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# Survival rate, recurrence rate, and complications of routine appendectomy for patients with borderline and malignant mucinous ovarian tumor: A systematic review and meta-analysis

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## Abstract:

**OBJECTIVE:** The objective of the study is to determine the survival rate, recurrence rate, and complication rate among patients diagnosed with borderline and malignant mucinous ovarian tumor (MOT) who underwent complete surgical staging with appendectomy.

**METHODOLOGY:** Eligibility criteria – A search of published literature was conducted in the electronic databases of MEDLINE (PubMed), Cochrane, and Google Scholar through 2000–2022, using a search strategy based on the PIO framework. Information of sources – The citations were identified with the use of a combination of the following text words: “mucinous ovarian tumors,” “MOT,” “appendectomy,” and “pseudomyxoma peritonei.” All retrospective studies with histopathologic diagnosis of borderline or malignant MOTs with patients who underwent appendectomy during primary surgery, including encompassing data on survival rate, recurrence rate, and/or incidence of complications (postoperative infections, appendectomy site leakage, hemorrhage, abscess, peritonitis, bowel perforation, and intestinal obstruction) that matched the terms set by the researchers were retrieved. Risk of bias – For the methodological quality of the individual clinical trials, the Jadad scale was used, which is based on the three following subscales: randomization (2, 1, or 0), blinding (2, 1, or 0), and dropouts/withdrawals (1 or 0). Guidelines for Cochrane collaboration were used to assess the risk bias. Synthesis of results – Review Manager version 5.3 (RevMan 5.4.1) was used by the researcher to perform the systematic review and meta-analysis of included studies.

**RESULTS:** There were eight retrospective studies included in this study. The random interval for survival rate is 64.9%–99.7% with a  $P < 0.1$ . The prediction interval for recurrence rate is 0%–100% with 95% confidence interval. The odds of complications occurring are  $<0.69$ – $2.99$  times with 95% confidence interval, with mean effect size is 0.083, and with a 95% confidence interval is 0.027–0.23.

**CONCLUSION:** The mean prevalence of abnormal histology of the appendix in patients diagnosed with borderline and malignant MOTs and underwent appendectomy during primary surgery is 3%–13%. There is no statistically significant difference in survival rate of patients who were diagnosed with borderline and malignant MOTs with or without appendectomy during primary surgery. The prediction interval for recurrence rate is 0%–100% with 95% confidence interval. There is no significant difference between the rate of complications in patients who underwent appendectomy and those without.

## Keywords:

Appendectomy, borderline mucinous ovarian tumors, malignant mucinous ovarian tumors, mucinous ovarian tumors

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## Introduction

Ovarian tumors originating from the epithelial cell layer make up about 65% to 75% of all types of ovarian tumors.<sup>[1]</sup> Epithelial ovarian cancer is classified, based on molecular and clinicopathologic differences, into Type 1 tumors, which include low-grade serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, mucinous ovarian carcinoma, and Type 2 tumors, which include high-grade serous carcinoma.<sup>[2]</sup> Ovarian mucinous tumors account for 10%–15% of total gynecologic cancers. These tumors may primarily have ovarian origin or may be metastatic with their origins in other parts of the body, particularly from gastrointestinal tract. The appendix is the source of 8% of ovarian mucinous tumors.<sup>[3]</sup>

Mucinous ovarian cancer may metastasize to the peritoneum giving rise to pseudomyxoma peritonei (PMP), a rare clinical entity characterized by diffuse intraabdominal gelatinous ascites with mucinous implants on peritoneal surfaces and no obvious invasion of underlying tissues.<sup>[4]</sup> Thus, careful evaluation of the gastrointestinal tract is required to rule out the possibility of metastatic cancer to the ovaries. To eliminate missing a possible appendiceal tumor, an appendectomy may be warranted.<sup>[5]</sup> In the past, guidelines often recommended removal of the appendix in patients with mucinous borderline ovarian tumor (mBOT). However, routine appendectomy is controversial today, and some authors suggest appendectomy only if the appendix appears macroscopically abnormal.<sup>[6]</sup> According to the International Federation of Gynecology and Obstetrics (FIGO) committee and the National Comprehensive Cancer Network, routine appendectomy is recommended for mucinous ovarian cancer to differentiate between primary and metastatic ovarian tumor with appendiceal primary.<sup>[7-9]</sup>

### Objectives of the study

To provide a comprehensive evaluation of this clinical practice, we presented the available evidences and reviewed all the related studies in an attempt to provide a more objective assessment of routine appendectomy in women having surgery for mucinous ovarian borderline and malignant neoplasm. During the period, this study was conducted; there was still no published level I recommendation regarding this management dilemma. This study aims to determine the survival rate, recurrence rate, and complication rate among patients diagnosed with borderline and malignant mucinous ovarian tumor (MOT) who underwent complete surgical staging with appendectomy.

