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ORGINAL ARTICLE / ORJİNAL MAKALE

Clinicopathological characteristics and prognosis in ovarian metastatic tumors from non-gynecologic primary sites

Jinekolojik olmayan primer bölgelerden kaynaklanan overin metastatik tümörlerinde klinikopatolojik özellikler ve prognoz

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ABSTRACT

Aim: To investigate clinicopathological characteristics and prognosis in ovarian metastatic tumors from non-gynecologic primary sites.

Materials and methods: This study was a retrospective trial enrolling consecutive patients with ovarian metastasis from non-gynecologic primary sites, either diagnosed synchronous or metachronously, who underwent surgery at a single institution between January 2015 and December 2021. Clinicopathological characteristics of patients were extracted from patients' charts and electronic database; and analyzed using Cox proportional hazard models.

Results: Of the 291 malignant ovarian tumors that underwent surgery, 33 (11.3%) had a diagnosis of ovarian metastasis from non-gynecologic primary sites. The most common primary tumor sites were colorectum (45.5%), stomach (15.2%), and breast (12.1%). Most of the patients exhibited elevated preoperative serum Ca-125 levels (71.4%); roughly half of the patients had syncronous ovarian metastases (48.5%); and approximately one third had peritoneal involvement (36.4%) and/or ascites (30.3%). A complete resection (R0) was achieved in 72.0% of the patients. The median follow-up time was 15.5 months, ranging from 2 to 85 months. The median overall survival (OS) was 41 months with estimated 18-, 24- and 36-month OS rates of 60.1%, 56.1% and 50.5%, respectively. Age (>45 years; hazard ratio (HR): 3.199; 95% confidence interval (CI): 0.899 – 11.380) and presence of ascites (HR: 4.109, 95% CI: 1.436 – 11.757) were independent predictors of OS.

Conclusion: In ovarian metastatic tumors from non-gynecologic primary sites, age and the presence of ascites are the main determinants of prognosis, while no survival benefit of cytoreductive surgery was demonstrated.

Keywords: Ovarian, Metastasis, Prognosis, Survival

ÖZ

Amaç: Jinekolojik olmayan primer bölgelerden kaynaklanan overin metastatik tümörlerinde klinikopatolojik özellikler ve prognozun araştırılması.

Gereç ve yöntem: Bu çalışma, Ocak 2015 ile Aralık 2021 tarihleri arasında tek bir merkezde ameliyat edilen, senkron veya metakron tanı konmuş, jinekolojik olmayan primer bölgelerden over metastazı olan ardışık hastaları içeren retrospektif bir çalışmadır. Hastaların klinikopatolojik özellikleri hasta dosyalarından ve elektronik veri tabanından elde edilmiş ve Cox orantılı hazard modelleri kullanılarak analiz edilmiştir.

Bulgular: Cerrahi uygulanan 291 malign over tümöründen 33'ünde (%11.3) jinekolojik olmayan primer bölgelerden overe metastaz tanısı saptandı. En sık primer tümör bölgeleri sırası ile kolorektum (%45.5), mide (%15.2) ve meme (%12.1) idi. Hastaların çoğunda ameliyat öncesi serum Ca-125 düzeyleri yüksekti (%71.4); yaklaşık yarısında senkron over metastazı (%48.5); yaklaşık üçte birinde peritoneal tutulum (%36.4) ve/veya asit (%30.3) mevcuttu. Hastaların %72.0'sinde tam rezeksiyon (R0) elde edildi. Ortanca takip süresi 15.5 ay olup, 2 ila 85 ay arasında değişmektedir. Ortanca genel sağkalım 41 ay iken tahmini 18, 24 ve 36 aylık sağkalım oranları sırasıyla %60,1, %56,1 ve %50,5 idi. Yaş (>45 yıl; hazard oranı (HR): 3.199; %95 güven aralığı (CI): 0.899 - 11.380) ve asit varlığı (HR: 4.109, %95 CI: 1.436 - 11.757) sağkalımın bağımsız belirleyicileri olarak saptandı.

Sonuç: Jinekolojik olmayan primer bölgelerden kaynaklanan overin metastatik tümörlerinde, yaş ve asit varlığı prognozun ana belirleyicileri iken sitoredüktif cerrahinin sağkalım yararı gösterilememiştir.

