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Letter to the editor



## Comment on gallbladder polyps: Correlation of size and clinicopathologic characteristics based on updated definitions

To the Editor;

We read the recent article “Correlation of size and clinicopathologic characteristics based on updated definitions” published by Taskin and colleagues with great interest [1]. The authors have designed a study to correlate the size and the pathologic characteristics of gallbladder polyps. The aim of this letter was to make a detailed analysis of the mentioned study with the guidance of the current literature and our clinical experience about relationship between gallbladder polyp size and risk gallbladder cancer.

Gallbladder polyps are defined as lesions protruding from the gallbladder wall to the lumen [2]. Generally, these lesions are benign in nature; however, the main challenge is to differentiate the lesions with malignant potential. Therefore, early detection of these lesions provides early treatment and prevention of development of the gallbladder cancer [3]. The prevalence of polypoid lesions of the gallbladder ranges between 4.3 and 6.9% and it is even more common in cholecystectomy specimens which may be seen up to 12% of the specimens [4,5]. The median age at diagnosis is reported to be nearly 50 years of age and although, it has been reported to be 1.5 times more common in male than the incidence in the female, there are studies suggesting an equal distribution among gender [6–8].

The polypoid lesions of the gallbladder are divided into benign and malignant subdivisions. The malignant polypoid lesions are gallbladder cancer. The benign polypoid lesions can be pseudotumor including cholesterol polyps, inflammatory polyps, cholesterolosis, and hyperplasia. Other benign polypoid lesions are epithelial tumors including adenoma; and mesenchymal tumors such as fibroma, lipoma and hemangioma can also form polypoid lesions in the gallbladder [3].

The risk factors for developing gallbladder polypoid lesions include old age, male gender, lipid metabolism disorders, obesity, diabetes mellitus, fatty liver, and polypoid lesions such as Peutz - Jeghers and Gardner syndromes. There seems to be an inverse relationship between the occurrence of gallbladder polyps and cholelithiasis [9,10]. Because, the presence of cholelithiasis may obscure the diagnosis of polypoid lesions of the gallbladder. The risk factors associated with developing cancer in gallbladder polyps include polyp size, growth of the polyps over time, old age, diabetes mellitus, sessile polyp, sclerosing cholangitis, ethnicity, single polyp, concomitant cholelithiasis, and gastrointestinal polyposis syndrome [11–14]. There is no specific tumor marker to differentiate between malignant and benign lesions. This may be due to the fact that malignant polypoid lesions are early-stage gallbladder cancer and the lesion too small to produce detectable tumor markers [5]. Recently, a large cohort including 622,227 patients, the gallbladder cancer incidence was 11.3 per 100,000 population. The risk increased 98 times when the polyps smaller than 6 mm was compared to polyps ranging between 6 and 10 mm. Increase in polyp diameter during follow-up was not associated with increased risk of gallbladder cancer development [15].

The most important point related with the study is that there is discrepancy in the number of patients reported in different parts of the article. In the abstract section, the authors have stated that they have analyzed a total of 4231 patients with gallbladder polyps and 606 of which were gallbladder cancer. However, in Fig. 3, the total number of patients (3715 + 606) with gallbladder polyps adds up to 4321. This unintentional mistake should be corrected because a difference of 90 patients could affect the outcome of the statistical analysis.

We would also like to emphasize the statistical analysis method and style of expression of the variables. The authors have stated that they have used Shapiro-Wilks test for evaluation of normal distribution of the continuous variables. Furthermore, the authors state that they have used Mann-Whitney *U* test for evaluation of the two independent samples and Kruskal-Wallis test for evaluation of multiple group variables. This means that the data did not distribute normally and therefore, the authors used the non-parametric tests to evaluate the data. In addition, the mean and the SD values in the present study is very close to each other and therefore, we can certainly say that the data does not show a normal distribution. We would like to make a critical suggestion at this point. Shapiro-Wilks test is not a suitable test for evaluation of normal distribution if the sample size is more than 50. The test that should have been chosen would be the Kolmogorov-Smirnov test [16]. Since the data did not show a normal distribution, the continuous variables should be expressed as median (minimum-maximum) or median (interquartile range (IQR)) [17–19]. In Table 1 of the mentioned study, the age of the patients was expressed as mean (min-max) and diameter of the polyps were expressed as mean  $\pm$  standard deviation (SD) and median (IQR).