## Methodology

### Research design

The present study was designed as a systematic review and meta-analysis [Table 1].

### Data sources and search strategy

A search of published literature was conducted in the electronic databases of MEDLINE (PubMed), Cochrane, and Google Scholar through 2000–2022, using a search strategy based on the PIO framework, as described above. The citations were identified with the use of a combination of the following text words: “mucinous ovarian tumors,” “MOT,” “appendectomy,” and “pseudomyxoma peritonei.” All studies that matched the terms set by the researchers were retrieved. Titles and research abstracts were reviewed individually. No restrictions for geographic or location will be applied. However, restriction on English language was applied. The flow of identification of the studies is seen on Figure 1.

### Inclusion criteria

Retrospective studies with histopathologic diagnosis of borderline or malignant MOTs with patients who underwent appendectomy during primary surgery including encompassing data on survival rate, recurrence rate, and/or incidence of complications (postoperative infections, appendectomy site leakage, hemorrhage, abscess, peritonitis, bowel perforation, and intestinal obstruction) were included in the study.

### Exclusion criteria

Cases with histopathologic diagnosis of benign MOTs, history of previous appendectomy, history of primary gastrointestinal malignancy, and complications not related to appendectomy were excluded from the study.

### Data extraction and management

Standard data extraction templates and operational definitions of outcomes and explanatory variables were prepared before abstraction. The researchers independently did an abstracted data form on each study before pooling of results. Information on participant

**Table 1: Research design**

Research Component	Description
Population (P)	Patients with borderline and malignant mucinous ovarian tumor with no gross appendiceal involvement
Intervention (I)	Routine appendectomy
Outcome (O)	Survival rate Recurrence rate Complications (incidence of postoperative infections, appendectomy site leakage, hemorrhage, abscess, peritonitis, bowel perforation, and intestinal obstruction)