Anahtar Kelimeler: Over, Metastaz, Prognoz, Sağkalım

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INTRODUCTION

When a malignancy is diagnosed or suspected, patients often expect to be informed about the prognosis and treatment options. However, answering this basic request is not always easy for many reasons. The histopathological type and extent of the disease are the most important among the many parameters needed to answer these vital questions. As physicians dealing with gynecologic oncology, we have the chance to clearly inform our patients when the diagnosis of malignancy is of direct gynecologic origin. On the other hand, metastatic tumors of the ovary which is reported to be found in 15 to 20% of all malignant ovarian tumors (1,2), may pose a challenge for the physicians in adequately informing patients preoperatively since they may be the presenting finding in a significant proportion of cases. (3) Moreover, in some cases, the correct diagnosis may not be made even with extensive histopathological and immunohistochemical examinations.

Histopathologically, ovarian metastases containing a significant amount of mucin-filled signet-ring cells (more than 10% of tumor size) are called Krukenberg tumors. (4) The most common primary site of Krukenberg tumors is the stomach (~40%), followed by the colorectum (~25%), breast (~10%) and appendix (5%). (4) The metastases to the ovaries from other sites that do not fullfill the diagnostic criteria of Krukenberg tumors may arise from colon, breast, small intestine, pancreas, and skin. (1-3)

In the current study, we aimed to investigate the clinicopathological characteristics, prognosis, and factors associated with overall survival (OS) in patients with ovarian metastasis from non-gynecologic primary sites.

METHODS

Study design and endpoints

The study was a retrospective trial enrolling consecutive patients with ovarian metastasis from non-gynecologic primary sites, either diagnosed synchronous or metachronously, who underwent surgery at a single institution between January 2015 and December 2021. The study was approved by the local ethics committee. Due to the retrospective nature of the study, the need for informed consent was waived by the ethics committee. The study was performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2013.

Data regarding age, preoperative levels of serum tumor markers and albumin, primary tumor site, time of ovarian metastasis (synchronous vs. metachronous), site of ovarian metastasis (unilateral vs. bilateral), the largest size of ovarian metastasis, presence of extraovarian disease, ascites and peritoneal carcinomatosis, surgical resections, operative time, 30-day postoperative mortality, length of follow-up time, and survival status were extracted from the patient charts and institutional electronic database following the ethics committee approval. The timing of ovarian metastasis was defined as metachronous if the metastasis was detected more than three months after the initial diagnosis of the primary tumor, or synchronous if the metastasis was detected at the initial diagnosis or within the first three months. (5) Ascites was defined as determination of free-fluid in the peritoneal cavity exceeded 100 ml at the beginning of the surgical exploration.

The primary endpoint of the study was determination of clinicopathological characteristics and prognosis of patients; and the secondary endpoint was determination of factors associated with OS. The duration in months between the date of surgery and the date of death from any cause or the date of last contact was defined as OS.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 20.0 (SPSS Inc, Chicago, IL, USA) software. The binary variables were reported as

counts and percentages, while the continuous variables were reported as median and range. Univariate analyses were performed to determine factors associated with OS. Variables with a p-value <0.05 in univariate analyses were included in the Cox proportional hazard models for multivariate analyses. The model results were presented as hazard ratios (HR) with 95% confidence intervals (CI). Survival curves were generated with the Kaplan–Meier method, and compared using the log-rank test. Patients alive at the last known follow-up were censored in OS analyses.

RESULTS

During the study period, a total of 291 histologically confirmed malignant ovarian tumors were treated at our clinic. Of those, 33 (11.3%) had a diagnosis of ovarian metastasis from non-gynecologic primary sites.

