Original Article

Differentiation of Tuberculous Peritonitis from Peritonitis Carcinomatosa without Surgical Intervention

Muhsin Kaya, Mehmet A. Kaplan[1], Abdurrahman Isikdogan[1], Yusuf Celik[2]

Departments of Gastroenterology, [1]Medical Oncology, [2]Biostatistics; Dicle University School of Medicine, Diyarbakır, Turkey

Address for correspondence:
Prof. Muhsin Kaya, Department of Gastroenterology, Dicle University, School of Medicine, Diyarbakır, Turkey.
E-mail: muhsinkaya20@hotmail.com

ABSTRACT

Background/Aim: Ascites of tuberculous peritonitis (TBP) is an exudative type and may well be misdiagnosed as carcinomatous peritonitis, especially in the elderly. The aim of this study was to identify independent predictors that can differentiate TBP from peritonitis carcinomatosa without surgical intervention. **Patients and Methods:** This prospective cohort study was performed on 75 subjects in the following groups: TBP (n=27) (TBP group), ovarian cancer complicated with ascites (n=24) (Ov Ca group), and gastric cancer complicated with ascites (n=24) (Ga Ca group). The frequency of clinical symptoms, laboratory parameters, and serum tumor markers levels were compared. **Results:** In univariate analysis; fever, night sweats, and abdominal pain were significantly more frequent in the TBP group compared to those in the Ov Ca group ($P < 0.001$, $P < 0.001$, and $P = 0.035$, respectively) and the Ga Ca group ($P < 0.001$, $P < 0.001$, and $P = 0.015$, respectively). Serum CA 19-9 and carcino embryonic antigen (CEA) levels were significantly lower in the TBP and Ov Ca group compared to the Ga Ca group ($P < 0.001$ and $P < 0.001$, respectively). Elevated serum CA 125 level was found in all patients with TBP and Ov Ca and in 86.6% of patients with Ga Ca. In the multivariate analysis, presence of fever ($P < 0.001$), night sweats ($P < 0.001$), age under 40 years ($P = 0.008$), and normal serum CA 19-9 level ($P = 0.044$) were independent predictor of diagnosis of TBP. **Conclusion:** The presence of fever, elevated serum CA 125 level, normal serum CA 19-9, and CEA associated with lymphocyte predominant benign ascites may establish the diagnosis of TBP.

Key Words: Ascites, gastric cancer, ovarian cancer, peritonitis carcinomatosa, tuberculous peritonitis, tumor markers

Received 22.12.2010, Accepted 08.03.2011

How to cite this article: Kaya M, Kaplan MA, Isikdogan A, Celik Y. Differentiation of tuberculous peritonitis from peritonitis carcinomatosa without surgical intervention. Saudi J Gastroenterol 2011;17:312-7.

Peritoneal tuberculosis is uncommon in developed countries, although an increase in this disease has been noted in immigrants from countries with a high prevalence of tuberculosis and in AIDS patients. Tuberculosis can spread to the peritoneum through the gastrointestinal tract via mesenteric lymph nodes or directly from the blood, lymph, and fallopian tubes.[1] Ascites of tuberculous peritonitis (TBP) is in exudative form and may commonly be misdiagnosed as carcinomatous peritonitis, especially in the elderly. The symptoms of TBP are generally non-specific and highly variable, with microbiologic diagnostic methods being slow and usually inadequate. The ascitic fluid levels of total protein, lactate dehydrogenase (LDH), cancer antigen (CA) 125 and the serum/ascites glucose ratio are usually insufficient to distinguish TBP from peritoneal carcinomatosis. Furthermore, it remains a difficult disease to diagnose due to the non-specific ultrasonography and computed tomography findings.[2,3] Laparoscopy and peritoneal biopsy have been advocated as the ideal method for early diagnosis in patients with suspected TBP.[1,4,5] However, these are invasive procedures and may cause some complications.[1] Diagnosis is often delayed due to the lack of specific symptoms and laboratory findings. As a result, delayed effective treatment may cause morbidity and mortality in some cases.[6]

Gastrointestinal malignancies[7-9] and ovarian carcinoma[10] commonly cause peritoneal carcinomatosis and the development of ascites in exudative form. Serum tumor markers are non-specific and elevated serum tumor markers including CA 19-9, carcino embryonic antigen (CEA) and CA 125 in both malignant[7-9] and benign gastrointestinal diseases[11] have been reported previously. CA 125 is a

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

PubMed ID: 21912057

DOI: 10.4103/1319-3767.84484

sensitive, but not specific, tumor marker used for diagnosing and monitoring the efficiency of therapy in patients with epithelial ovarian cancer.[10,12]

The aim of this study was to identify the predictive factor that can differentiate TBP from peritonitis carcinomatosa without surgical intervention including laparotomy and laparoscopy.