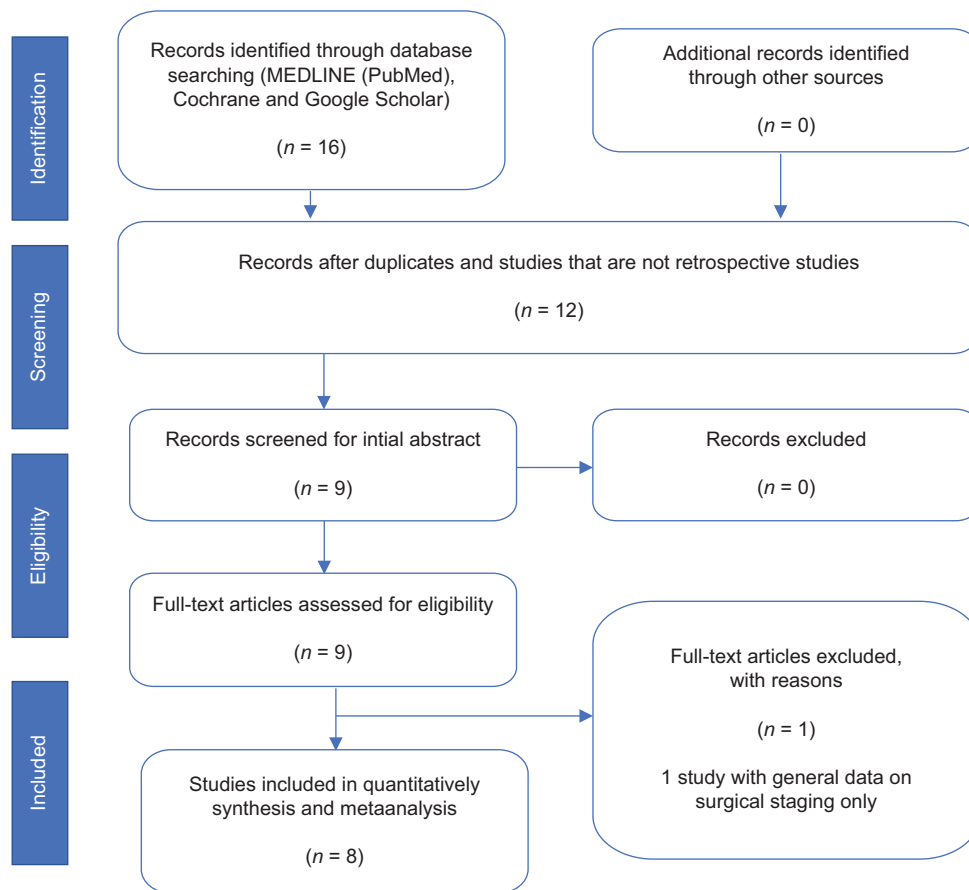


Figure 1: Flow of identification of the study

characteristics (study inclusion and exclusion criteria), diagnosis, study duration, and geographical location were collected. Information on each of the following outcomes were extracted whenever available: frequency of appendiceal involvement, survival rate, recurrence rate, and complications.

The researchers extracted the number of events of interest and total number that were analyzed in each group for dichotomous data. On the other hand, the researchers extracted the mean and standard deviations (SDs) for continuous data. However, in case, mean change and SD were not available, calculations were from presented data such as standard error, confidence intervals, baseline, and follow-up means and SD to obtain the mean change and SD values. The researcher settled any inconsistencies by discussion.

### Risk of bias assessment in individual studies

For the methodological quality of the individual clinical trials, Jadad scale was used, which is based on the three following subscales: randomization (2, 1, or 0), blinding (2, 1, or 0), and dropouts/withdrawals (1 or 0). Guidelines for Cochrane collaboration were used to assess the risk bias. The researcher evaluated the methods of random sequence generation and allocation

concealment for selection bias. The methods of blinding among the participants and investigator of each trial were noted for performance bias. Meanwhile, blinding for outcome assessment was used to calculate detection bias. Completeness of the outcome data was used to evaluate attrition bias. Finally, the publication bias was evaluated using funnel plot.

### Statistical analysis

Review Manager version 5.3 (RevMan 5.4.1) (The Nordic Cochrane Centre, The Cochrane Collaboration Copenhagen, Denmark) was used by the researcher to perform the systematic review and meta-analysis of included studies. The random-effects model was employed for the analysis. The studies in the analysis were assumed to be a random sample from a universe of potential studies, and this analysis was used to make an inference to that universe. To test the heterogeneity among clinical trials included in the study,  $Q$  and  $I$ -tests were performed. The  $Q$ -statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. The  $I$ -squared statistic states that some of the variance in observed effects reflects variance in true effects rather than sampling error. Finally, to summarize information on individual studies and give a visual suggestion of the amount of study heterogeneity

and show the estimated common effect, forest plot was used for representation.

### Results

There were eight retrospective studies included in this review. The study characteristics are summarized in Table 2. Studies relevant to the study are dated from 2013. Published studies which fit the selection criteria without data on abnormal histology of the appendix, survival rate, recurrence rate, and complication rate were excluded.

#### Abnormal histology of the appendix

All eight studies included presented data on the incidence of abnormal histology of appendix on patients diagnosed with borderline and malignant MOTs who underwent appendectomy during primary surgery. The mean effect size is 0.070, with a 95% confidence interval of 0.035–0.133. The mean prevalence of abnormal histology of the appendix in patients diagnosed with borderline and malignant MOTs and underwent appendectomy during primary surgery is 3%–13%.

The *Q* value is 28.865 with 7° of freedom and *P* < 0.001. Using a criterion alpha of 0.100, the null hypothesis implying that the true effect size is the same in all studies. The *I*-squared statistic is 76%, which tells us that some 76% of the variance in observed effects reflects variance in true effects rather than sampling error. Tau squared, the variance of true effect sizes, is 0.661 in logit units. Tau, the SD of true effect sizes, is 0.813 in logit units. If we assume that the true effects are normally distributed (in logit units), we can estimate that the prediction interval is

0.008–0.399. The true effect size in 95% of all comparable populations falls in this interval [Figure 2].

#### Recurrence rate

There were three studies which presented data of recurrence among patients who were diagnosed with borderline and malignant MOTs and underwent appendectomy during primary surgery. The prediction interval for recurrence rate is 0%–100% with 95% confidence interval. However, the data comparison had a *P* = 0.062 which means that the data are heterogeneous and cannot be combined [Figure 3].

#### Survival rate

There were two studies which presented data on survival rate among patients who were diagnosed with borderline and malignant MOTs with or without appendectomy during primary surgery. The random interval is 64.9%–99.7% with a *P* < 0.1 [Figure 4]. There is no statistically significant difference in survival rate of patients who were diagnosed with borderline and malignant MOTs with or without appendectomy during primary surgery.