Table 1 displays the clinicopathological characteristics of patients. The median age was 51 years (range, 30 – 90 years). Preoperative serum Ca-125 levels were measured in 28 of 33 patients and found to be increased (>35 U/ml) in 71.4% of these patients. The median Ca-125 level was 66.9 U/ml (range, 10.8 – 1064 U/ml). The most common primary tumor site was the colorectum (15/33, 45.5%), followed by stomach (5/33, 15.2%), breast (4/33, 12.1%), lung (2/33, 6.1%), pancreas (2/33, 6.1%), appendix (2/33, 6.1%), small intestine (1/33, 3.0%), mesothelioma (1/33, 3.0%), and unknown site (1/33, 3.0%). Sixteen patients (48.5%) presented with synchronous ovarian metastasis, while 17 (51.5%) developed metachronous ovarian metastasis after the initial diagnosis of primary tumor. In metachronous metastases, the median time interval was 18 months. Roughly half of the patients (51.5%) had bilateral ovarian metastasis. Extraovarian disease was evident in most of the patients (72.7%), whereas only 36.4% had peritoneal involvement and 30.3% had ascites.

Table 1. Clinicopathologic chararacteristics of patients

Variables	Values	
	n	%
Age, years, median (range)	51 (30 – 90)	
Preoperative tumor markers, median (range)		
Ca-125, U/mL (n=28)	66.90 (10.8 – 1064)	
> 35 U/mL, n (%)	20/28	71.4
CEA, µg/L (n=23)	6.08 (1.22 – 205.05)	
Ca-19.9, U/mL (n=21)	42.40 (2- 4836)	
Ca-15.3, U/mL (n=16)	12.75 (4.40 – 77)	
Preoperative serum albumin level, g/dL, median (range), (n=12)	4.05 (3.20 – 4.50)	
Primary tumor site, n (%)		
Colorectal	15	45.5
Stomach	5	15.2
Breast	4	12.1
Lung	2	6.1
Pancreas	2	6.1
Appendix	2	6.1
Small intestine	1	3.0
Mesothelioma	1	3.0
Unknown primary	1	3.0
Time of ovarian metastasis, n (%)		
Synchronous	16	48.5
Metachronous	17	51.5
Time interval, months, median (range)	18 (3–30)	
Site of ovarian metastasis, n (%)		
Unilateral	16	48.5
Bilateral	17	51.5
Largest size of ovarian metastasis, cm, median (range)	8.5 (0.30 – 32)	
Extraovarian disease, n (%)	24	72.7
Ascites, n (%)	10	30.3
Peritoneal carcinomatosis, n (%)	12	36.4
Localized	4	12.1
Diffuse, miliary	8	24.2

Surgical and postoperative chararacteristics of patients are presented in Table 2. Almost all (96.9%) patients underwent salpingo-oophorectomy, 23 (69.6%) received total hysterectomy, 22 (66.6%) received omentectomy, 9 (27.2%) received large bowel resection, 8 (24.2%) received appendectomy, 5 (15.1%) received systematic pelvic-paraaortic lymph node dissection, 4 (12.1%) received liver resection, 4 (12.1%) received pelvic periton excision, 4 (12.1%) received paracolic periton

excision, 4 (12.1%) received diaphragmatic periton stripping, 3 (9.1%) received small bowel resection, 2 (6.0%) received pancreatectomy, 1 (3.0%) received splenectomy, and 1 (3.0%) received total gastrectomy with esophagojejunostomy. The median operative time was 225 minutes. A complete resection (R0) was achieved in 72.0% of the patients.

Postoperative 30-day mortality was observed in 2 (6.0%) patients. One of those patients had pancreatic primary tumor origin. She developed deep and uncontrolled metabolic acidosis postoperatively, and died of disease on postoperative day-7. The other one had an advanced and unserectable gastric cancer. An attemp to replace a jejunostomy tube was failed, and she died of disease on postoperative day-28. The median follow-up time was 15.5 months, with a range of 2 to 85 months. At the time of analysis, 6 patients (18.2%) were alive with no evidience of disease, 9 patients (27.3%) were alive with disease, 16 patients (48.5%) were dead of disease, and 2 (6.1%) were lost to follow-up (Table 2).

The median OS was 41 months, with a 95% CI ranging from 12.7 to 69.2 months. The estimated 18-, 24-, 36-, and 60-months OS rates were 60.1%, 56.1%, 50.5%, and 42.1%, respectively (Figure 1).