PATIENTS AND METHODS

Study population

This prospective study was conducted in the department of Gastroenterology and Medical Oncology of Dicle University Hospital. The study population consisted of 75 subjects in the following groups: TBP with ascites (TBP group), ovarian cancer complicated with peritonitis carcinomatosa (Ov Ca group), and gastric cancer complicated with peritonitis carcinomatosa (Ga Ca group). All patients gave written informed consent and the study was approved by local Ethics Committee.

TBP group: Twenty-seven consecutive patients with a diagnosis of TBP were included in the study. The diagnosis of TBP was confirmed by complete clinical and laboratory response after antituberculous therapy. All patients were receiving Isoniazid (300 mg/day; for 9 months), rifampicin (10 mg/kg/day; for 9 months), ethambutol (15-20 mg/kg/day; for 2 months), and pyrazinamide (20-25 mg/kg/day; for 2 months).

Ov Ca group: Twenty-four consecutive patients with diagnosis of ovarian cancer complicated with peritonitis carcinomatosa were included in the study. The diagnosis was confirmed with the presence of mass lesion localized to the ovary, ascites, presence of malignant epithelial cells in the cytological examination of ascites, and the absence of additional malignancy that can cause peritonitis carcinomatosa.

Ga Ca group: Twenty-four consecutive patients with gastric cancer complicated with peritonitis carcinomatosa were included in the study. The diagnosis was confirmed with the presence of gastric tumor in endoscopic examination, histological confirmation of gastric malignant tumor after endoscopic biopsy, and the presence of malignant epithelial cells in the cytological examination of ascites.

In patients with TBP, the most common clinical symptoms, as previously reported, are ascites, fever, night sweat, and abdominal pain;[4,13] therefore, we investigated the presence of these symptoms in all patients. Complete physical examination findings were recorded in all patients. In the TBP group, all clinical and laboratory parameters were recorded before treatment. The presence of body temperature above 38°C at least once per day during seven-day follow-up was accepted as the presence of fever. In febrile patients, we excluded all known etiologies such as genitourinary, respiratory, gastrointestinal infection, and secondary bacterial peritonitis.

Blood samples were obtained by peripheral venipuncture after overnight fasting. All samples were centrifuged at 4,000 rpm and then biochemical analysis was performed.

Complete blood count, erythrocyte sedimentation rate (ESR), routine biochemical tests were determined in routine laboratory. Serum CA 125 concentration was determined by a commercial enzyme immunoassay kit (CA 125 EIA monoclonal, Abbot Laboratories, North Chicago, IL). Serum CA 19-9 was determined by CA 19-9 RIA kit (centocor) and CEA was determined by CEA RIA kit (Dinabot). The cut-off level was accepted as 35 U/mL for CA 125, 37 U/mL for CA 19-9, and 5 ng/mL for CEA. Chest radiograph, abdominal ultrasonography, and computed tomography of abdomen were performed in all patients.

Abdominal paracentesis with or without ultrasonographic guidance was performed in all patients and 10 ml of ascites was taken for cytological examination and 10 ml for measurement of albumin, total protein levels. Serum and ascites albumin gradient was calculated by subtraction of ascites-albumin from serum-albumin.

Cytological examination of ascites was performed by light microscopy after Giemsa staining of material.