#### Complications

There were four studies which presented data on complication rate among patients who were diagnosed with borderline and malignant MOTs and underwent appendectomy during primary surgery. The complications studied were postoperative infections, appendectomy site leakage, hemorrhage, abscess, peritonitis, bowel perforation, and intestinal obstruction. The odds ratio was 1.43, which implies that it is not significant. This implies that the odds of complications occurring are <0.69–2.99 times with a 95% confidence interval. The mean effect size is 0.083,

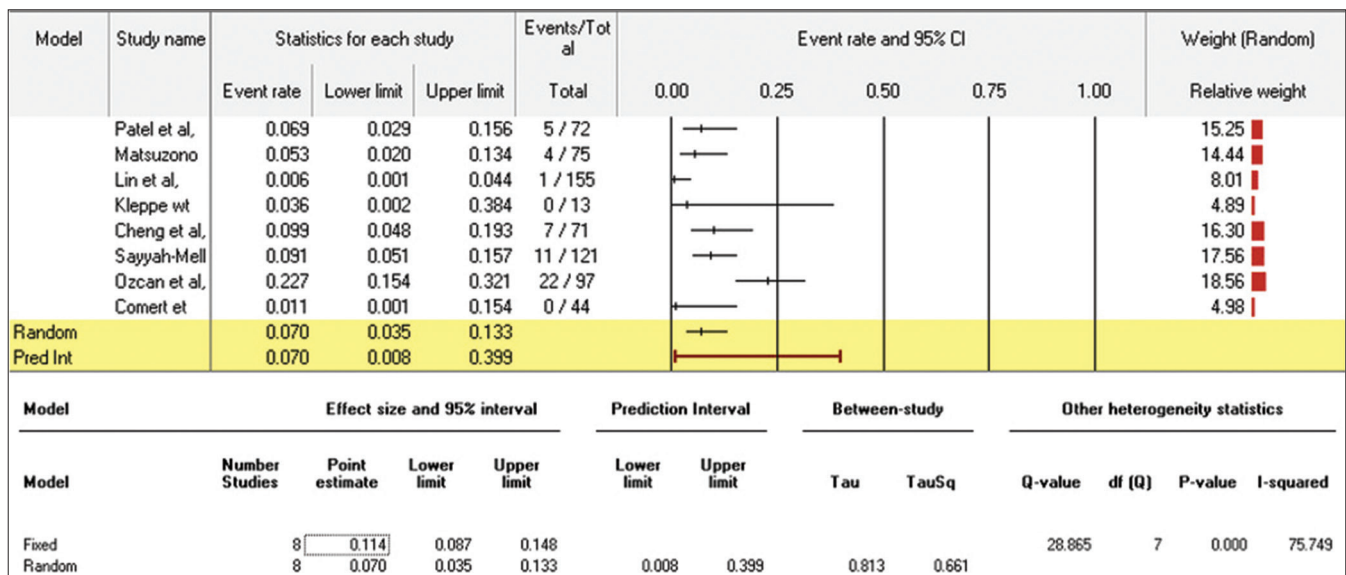


Figure 2: Random-effects meta-analysis of incidence of abnormal histology of the appendix among patients diagnosed with borderline and malignant mucinous ovarian tumors who underwent appendectomy during primary surgery



**Table 2: Characteristics of studies included in the analysis**

Author, year	Design	Routine appendectomy	Participants		Outcomes
			RA	NA	
Patel <i>et al.</i> , 2018	Retrospective study	29 (18.95%) borderline (mBOT) and 124 (81.05%) malignant mucinous ovarian tumors (IMOT) who underwent surgery with appendectomy	124	113	Abnormal histology of appendix
Matsuzono <i>et al.</i> , 2020	Retrospective study	75 (96.2%) patients diagnosed with mBOT and IMOT	75	3	Abnormal histology of appendix, complications (hemorrhage, infection, abscess, peritonitis, bowel perforation, intestinal obstruction)
Lin <i>et al.</i> , 2013	Retrospective study	41 (60%) mBOT and 26 (59%) malignant underwent appendectomy	67	96	Abnormal histology of appendix, Complications (wound complication, abscess formation)
Kleppe <i>et al.</i> , 2014	Retrospective cohort study	73 (75%) mBOT underwent appendectomy	13	60	Abnormal histology of appendix, Recurrence rate, Complications (postoperative infections)
Cheng <i>et al.</i> , 2016	Retrospective study and metaanalysis	29 with mBOT and 40 malignant mucinous tumors underwent appendectomy at time of primary surgery	71	0	Abnormal histology of appendix, Survival rate
Sayyah-Melli, 2018	Retrospective and cross-sectional study	121 patients with ovarian tumors underwent appendectomy at time of primary surgery	121	136	Abnormal histology of appendix
Ozcan <i>et al.</i> , 2015	Retrospective study	69 patients with mBOT and 51 invasive mucinous ovarian tumor	97	23	Abnormal histology of appendix, Recurrence rate, Complications (appendectomy site leakage)