Analysis of factors associated with OS is presented in Table 3. In univariate analysis, two variables were significantly associated with death: age and ascites. In multivariate analysis, both age (HR: 1.056, 95% CI: 1.012 - 1.103) and presence of ascites (HR: 4.109, 95% CI: 1.436 – 11.757) remained independent factors associated with death. Optimal cutoff value of age for predicting death was found to be 45 years (HR: 3.199; 95% CI: 0.899 – 11.380), with a sensitivity of 81.3% and specificity of 66.7% (Figure 2). Kaplan-Meier analyses revealed that patients with an age greater than 45 years had a significantly poorer OS than those with an age younger than 45 years, (18 months OS, 49.4% vs. 75.0%, p=0.033), (Figure 3A). Similarly, patients wih ascites had significantly poorer OS than those without ascites (18 months OS, 34.3% vs. 71.1%, p=0.014), (Figure 3B).

Table 2. Surgical and postoperative chararacteristics of patients

Variables	Values	
	n	%
Salpingo-oophorectomy, n (%)	32	96.9
Unilateral	4	12.1
Bilateral	28	84.8
Hysterectomy, n (%)	23	69.6
Omentectomy, n (%)	22	66.6
Bowel resection, n (%)		
Large bowel	9	27.2
Colorectal resection	5	15.1
Right hemicolectomy	2	6.0
Transverse colon resection	2	6.0
Small bowel	3	9.1
Peritonectomy (partial and/or total), n (%)		
Pelvic	4	12.1
Paracolic	4	12.1
Diaphragm	4	12.1
Appendectomy, n (%)	8	24.2
Total gastrectomy with esophagojejunostomy, n (%)	1	3.0
Liver resection, n (%)	4	12.1
Splenectomy, n (%)	1	3.0
Pancreatectomy, n (%)	2	6.0
Systematic pelvic-paraaortic LN dissection, n (%)	5	15.1
Residual disease after surgery, n (%)		
No residual	24	72.0
<1 cm in maximum size	3	9.1
≥1 cm in maximum size	6	18.2
Operative time, minutes, median (range)	225 (45 – 630)	
Postoperative 30-day mortality, n (%)	2/33	6.0
Follow-up time, months, median (range)	15.5 (2 – 85)	
Survival status, n (%)		
Alive with no evidience of disease	6	18.2
Alive with disease	9	27.3
Dead of disease	16	48.5
Lost to follow-up	2	6.1
Overall survival, months, median (95% CI)	41 (12.71 – 69.28)	
18 months, %	60.1	
24 months, %	56.1	
36 months, %	50.5	
60 months, %	42.1	

LN; lymph node, CI; confidence interval.

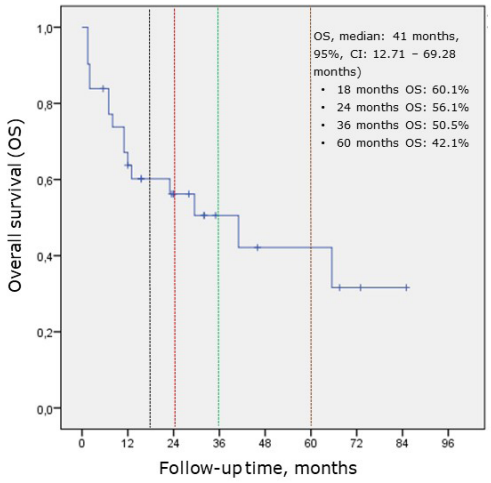

Figure 1. Overall survival analysis of whole cohort

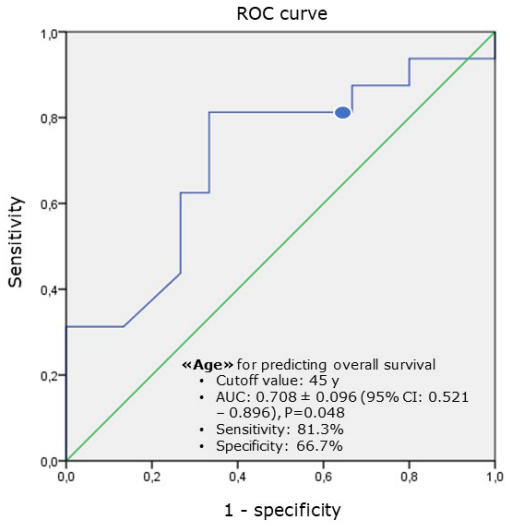

Figure 2. Receiver operating characteristic (ROC) analysis to calculate optimal cutoff value of age for predicting death