Statistical analysis

Mean and standard deviation (SD) were calculated for continuous variables. Univariate analysis was performed using Chi-square (χ^2) test and Fischer exact test. The mean values of the three groups were compared using analysis of variance (ANOVA) followed by post hoc Bonferroni test. Kruskal–Wallis test was also used in case of the presence of high value that can disturb the distribution of date. Two-sided P values were considered statistically significant at $P \leq 0.05$. Multivariate analysis was performed by logistic regression analysis test for identification of independent predictor for diagnosis of TBP. Statistical analyses were carried out by using the Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

TBP group: Twenty-one patients (77%) were women and the mean age was 32.7 ± 13.6 years (range, 14-65). There were no predisposing factors such as HIV positivity in any of the patients. Before initiation of treatment, all patients

had abdominal pain and ascites, fever in 26 (96%), night sweats in 26 (96%), and mild ascites in 24 (89%) patients. In 11 of 27 (41%) patients, fever was not the presenting symptom, but it was identified during follow-up in the Gastroenterology clinic. We also identified fever and night sweats concomitantly in the same patients.

Anemia (hemoglobin lower than 12 g/dl) was noted in 16 (59%) patients, leukocytosis (white blood cells more than 10.000/mm^3) in 1 (4%) patient, and thrombocytosis (platelet more than 425.000/mm^3) in 14 (51%) patients. Elevated ESR (>20 mm/h) was found in 26 (96%) patients. There was mild elevation in aspartate transaminase (AST) level in 5 (19%) patients, alkaline phosphatase (ALP) level in 3 (11%), and gamma glutamyl transferase (GGT) level in 3 (11%) patients. Seventeen (63%) patients had decreased serum albumin (<3.5 g/dl). Total bilirubin, alanine transaminase (ALT), CA 19-9, and CEA levels were within normal limits in all patients. Mean serum CA 125 level was 229 ± 52 (range, 154-1031) U/ml. Elevated CA 125 level was found in all patients, and it progressively decreased during treatment and returned to normal level after completion of treatment (data not shown) in all patients. Serum-ascites albumin gradient was lower than 1.1 in all patients. Cytological examination of ascites showed benign cytology and the percentage of lymphocyte was more than 70% in all patients.

After exclusion of all systemic diseases such as liver cirrhosis, heart failure, and renal disease that can cause ascites, antituberculous treatment was initiated in 26 patients without peritoneal biopsy. In one female patient who had no fever and mild ascites, antituberculous treatment was given after laparoscopic peritoneal biopsy, which showed granulomatous peritonitis. All patients were followed up until completion of treatment (9 month). During the follow-up, one female patient experienced recurrent transient bowel obstruction that was treated conservatively without surgical intervention. Complete clinical and laboratory improvement was observed in all patients after completion of treatment. The diagnosis of TBP was made after achieving complete response after treatment in all patients.

Ov Ca group: The mean age was 52.65 ± 14.12 years (range, 31-75). Abdominal pain was noted in 16 (67%) patients, ascites in 19 (79%), fever in 1 (4%), and night sweats in 1 (4%) patient. Anemia was observed in 18 (75%) patients, leukocytosis in 6 (25%), thrombocytosis in 9 (37%), and elevated ESR in 20 (83%) patients. There was mild elevation in the AST level in 1 patient (4%) and GGT level in 1 patient (4%). Serum albumin level decreased in 9 (38%) patients. Serum ALT, ALP, total bilirubin, and CEA level were within normal limits in all patients. Mean serum CA 125 level was 2241 ± 565 U/ml (range, 98-5000). Elevated serum CA 125 level was found in all patients. In 9 of 24 patients, the CA 125 level was higher than 1031 U/ml, which is the upper limit of patients with TBP. Mean serum CA 19-9 level was 24 ± 20 U/ml (range, 2.6-81). Elevated CA 19-9 level was found in 3 (13%) patients. Serum-ascites albumin gradient was lower than 1.1 in all patients. Cytological examination of ascites showed malignant cytology in all patients.

Ga Ca group: Out of 24 patients, 13 were men and the mean age was 52.16 ± 14.12 years (range, 25-71). There was abdominal pain in 14 (58%) patients and ascites in 11 (45%); however, night sweats and fever were not found in any patient.

Anemia was present in 14 (58%) patients, leukocytosis in 6 (25%), thrombocytosis in 8 (33%), and elevated ESR in 19 (79%) patients. There was mild elevation in serum ALT level in 3 (13%) patients, AST in 3 (13%), ALP in 3 (13%), GGT in 12 (50%), and total bilirubin in 1 (4%) patient. Serum albumin level was decreased in all patients. Mean serum CA 125 level was 167 ± 138 U/ml (range, 29-596). Elevated serum CA 125 level was found in 20 (83%) patients. Mean serum CA 19-9 level was 405 ± 452 U/ml (range, 1.7-1000). Elevated serum CA 19-9 level was found in 14 (58%) patients. Mean serum CEA level was 74 ± 253 ng/dl (range, 1.3-1000). Elevated serum CEA level was found in 9 of 24 (38%) patients. Cytological examination of ascites showed malignant cytology in all patients.