with a 95% confidence interval of 0.027–0.23. This depicts that the mean effect size in the complications of comparable studies could fall anywhere in this interval. The random interval is 0.1%–91.3% [Figure 5]. There was no significant difference between the incidence of complications in patients who underwent appendectomy and those who did not.

## Discussion

In a retrospective study done by Lin *et al.*, they determined how frequently the appendix harbors pathology in women having surgery for mucinous neoplasms of the ovary and subsequently assessed the associated morbidity. The study was conducted in Wisconsin, USA, with 309 cases reviewed. Findings of their study showed that no primary or metastatic appendiceal tumors of mucinous histology were identified when appendectomy was performed for a mucinous ovarian neoplasm when the appendix is grossly normal and no evidence of PMP was encountered. Moreover, they reported that all primary appendiceal tumors of mucinous histology were associated with either grossly abnormal appendices or PMP.<sup>[10]</sup>

In a similar study done by Ozyurek *et al.* in Poland, they determined if appendectomy as an adjunctive procedure is necessary for the surgical treatment of benign ovarian mucinous cystadenomas. A total of 59 cases of benign ovarian mucinous cystadenomas were included in the study. Among the 59 cases, 13 of them (20.6%) went through appendectomy. Findings of their study suggest that appendectomy is not a necessary additional procedure in the presence of benign or borderline

unilateral ovarian mucinous tumors, with normal peritoneal and appendiceal morphology and probably larger than 10–12 cm.<sup>[11]</sup>

Ozcan *et al.* determined how often the appendix is involved or the primary source of cancer in women undergoing surgery for mBOT or invasive mucinous ovarian tumor (IMOT) and evaluated whether appendectomy is necessary. This was a retrospective study of 129 cases done in Turkey. Overall, their findings suggest that if the appendix is grossly normal during surgery for an ovarian mBOT or IMOT without evidence of PMP, primary or metastatic appendiceal neoplasms are not expected.<sup>[12]</sup>

Another study by Patel *et al.* in India determined the frequency of malignancy in a grossly normal appendix in women undergoing surgery for borderline or malignant MOT. Results showed that of the 29 patients, 16 (55.17%) with grossly normal appendices did not undergo appendectomy. Appendectomy was performed in 13 (44.83%) patients and among the 13 cases, 8 had grossly normal appendix while 5 patients had grossly abnormal appendix. Moreover, of the five patients, one patient had mucinous cystadenoma, 3 had borderline mucinous tumor, and 1 had mucinous cystadenocarcinoma of the appendix. Of three patients with borderline mucinous tumor of ovary and appendix, 2 had immunohistochemical staining suggestive of a primary appendicular tumor. In the remaining case, omentum showed changes consistent with PMP.<sup>[13]</sup>

A cross-sectional study by Sayyah-Melli *et al.* in Tabriz, Iran, investigated the correlation between the macroscopic

