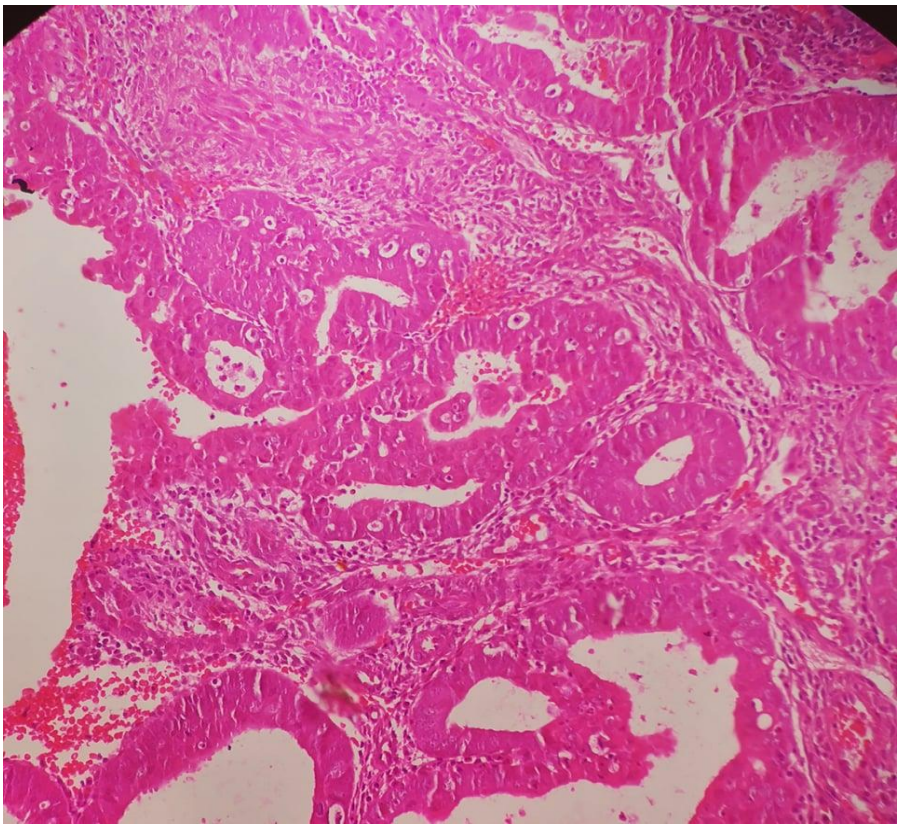

Figure 4 A histopathological picture of a case of endometrial carcinoma, endometriod type, grade 2 (H&E, 200x)

4. DISCUSSION

AUB describes a range of symptoms including inter-menstrual bleeding, heavy menstrual bleeding, and a combination of both prolonged and heavy menstrual bleeding. The terminology was established in 2011 by the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics (FIGO) and has been gaining global acceptance (Cheong et al., 2017). Specialist diagnostic procedures for endometrial changes and cancer diagnosis include sonohysterogram, diagnostic hysteroscopy, pipelle biopsy and D&C. The D&C procedure does not sample the entire endometrial surface and can miss up to 10% of diseases and a number of associated operative risks also had been recorded (Oehler and Rees, 2003; Telner and Jakubovicz, 2007). Outpatient-based biopsy is an excellent choice compared to standard fractional D&C and both showed almost equal success rate in diagnosing of endometrial pathologies. Pipelle biopsy is less painful with no need for high potency anesthesia and can help cancer diagnosis but the direct hysteroscopic D&C is required for the definitive diagnosis for polyps and focal endometrial lesions (Ilavarasi et al., 2019; Berek, 2012). Neither D&C nor pipelle is an adequate method for focal endometrial lesions (Demirkiran et al., 2012).

In our study, we recorded using of the three tools for biopsy and the most commonly used method was the D&C biopsy with general anesthesia which is performed for 172/210 (82%) cases followed by Pipelle biopsy in 18 (8.5%) and lastly hysteroscopic biopsy in 20 cases (9.5%). Administration of conscious sedation provides the dual goals of safely and rapidly establishing satisfactory procedural condition (therapeutic or diagnostic procedures) like endometrial biopsy while ensuring rapid predictable recovery with a minimal post-operative sequel. Dexmedetomidine is a highly selective alpha 2 agonist providing cooperative and anxiolysis sedation without respiratory depression (Ali et al., 2017). The dexmedetomidine is a safe drug with good hemodynamic and recovery time, in addition to exertion of sedation and analgesia without respiratory depression, unlike most of the analgesic/sedative drugs, such as opioids, ketamine benzodiazepines, and propofol (Tammam, 2013).