Comparison of demographic, clinical, and laboratory features in the three groups

The mean age of TBP group was significantly lower than that of the Ga Ca group ($P < 0.001$) and the Ov Ca group ($P < 0.001$). Table 1 shows the frequency of clinical symptoms in the three groups. There was no significant difference between the Ga Ca and Ov Ca groups with regard

Table 1: Comparison of frequency of symptoms in the three groups

Variable	TBP group[a] *n*=27	Ov Ca group[b] *n*=24	Ga Ca group[c] *n*=24	χ^2	*P*
Abdominal pain (%)	100	67	58	a-b: 4.43	0.035
				a-c: 5.95	0.015
				b-c: 0.00	1.000
Ascites (%)	89	79	45	a-b: 0.45	0.503
				a-c: 6.68	0.010
				b-c: 2.29	0.130
Fever (%)	96	4	0	a-b: 21.9	<0.001
				a-c: 24.6	<0.001
				b-c: 0.00	1.000
Night sweats (%)	96	4	0	a-b: 21.9	<0.001
				a-c: 24.6	<0.001
				b-c: 0.00	1.000

[a]Tuberculous peritonitis group; [b]Ovarian cancer complicated with peritonitis carcinomatosa group; [c]Gastric cancer complicated with peritonitis carcinomatosa. χ^2: Chi-square test

to the frequency of abdominal pain. Abdominal pain was significantly more common in the TBP group compared to the Ov Ca ($P = 0.035$) group and the Ga Ca group ($P = 0.015$). Ascites was significantly more common in the TBP group as compared to the Ga Ca group ($P = 0.01$). There was no significant difference between the TBP group, the Ov Ca or Ga Ca groups, and the Ov Ca group with regard to the frequency of ascites. Fever and night sweats were significantly more frequent in the TBP group as compared to the Ga Ca ($P < 0.001$ and $P < 0.001$, respectively) and the Ov Ca group ($P < 0.001$ and $P < 0.001$, respectively). There was no significant difference between the Ga Ca and Ov Ca groups with regard to the frequency of fever and night sweats.

Hematocrit, platelet, ESR, ALT, AST, ALP, GGT, total bilirubin, mean serum albumin, and serum-ascites albumin gradient level were not significantly different in three groups. Table 2 shows the comparison of tumor markers in the three groups. Mean serum CA 125 level was significantly higher in the Ov Ca group as compared to the TBP group ($P = 0.004$) and the Ga Ca group ($P = 0.001$). Serum CA 125 level was not significantly different in the TBP group compared to the Ga Ca group. Serum CA 19-9 level was significantly higher in the Ga Ca group compared to TBP ($P < 0.001$) and the Ov Ca group ($P < 0.001$). Serum Ca 19-9 level was not significantly different in the TBP group as compared to the Ov Ca group. Serum CEA level was significantly higher in the Ga Ca group as compared to the Ov Ca ($P < 0.001$) and the TBP group ($P < 0.001$).

In the multivariate analysis, we identified that the presence of fever [odds ratio (OR) =0.007, 95% confidence interval (CI) =0.000-0.335; $P < 0.001$), night sweats (OR= 0.007, 95% CI =0.000-0.335; $P < 0.001$), young age under 40 years (OR =1.13, 95% CI =1.008-1.270; $P = 0.008$), and normal CA 19-9 level (OR =1.15, 95% CI =0.879-1.493; $P = 0.044$) were independent predictors of diagnosis of TBP. Serum CA-125 ($P = 0.06$) and serum CEA (0.125) levels were not important discriminant factors for diagnosis.

Specificity, sensitivity, and positive and negative predictive values of discriminative parameters

Table 3 shows the specificity, sensitivity, positive predictive value, and negative predictive value of different parameters in the TBP. We found that the presence of fever and elevated CA 125 level with normal CA 9-9 and CEA level have the highest specificity (100%), positive predictive value (100%), sensitivity (88.2%), and negative predictive value (93.8%) for the diagnosis of peritoneal tuberculosis.