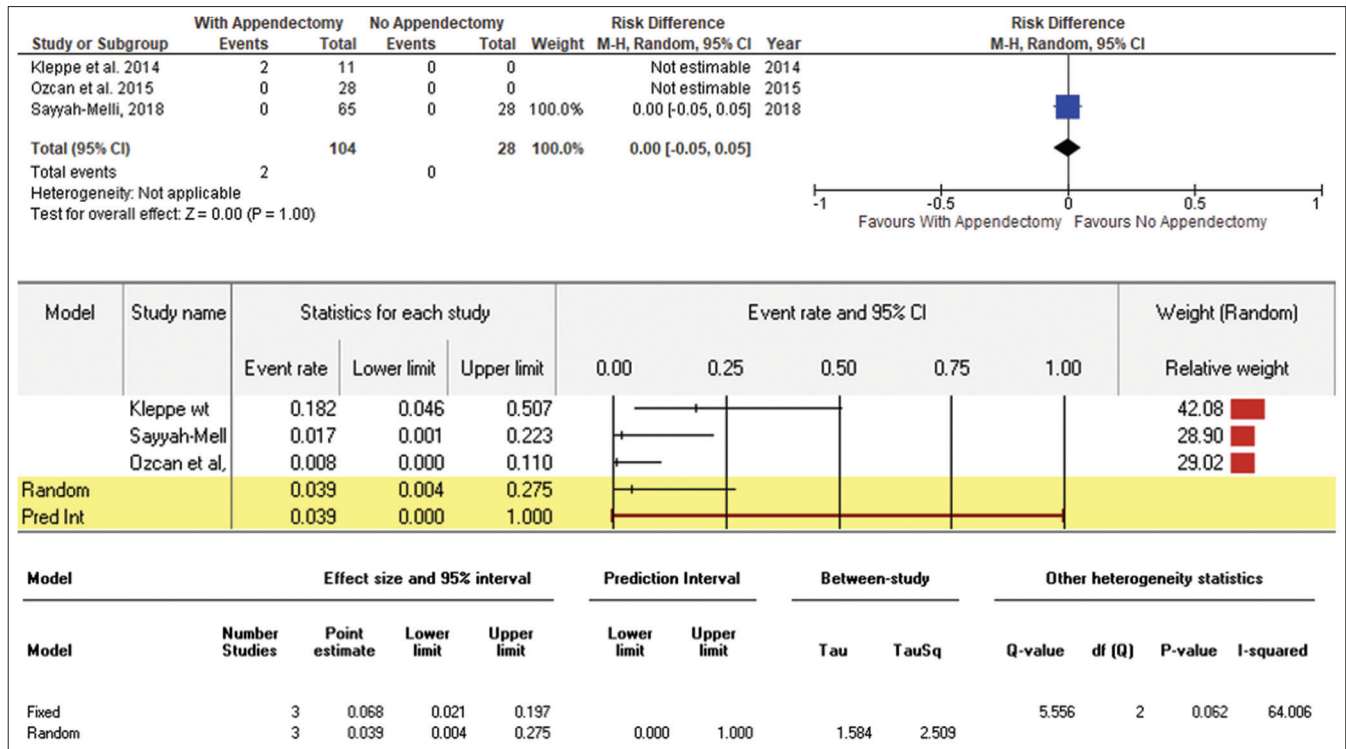


Figure 3: Random-effects meta-analysis on recurrence rate among patients diagnosed with borderline and malignant mucinous ovarian tumors with or without appendectomy during primary surgery