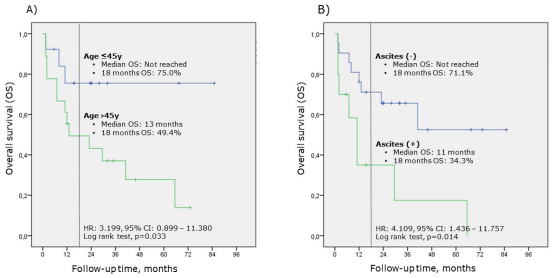

Figure 3. Impact of age (A) and presence of ascites (B) on overall survival

Table 3. Factors associated with overall survival

Variables	Unadjusted			Adjusted		
	HR	95% CI	p	HR	95% CI	p
Age, years	1.043	1.005- 1.083	**0.028**	1.056	1.012- 1.103	**0.013**
Preoperative serum Ca-125 level, U/mL	1.000	0.998 – 1.002	0.897	–	–	–
Preoperative serum albumin level, g/dL	1.133	0.170 – 7.528	0.897	–	–	–
Primary tumor site						
Colorectal vs. Non-colorectal	1.078	0.400 – 2.907	0.881	–	–	–
Largest size of ovarian metastasis, cm	1.006	0.918 – 1.104	0.892	–	–	–
Site of ovarian metastasis						
Unilateral vs. Bilateral	1.799	0.665 – 4.865	0.248	–	–	–
Time of ovarian metastasis						
Synchronous vs. Metachronous	0.897	0.336 – 2.391	0.828	–	–	–
Ascites						
No vs. Yes	3.219	1.192 – 8.695	**0.021**	4.109	1.436 – 11.757	**0.008**
Diffuse peritoneal carcinomatosis						
No vs. Yes	2.757	0.992 – 7.663	0.052	–	–	–
Residual disease after surgery						
No vs. Yes	2.019	0.729 – 5.597	0.177	–	–	–
<1 cm vs. ≥1 cm	2.254	0.779 – 6.521	0.134	–	–	–

HR, Hazard ratio; CI, confidence interval Note: Bold values denote statistical significance at the P <0.05 level

DISCUSSION

This study investigated the clinicopathological characteristics, prognosis, and factors associated with OS in patients with ovarian metastasis from non-gynecologic primary sites. The study revealed that 11.3% of the malignant ovarian tumors were the metastases to the ovaries from non-gynecologic primary sites, and the most common primary tumor site was the colorectum (45.5%). Most patients exhibited elevated preoperative serum Ca-125 levels (71.4%); roughly half of the patients developed syncronous ovarian metastases (48.5%), and had bilateral disease (51.5%); and approximately one third of the patients had peritoneal involvement (36.4%) and/or ascites (30.3%). Age and presence of ascites were independent predictors of OS. Patients who had an age >45 years were 3 times more likely to experience death as compared to those with an age younger than 45 years; while patients wih ascites were 4 times more likely to experience death as compared to those without ascites.

The rate of non-gynaecologic ovarian metastasis in our study (11.3%) is slightly lower than the average rates of 15-20% reported in the literature. (1,2) The reason for this disparity might be due to that our institution is a tertiary-care center and the indications for surgeries are determined in a multidisciplinary manner, thus some of the patients may have been operated on by other disciplines such as general/gastrointestinal surgery. Other clinicopathological data in our study regarding the median age of the patients, laterality of the ovarian mass, timing of metastasis, and the primary sites of tumors were found to be in accordance with the literature as to reflect-population based prevalances of each cancer type. (1-3,6,7)

A meticulous preoperative effort to diagnose an adnexal metastatic tumor of non-gynecologic origin is invaluable because the surgical management of ovarian metastases from non-gynecologic sites differs from that of primary ovarian cancers. For example, a systematic lymph node dissection is not indicated for non-gynecologic metastatic ovarian tumors, an intervention that will only lead to increased morbidity and operative time. (8) Furthermore, in contrast to the clear evidence provided for primary ovarian cancers, there are no randomized controlled trials evaluating the potential benefits of cytoreductive surgery for metastatic tumors of the ovary, although some retrospective series have reported that cytoreductive surgery may be beneficial in a selected group of patients with ovarian metastases from colorectal cancers confined to the pelvis. (3, 8-10)