DISCUSSION

The clinical presentation of TBP is extremely varied, and therefore clinical features alone cannot confirm the diagnosis. The most frequent clinical form of the disease, is wet-type peritonitis in which ascites may be localized or generalized throughout the peritoneal cavity.[1] Clinical or subclinical ascites is reported in virtually all patients with TBP.[4,5] Sanai FM *et al.*, have done a meta-analysis of

Table 2: Comparison of tumor markers in the three groups

Variable	TBP group[a]	Ov Ca group[b]	Ga Ca group[c]	F	ANOVA *P*	Bonferroni test (*P*)
CA 125 (U/mL)	229.2 ± 52	2241 ± 565	167 ± 138	9.2	<0.001	a-b: $P = 0.004$ a-c: $P = 1$ b-c: $P = 0.001$
CA 19-9 (U/mL)	6.3 ± 6.5	24 ± 20	405 ± 452	12.1	<0.001	a-b: $P = 1$ a-c: $P < 0.001$ b-c: $P < 0.001$
CEA (ng/mL)	1.15	1.25	4.5	17.57*	<0.001*	

*Kruskal–Wallis test was used. [a]Tuberculous peritonitis group; [b]Ovarian cancer complicated with peritonitis carcinomatosa group; [c]Gastric cancer complicated with peritonitis carcinomatosa group . TBP: Tuberculous peritonitis, ANOVA: Analysis of variance, CEA: Carcino embryonic antigen, CA: Cancer antigen

Table 3: Specificity, sensitivity, positive predictive value, and negative predictive value of different parameters in the tuberculous peritonitis

Parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Fever (+)[¶]	88.2	96.6	93.7	93.5
Fever (+) and elevated CA 125	88.2	96.6	93.7	93.5
Fever (+), elevated CA 125, normal CA 19-9 and normal CEA	88.2	100	100	93.8
Fever (-) and	13.3	3.4	6.4	6.3
Fever (-) and elevated CA 125	13.3	10	6.9	16.7
Fever (-), elevated CA 125, normal CA 19-9 and normal CEA	13.3	50	11.8	50

[¶]Presence of fever higher than 38°C; and the absence of fever higher than 38°C. CEA: Carcino embryonic antigen, CA: Cancer antigen

35 studies and found abdominal pain in 64.5%, fever in 59%, weight loss in 61%, diarrhea in 21.4%, and constipation in 11% of patients with TBP.[14] Aguado JM *et al.*, have reported in their study that 49% of patients with TBP did not have the history of fever and night sweat. But, they found fever in these patients during clinical follow-up before treatment.[15] In our patients with TBP, there was fever and night sweats in 96% of the patients, abdominal pain all patients, and abdominal swelling in 88% of the patients. All previously reported series are retrospective studies, and there may be some missed data about symptoms of patients before initiation of treatment during follow-up. Therefore, the symptoms mentioned earlier in our patients may be higher as compared to previously reported series. In our study, we found that fever and night sweats are independent discriminative symptoms for diagnosis of TBP as compared to peritonitis carcinomatosa. Abdominal pain and abdominal swelling were not discriminative symptoms between TBP and peritonitis carcinomatosa.

Many tumor markers including CEA, CA 19-9, and CA 242 levels have been studied in the diagnosis of various gastrointestinal tract malignancy,[16,17] and elevated serum levels of these markers have also been reported in various benign gastrointestinal tract diseases.[7,18] A positive correlation between elevated serum CA 125 level and peritoneal metastasis in patients with gastric cancer has been reported.[9,19] Elevated serum CA 125 levels have been reported in 97% of the patients with ovarian cancer complicated with peritoneal carcinomatosis,[12] and in patients with peritoneal tuberculosis.[20,21] Mas *et al.*, have also reported the presence of a positive correlation between treatment response and normalization of elevated serum CA 125 level in patients with TBP.[21] The combination of ascetic fluid LDH, pH, adenosine deaminase (ADA), CEA, and CA 125 levels has been studied in the differentiation of exudative ascites secondary to tuberculosis, bacterial peritonitis, and peritonitis carcinomatosa.[22] We did not find any study using the combination of serum tumor markers including CEA, CA 19-9, and CA 125 level in the differentiation of TBP and peritonitis carcinomatosa. We found that serum CEA and CA 19-9 levels are not elevated in patients with TBP as well as ovarian cancer complicated with peritonitis carcinomatosa. Therefore, serum CEA and CA 19-9 levels are not a discriminative marker between TBP and ovarian cancer complicated with peritonitis carcinomatosa. This study showed that normal serum CA 19-9 level was the only independent predictor for the diagnosis of TBP. Therefore, in case of the presence of ascites, the elevated serum CA 19-9 level may exclude the possibility of TBP.