A main point that we would like to emphasize about the present study is related to the absence of correlation analysis. The authors have stated in the heading of the study and also multiple parts of the article that the objective of the study was to correlate the size of the gallbladder polyps and clinicopathologic characteristics of the patients. However, they have not performed any correlation analysis. Scientifically, correlation analysis is vital. We have performed the correlation analysis according to the data presented by the authors. We present our data in a table (Table 1) through this commentary.

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**Table 1**

Evaluation of OR, Phi correlation coefficient, sensitivity, specificity, PPV and NPV values of different polyps size in terms of prediction of gallbladder cancer.

Polyps Size	Neoplastic	Non-neoplastic	OR	95% CI	p	Phi	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
≥10 mm	155	17	54	31–95	<0.001	0.704	70 (63–76)	96 (94–98)	90 (85–94)	86 (83–88)
<10 mm	68	403								
10–19 mm	62	16	23	13–42	<0.001	0.534	48 (39–57)	96 (94–98)	80 (70–87)	85 (81–88)
<10 mm	68	403								
≥20 mm	93	1	24	3–186	0.0023	0.324	60 (52–68)	94 (71–100)	99 (93–100)	21 (17–24)
10–19 mm	62	16								
≥20 mm	93	1	551	76–4021	<0.001	0.697	58 (50–66)	100 (99–100)	99 (93–100)	86 (83–88)
<10 mm	68	403								
≥20 mm	93	1	300	41–2172	<0.001	0.559	42 (35–49)	100 (99–100)	99 (93–100)	76 (74–78)
<20 mm	130	419								

OR: Odds ratio, PPV: positive predictive values, NPV: negative predictive values, CI: Confidence Interval.

We have used the variables presented by Taskin and colleagues [1] in Table 2 and calculated the risk of cancer development in accord with the size of the gallbladder polyps. The data presented in Table 2 of the mentioned study were uploaded to SPSS v 25.0 and MedCalc software packages and a correlation between the size of the polyp and the risk of cancer development was performed. Furthermore, we used MedCalc software to calculate the specificity, sensitivity, positive predictive (PPV) and negative predictive values (NPV). Here we present the results of our analysis:

In polyps with a diameter  $\geq 10$  mm the risk for gallbladder cancer increases 54 times when compared to polyps  $<10$  mm (OR = 54 [95% CI = 31–95]) ( $p < 0.001$ ). The Phi correlation coefficient ( $r = 0.704$ ) shows that this is a high positive correlation [20]. The sensitivity, specificity, negative predictive and positive predictive values for polyps with a diameter  $\geq 10$  mm in determining the development of cancer were 70%, 96%, 90% and 86%; respectively.

In polyps with a diameter between 10 and 19 mm the risk for gallbladder cancer development increased 23 times when compared to polyps  $<10$  mm (OR = 23 [95% CI = 13–42]) ( $p < 0.001$ ). The Phi correlation coefficient ( $r = 0.534$ ) shows that there is a moderate positive correlation between the polyp diameter between 10 and 19 mm and development of gallbladder cancer. The sensitivity, specificity, PPV and NPV values were 48%, 96%, 80% and 85%; respectively.

The risk for gallbladder cancer development in polyps with a diameter  $\geq 20$  mm 24 times higher than polyps with a diameter between 10 and 19 mm (OR = 24 [95% CI = 3–186]) ( $p = 0.0023$ ). The Phi correlation coefficient ( $r = 0.324$ ) shows that there is a low positive correlation between the polyps with a diameter  $\geq 20$  mm versus polyp diameter and 10–19 mm the risk of gallbladder cancer. Sensitivity, specificity, PPV and NPV values were 60%, 94%, 99% and 21%; respectively.