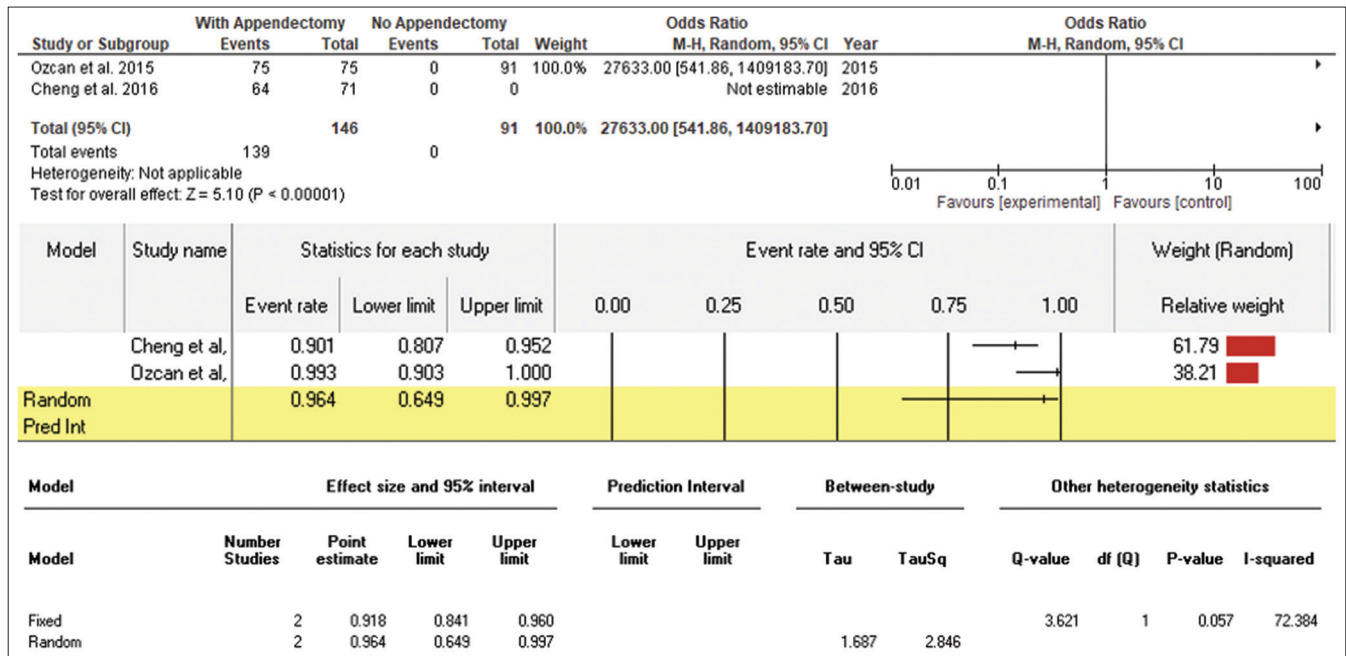


Figure 4: Random-effects meta-analysis on survival rate among patients diagnosed with borderline and malignant mucinous ovarian tumors with or without appendectomy during primary surgery

appearance of appendix and histopathology results of ovarian mucinous tumors as well as determining the stage of ovarian cancer appendices. Of 257 patients, 121 cases underwent appendectomy concurrent with ovarian surgery, 84 of these patients (39.8%) had benign, 17 cases (73.9%) had borderline, and 20 cases (87%) had

malignant ovarian mucinous tumors. Furthermore, based on microscopic results, 9 cases, out of 121 appendectomy cases, had appendiceal mucinous tumoral involvement. Primary findings of their study showed that appendectomy during ovarian tumor surgery is the only recommended option in cases with the abnormal

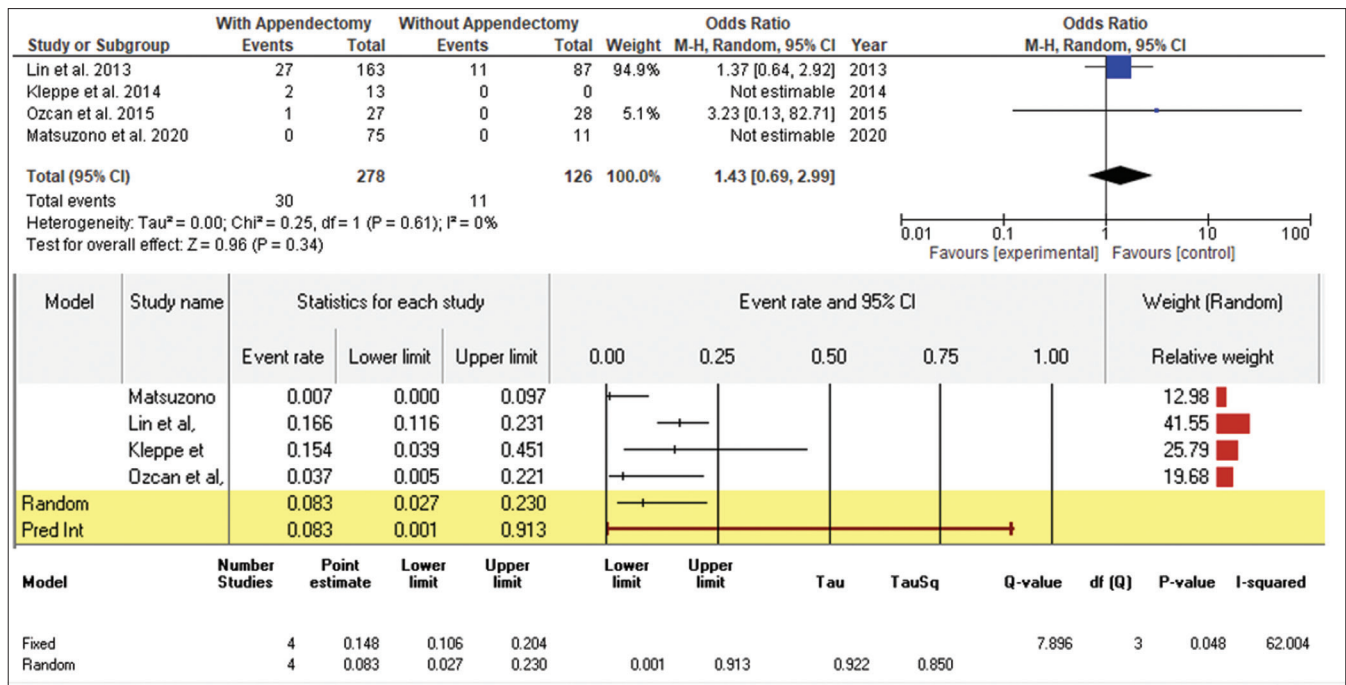


Figure 5: Random-effects meta-analysis on complications among patients diagnosed with borderline and malignant mucinous ovarian tumors with or without appendectomy during primary surgery

macroscopic appearance of appendix and advanced stages of ovarian mucinous cancer.<sup>[3]</sup>