Ayhan et al. (8) investigated the prognostic factors and role of cytoreductive surgery in 154 patients with nongenital cancers metastatic to the ovaries. The authors reported that age, menopausal status, primary tumor site, diffuse peritoneal involvement and optimal cytoreductive surgery were prognostic factors for OS. The median OS of patients that underwent optimal (R<10 mm) cytoreductive surgery was 48 months, compared with 26 months for patients with suboptimal (R≥10 mm) cytoreduction (P=0.003). The authors concluded that cytoreductive surgery seems to have a beneficial effect on survival of selected patients, especially for patients with colorectal cancer metastatic to the ovary. (8) Sal et al. (9) investigated the prognostic factors in 131 patients with metastatic ovarian tumors from extragenital primary sites, and reported that residual disease, preoperative serum CA 19-9 level, and primary cancer site were the independent prognostic factors for OS. The authors noted that the survival benefit of cytoreductive surgery was significant especially if the residual disease was less than 5 mm. They also stated that the presence of concurrent ovarian and extraovarian metastases exhibited a significantly worse prognosis and that an optimal cytoreduction was less frequently possible in this group of patients. (9) Zhang et al. (3) studied the clinicopathologic features

of 177 patients with ovarian metastases from non-gynecologic primary sites operated on over a 13-year period. The authors reported that while optimal cytoreduction (defined as largest residual lesion <2 cm), primary tumor site, tumor differentiation, and postoperative adjuvant treatment were prognostic indicators, age, menopausal status, presence of ascites, CA-125 level, bilaterality of ovarian metastasis, extraovarian disease, and time of diagnosis (synchronous vs. metachronous) were not associated with OS. The median OS was 25 months in patients with optimal cytoreduction whereas it was 14 months in patients with suboptimal cytoreduction ($p = 0.001$). On the other hand, the authors noted that an optimal cytoreduction could be achieved in only half of the patients.

In our study, a complete resection was achieved in 72% of patients. However, neither optimal cytroreduction nor primary tumor site (colorectal vs. non-colorectal) was found to be associted with OS. The small sample size of our study might have precluded us from achieving a statistically significant relationship. Similarly, in a recent study analyzing outcomes of 70 patients with metastatic tumors to the ovary, Ramesan et al. (11) reported no statistically significant difference in OS between patients with peritoneal carcinomatosis and patients with metastases confined to the ovary. While OS rates were comparable between different primary tumor sites, the sole factor associated with better OS was performance status. Thus, the authors concluded that the evidence for the benefit of cytoreductive surgery is lacking, so the focus of the treatment should be on improving the quality of life.

The main limitation of the current study is its retrospective design, which potentially could lead to a selection bias. Single-center nature of the study, small sample size and relatively short follow-up period are other limitations that may hamper the generalizability of our findings. Additionally, data from small samples or with short follow-up periods can lead to inaccuracies in survival estimates. However, studies with time-to-event endpoints may not always meet the accurate sample size requirement owing to main reasons including the rarity of the disease and the nature of the study design, as was the case in our study. Despite the limitations, this study is valuable in terms of demonstrating the significance of the presence of ascites, which is an easily detectable finding preoperatively that helps to inform patients about the prognosis.

CONCLUSION

In conclusion, ovarian metastases from non-gynecologic primary sites should be kept in mind in the preoperative differential diagnosis of suspicious adnexal masses as the treatment algorithms and prognoses may significantly differ from that of primary ovarian malignancies. Based on our results, age and the presence of ascites are independent risk factors for poor disease outcomes, but there is no survival benefit of cytoreductive surgery in patients with ovarian metastases from non-gynecologic primary sites. Further trials with larger sample sizes are needed to clarify the role of cytoreductive surgery in this group of patients.

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Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Ethical Decleration

Ethical permission was obtained from the Local Ethics Committee of the Antalya Training and Research Hospital for this study with date March 27, 2023 and number 013 and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: TT, IU and MCK, Design: TT and IU, Supervising: IU, SK and MG, Data acquisition and curation: AK, MG, AA, NY, and MCK, Analysis and interpretation: TT and MCK, Literature search: AK, MG, AA, NY and SK, Writing: MCK and TT, Critical review: MG and IU

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