Hysteroscopy allows direct visualization of the cavity of the uterus and is usually combined with the endometrial biopsy (Telner and Jakubovicz, 2007). Saline sonohysterogram involves introducing amount of 5 to 15 mL of saline solution in the uterine cavity, then transvaginal ultrasound scan is performed that can help diagnose an intrauterine mass (Vilos et al., 2001). Saline infusion sonohysterography using feeding artery visualization can be a very useful method in the diagnostics of endometrial cancer and endometrial polyps in perimenopausal and postmenopausal women (Anioł et al., 2017). In normal menstrual cycles, the shedding is followed by the endometrial proliferation under estrogen stimulation, in such phase, endometrial glands become tortuous after growing (Schorge et al., 2008). The secretory activity occurs in the second half of the cycle showing endothelial proliferation with wall thickening and coiling forming spiral arterioles (Liane, 2000).

The disordered proliferative endometrium which is considered an exaggeration of the normal proliferative endometrium without a significant increase in overall glands to stroma ratio (Mutter et al., 2007). Histological characteristics of the different human pathologies including the endometrium remain the diagnostic standard for the accurate and final diagnosis (Baral and Pudasaini, 2011; Hasan et al., 2020[d], Hasan and Youssef, 2020; Al-Ghamdi et al., 2020; Hasan et al., 2021). In our study, the normal physiological changes (proliferative and secretory phases) occur in 10% of the female patients who underwent endometrial biopsy and 16% of the cases showed disordered proliferative endometrium. It is much lower than the percentage recorded by Baral and Pudasaini in 2011 and other researchers who found 50% of the total studies patients under category of normal physiological changes (Baral and Pudasaini in 2011). This lower percentage in our study could reflect the high selectivity of the gynecologists for the biopsied patients or may be due to refusal of some patients for this procedure and preferring to start with medical treatment. Exogenous hormonal therapy results in poorly developed secretory endometrium (Feeley and Wells). This diagnosis did not appear as a main diagnosis in the reviewed pathology reports in this study. Endometrial polyp was the most commonly diagnosed pattern an all cases of our study but the two types of the endometrial hyperplasia (non-atypical and atypical collectively) exceeded the polyp diagnosis in women of all age groups where the hyperplasia represents 40% of our studied cases. Our findings are in agreement with most of the previous studies (Salma et al., 2016). Four out of 210 cases of the assessed endometrial biopsies in this study revealed leiomyomas which were investigated by Ultrasonography before biopsy. Both transabdominal and transvaginal Ultrasonography should be performed for examining most female pelvis lesions. Transvaginal scans remain the most sensitive method for detecting small fibroids (Sue and Sarah, 2009).

The risk of endometrial cancer increases with many factors including obesity and age (Kumari et al., 2018; Baheeg et al., 2020), our results agreed with this finding where we recorded more than the malignant cases occurred in the post-menopausal age group. Our percentage for the malignant biopsies among the studied endometrial biopsies in all age groups was 6.2 % which is lower than the results of Baral and Pudasaini in 2011 who reported 20% malignant cases (Baral and Pudasaini, 2011). Some authors found also

high percentages but in the studies on older patients (Dawood et al., 2010; Dangal, 2003). Endometrial sampling requires an appropriate and good histologic specimen with no cervical tissue admixture for the pathologist to identify endometrial pathological lesion. There are different known histotypes of the endometrial carcinoma and assignment of the histotype in preoperative biopsy is straight forward in most endometrial malignant cases, but can be exceedingly difficult in several high-grade tumors exhibiting histological ambiguity (Gilks et al., 2013).

5. CONCLUSIONS

Postmenopausal age group with uterine bleeding carries the higher risk of malignancy. However, malignancy and atypical endometrial hyperplasia (Endometrial Intraepithelial Neoplasia) have also been seen in the reproductive age group. The clinico–histological agreement for diagnosis of the endometrial pathology was moderate, shedding a light on the high importance of proper endometrial biopsy and careful histology evaluation.

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Conflict of interest
The authors declare that there are no conflicts of interests.

Ethical approval
A local bioethical approval was provided.

Informed consent
Written informed consent was obtained from all individual participants included in the study.

Author Contributions
Study concept & design: MEAE, NO, KAR,SF, AMK, ME
Data collection& interpretation: MEAE, NO, KAR, MHA, SF, MAE, ME
Data analysis: MEAE, NO, KAR, ME
Histopathology revision: NO, MEAE, MAE
Radiology Revision: SF
Clinical revision: KAR, MHA
Anasthesia related revision: AMK, ME
Literature review: MEAE, NO, KAR, MHA, SF, AMK, ME
Drafting& editing of the paper: ALL
Manuscript revision: ALL

Data and materials availability
All data associated with this study are present in the paper.

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