The 2018 Clinical Practice Guidelines from the Society of Gynecologic Oncologists of the Philippines (Foundation), Inc., stated that appendectomy is mandatory for cases with borderline or malignant ovarian tumors with mucinous histopathology and gross involvement of the appendix (Level 3B). This recommendation is based on Clinical Practice Guidelines based on the collaboration between FIGO and IGCS by Pecorelli *et al.*, along with studies by Rose *et al.* and Fontanelli *et al.*<sup>[14-16]</sup>

The mean prevalence of abnormal histology of the appendix in patients diagnosed with borderline and malignant MOTs and who underwent appendectomy during primary surgery is 3%–13%. The study findings are similar to previously published literature on routine appendectomy for primary mucinous ovarian pathology. Abnormal histology of the appendix was rarely encountered when the appendix is grossly normal upon appendectomy was performed for a mucinous ovarian neoplasm.<sup>[1]</sup> The findings are also similar to the classically cited study of Malfetano in 1987 wherein routine appendectomy was recommended in mucinous cystadenocarcinomas to rule out a primary appendiceal pathology.<sup>[17]</sup> It should be noted though that appendiceal adenocarcinomas are rare comprising only 0.4% to 0.5% of gastrointestinal cancers.<sup>[18]</sup>

As most of the studies included were retrospective, it is likely that the results may be underestimated because appendectomy was not done in all cases. In addition,

the basis was the final histopathologic report of MOT and not intraoperative frozen section, which may have further underestimated the results. The need for routine appendectomy in case of borderline and malignant MOT is not definitely concluded in this study. This may be attributed to the statistical heterogeneity of the included studies. Thus, as in previously published studies in the matter, it is suggested that routine appendectomy should be performed in cases of the macroscopically abnormal appendix.

A common concern around the appendix would be another pathology arising correlated to mucinous tumors in the future. The data in this study regarding recurrence rate were deemed heterogeneous. However, in a study by Kleppe *et al.* and Ozcan *et al.*, no recurrence was noted in a follow-up period of 1–16 years in women whose appendix was grossly normal and those who did not undergo appendectomy.<sup>[12,19]</sup> Snyder and Selanders suggested incidental appendectomy in patients below age 35 regardless of gross findings and disease status.<sup>[20]</sup>

It was found that there is no statistically significant difference in the survival rate of patients who were diagnosed with borderline and malignant MOTs with or without appendectomy during primary surgery. Although in a study by Ozcan *et al.*, appendectomy did not provide survival advantage in patients with mBOT.<sup>[12]</sup>

The anticipation of complications related to an additional surgical procedure should not be overlooked. In this study, there was no significant difference between the



incidence of complications in patients who underwent appendectomy and those who did not. In general, there is no expected increase in complications upon performing appendectomy during primary surgery of MOTs.<sup>[1,12]</sup>

## Conclusion

The mean prevalence of abnormal histology of the appendix in patients diagnosed with borderline and malignant MOTs and who underwent appendectomy during primary surgery is 3%–13%. The data on recurrence rate among the borderline and malignant MOT patients with or without appendectomy on primary surgery cannot be combined. There is no statistically significant difference in the survival rate of patients who were diagnosed with borderline and malignant MOTs with or without appendectomy during primary surgery. There was no significant difference between the incidence of complications in patients who underwent appendectomy and those without.

## Recommendations

The researcher suggests further investigation on the risk factors for appendiceal metastasis and/or involvement in cases diagnosed with borderline or malignant epithelial ovarian tumors as this may further delineate a population which would greatly benefit from routine appendectomy with or without gross appendiceal involvement. However, the findings in this study must be seen in the light of the limitation that the researcher was only able to include eight studies total due to the lack of retrospective studies which accurately fitted the inclusion criteria. Another limitation would be that the literature included and stratification of study individuals was not included and hence there might have been other factors affecting the survival rate, recurrence rate, and complication rate of the population studied.

## Authorship contribution

Appenette April S.J. Manuel, MD - conceptualization, methodology, data curation, writing of the original draft, visual presentation, review and editing.

Maribel Emma Co-Hidalgo, MD - involved in conceptualization, methodology, review and editing of the draft, supervision.

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## Conflicts of interest

There are no conflicts of interest.

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