Since the clinical manifestation of peritoneal tuberculosis may resemble those of ovarian carcinoma with ascites, abdominopelvic masses, and elevated CA 125, a number of women with this disease are first seen by a gynecologist. [13,20] The gynecologist who is not aware of peritoneal tuberculosis is deceived by the clinical presentation and sometimes by the intraoperative findings of this disease. Consequently, patients with peritoneal tuberculosis are misdiagnosed as having ovarian malignancy and are subjected to unnecessary extended surgery. TBP may resemble peritonitis carcinomatosa originating from gastrointestinal tract malignancy because of elevated serum CA 125 level[19] and intense fluorine-18 fluorodeoxyglucose activity in the positron emission tomography (PET).[23] Thus, clinical discrimination between peritoneal tuberculosis and peritonitis carcinomatosa originating from ovary or gastrointestinal tract carcinoma may sometimes be extremely difficult. The most important minimally invasive diagnostic test that can separate malignant causes of ascites from the benign causes is cytological examination of the ascitic fluid. But, false negative results in malignant ascites and false positive results in benign ascites may be seen. Elevated lymphocyte count, decreased glucose level, elevated LDH level, elevated total protein level, elevated ADA level (>30 U/L), low serum-ascetic albumin gradient (<1.1) in the ascetic fluid have been used for the diagnosis of peritoneal tuberculosis. But, all these tests do not definitively confirm the diagnosis of TBP. The following laboratory tests of aspirates and/or biopsy specimens are needed to finally confirm the diagnosis of peritoneal tuberculosis before treatment: (a) the presence of acid-fast bacilli (Ziehl-Neelsen staining positive); (b) positive culture for *Mycobacterium tuberculosis*; (c) polymerase chain reaction (PCR) positive for *M. tuberculosis* complex. However, all tests have very low sensitivity and culture is required for as long as 4-8 weeks. Examination of peritoneal biopsy specimens with the available histological diagnostic procedures including laparotomy, laparoscopy, and percutaneous peritoneal biopsy have been used for diagnosis of peritoneal tuberculosis. Since chronic granulomatous reaction and inflammation are consistent but not diagnostic of tuberculosis, histologic confirmation of tuberculosis can be difficult.[14] The laparoscopic appearance of the peritoneal cavity in combination with directed biopsy established the diagnosis in 80-95% of patients with unexplained ascites.[1,4,13] However, laparoscopy requires hospitalization and has some complications.

We found that the presence of fever above 38°C and elevated CA 125 level with normal CA 19-9 and normal CEA level in patients with exudative ascites have 100% specificity and 100% positive predictive value for the diagnosis of peritoneal tuberculosis. In 26 of our 27 patients with exudative ascites, we commenced anti-tuberculous treatment after cytological examination of ascites, which showed benign cytology with lymphocyte predominance. We achieved complete clinical and laboratory improvement in all patients. For this reason, in case of presence of benign cytological examination of

ascites with lymphocyte predominance, fever, and elevated CA 125 level with normal CA 19-9 and CEA level, we are in favor of commencing anti-tuberculous treatment without further invasive procedure in patients with exsudative ascites.

In conclusion, in patients who have exudative ascites, after exclusion of all systemic diseases that can cause ascites, if there are following criteria, TBP should be considered and antituberculous treatment should be commenced without further diagnostic tests: (1) presence of fever above 38°C during clinical follow-up; (2) elevated serum CA 125 level; (3) normal CA 19-9 and normal CEA level; and (4) lymphocyte predominant benign ascites in cytological examination.

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Source of Support: Nil, **Conflict of Interest:** None declared.