The comparison of polyp diameter  $\geq 20$  mm with polyps  $<10$  mm showed that the risk for gallbladder cancer increases 551 times (OR = 551 [95% CI = 76–4021]) ( $p < 0.001$ ). The Phi correlation coefficient ( $r = 0.697$ ) showed that there was moderate positive correlation between polyp diameter  $\geq 20$  mm versus polyp diameter  $< 10$  mm and the risk of gallbladder cancer. Sensitivity, specificity, PPV and NPV values were 58%, 100%, 99% and 86%; respectively.

The patients with a polyp diameter  $\geq 20$  mm had a risk of (OR) gallbladder cancer development that was 300 times higher than the patients with polyps  $<20$  mm (OR = 300 [95% CI = 41–2171]) ( $p < 0.001$ ). The Phi correlation coefficient ( $r = 0.559$ ) showed that there was a moderate positive correlation between the polyp diameter  $\geq 20$  mm and the risk of gallbladder cancer development. The sensitivity, specificity, PPV and NPV values were 42%, 100%, 99% and 76%; respectively.

The summary of our analysis shows that the sensitivity for prediction of cancer development was highest in polyps with a diameter of 10 mm. Furthermore, this is the diameter threshold for which operative interventions is suggested according to the current guidelines in literature. The sensitivity and NPV for the polyp diameters that are analyzed are lower than expected but the PPV is very high. In fact, this is very crucial for prediction of cancer development.

In the abstract of the study, the authors have stated that the NPV and PPV for polyps  $\geq 10$  mm were reported to be 94.3% and 85% (in two other sections it is reported as 84.7%); respectively. However, in Table 3 of the mentioned study, the authors state that these PPV and NPV were for polyps  $>10$  mm. This is important for it will affect the results of the statistical analysis. Therefore, the exact cut-off value used for analysis should be clarified.

We would like to emphasize another point regarding the study that is related with the relationship between the age, gender, dimensions of the polyp and the gallbladder cancer. In the conclusion section, authors stated that (and we quote) “this study also illustrates that 30% of the neoplastic polyps are  $<10$  mm and therefore small polyps should also be closely watched, especially in older patients” but they do not have the statistical evaluation to support this statement. The authors should have performed a ROC curve analysis for age to determine a cut-off value and should have compared the age cut-off and gender between the neoplastic and non-neoplastic groups and calculate and OR value for risk of cancer development.

The final point that we would like to emphasize is related with the ROC curve analysis performed by the authors. The authors have performed ROC curve analysis and found the optimal cut-off value of 9 mm for polyp diameters. However, they have used 10 mm throughout the manuscript. In Table 3 of the mentioned study, the authors have evaluated six different diameters for evaluation of diagnostic test parameters. In our opinion, the authors could have used the cut-off value of that they have calculated for the evaluation and discussion of their results.

In summary, we have made necessary calculations and made the contributions regarding the odds ratio of different polyp diameters and the risk of development of gallbladder cancer. As we have stated earlier the strongest correlation exists for polyps  $\geq 10$  mm in diameter in terms of risk of development of gallbladder cancer. Since the correlation coefficient and PPV were high, polyp diameter  $\geq 10$  mm can be used for prediction. Of cancer and to screen the patients with a high risk of gallbladder cancer. We would like to point out an issue that has not been mentioned before. Our auxiliary results suggest that as the diameter of the polyp reaches 20 mm, it is necessary to plan a surgical treatment strategy as if the patient has gallbladder cancer.

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**Consent**

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**Research registration**

Not Applicable.

**Guarantor**

Akbulut S and Sahin TT, are the guarantors for the present commentary and they take full responsibility for the comments and the auxiliary data presented in the commentary article.

**CRedit authorship contribution statement**

Akbulut S and Sahin TT: Reviewed the literature and wrote the manuscript. Akbulut S and Sahin TT: Supervised the writing process and revised the manuscript.

**Declaration of competing interest**

No conflict of interest about this letter to the editor.

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