Original Article

Correlation of non-invasive parameters with upper gastrointestinal endoscopy findings for presence and grading of gastroesophageal varices in liver cirrhosis patients

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Abstract

Background: Development of esophageal varices is one of the major complications of liver cirrhosis, and endoscopy is used to see the presence, grading, and long-term monitoring of esophageal varices which is an invasive and unpleasant procedure. There is no adequate data available showing noninvasive methods can be used for the same. **Methods:** Seventy patients with liver cirrhosis participated in the study. Factors like portal vein diameter, spleen size, platelet count, serum bilirubin, Child-Pugh score, prothrombin time (PT), and PT INR were observed and correlated endoscopically with the presence and grading of esophageal varices in all patients. **Results:** The platelet count, portal vein diameter, serum bilirubin, spleen bipolar diameter, and PT had statistically significant correlations with the presence of varices. Among them, platelet count, portal vein diameter, and serum bilirubin also had statistically significant correlations with the grading of varices. Monitoring of these noninvasive parameters can help in monitoring variceal growth. **Conclusions:** Noninvasive parameters can be used effectively to predict the presence and grading of esophageal varices and at the same time keep the rate of undiagnosed varices acceptably low. By using noninvasive parameters, patients can be benefited by decreasing the requirement of repeated endoscopic evaluation which is an unpleasant procedure and availability is also limited.

Keywords: Esophageal varices, liver cirrhosis, platelet count, portal hypertension, portal vein diameter, spleen size, upper gastrointestinal endoscopy

Introduction

Cirrhosis is the end stage of chronic liver disease, resulting in disorganization of liver architecture, nodule formation, and development of portal hypertension. Portal hypertension is related to the development of hyperdynamic circulation which

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leads to the development of complications such as ascites, hepatic encephalopathy, and esophagogastric varices.[1-5]

Esophageal variceal bleeding is one of the most dreaded complications of cirrhosis because it is a leading cause of morbidity and mortality in cirrhosis.[6-10]

In cirrhotic patients, esophago- gastro- endoscopy is required to detect the presence and grading of the gastro-esophageal varices. But the procedure is invasive, uncomfortable for the patient, and is not available in all centers.

Noninvasive parameters like portal diameter and spleen size are directly related to portal hypertension,[11,12] and other noninvasive parameters like bilirubin, PT, PT INR, platelet count, and Child-Pugh score are related to liver failure and thus indirectly to portal hypertension.[13-16]

Portal diameter and spleen size can be measured easily by ultrasonography (USG). Serum bilirubin, prothrombin time (PT), PT INR, and platelet count can be obtained by blood examination in all cirrhotic patients as a part of their routine clinical checkup. Child-Pugh score can predict the prognosis of liver disease primarily cirrhosis. It provides a forecast of the increasing severity of liver disease.[17]

At the time of diagnosis, about 30% of cirrhotic patients have the development of esophageal varices, reaching 90% after approximately 10 years. In cirrhotic patients with no esophageal varices on initial endoscopy, there are chances to develop new varices at a rate of approximately 5% per year. Progression of small varices to large varices occurs at a rate of 10% to 15% per year and is related to the grade of liver dysfunction.[18]

Thus, repeated endoscopy is needed for screening for varices at diagnosis and long-term monitoring of varices, so there is a considerable burden of endoscopies, related cost and patients repeatedly undergo an unpleasant procedure and out of that only 9%–36% of cirrhosis patients have varices on screening endoscopy. Another important fact is that not all centers have endoscopic facilities.

The purpose of our study is to assess and correlate noninvasive parameters with the presence and grading of varices.

Material and Methods

After approval of the institutional ethical committee, this prospective observational study was conducted on patients of liver cirrhosis presenting at the Department of General Medicine and Gastroenterology (on both outdoor and indoor basis) at a tertiary health care center in western Rajasthan for the duration of one and a half year (January 2021 to June 2022).

All patients who fulfilled the inclusion and exclusion criteria were included in the study.

Inclusion criteria-

1. Patients with confirmed liver cirrhosis based on a combination of history, clinical findings, impaired liver function tests, deranged clotting profile, and abdominal ultrasound.
2. All adult patients >18 years of age.
3. Willing to participate in the study with written informed consent.

Exclusion criteria-

1. Patients with coexistent infection or illness that could influence platelet count.
2. Patients with a history of drug intake may alter liver enzyme levels and hematological and coagulation profiles. Patients on previous/current treatment with beta blockers, diuretics, and anti-platelet drugs.
3. Patients who are on drugs which can lead to thrombocytopenia were excluded.
4. Patients who have undergone sclerosis, band ligation of esophageal varices, TIPSS, and surgery for portal hypertension.
5. Patients with bleeding disorders.
6. Critically ill and hemodynamically unstable patients.

Data were collected through a structured proforma, which includes demographic profile, history, examinations, and investigations. Each patient was subjected to a detailed history and clinical examination. Relevant investigations like platelet count, serum bilirubin, PT, PT INR, HBsAg, anti-HCV antibody, serum protein, and USG abdomen for the presence of ascites, spleen size, and portal diameter were performed.

All patients were also evaluated for the presence and grading of gastroesophageal varices by upper GI endoscopy. Olympus XG20 endoscope was used. Endoscopically esophageal varices were graded as I to IV using *Japanese Research for Portal Hypertension classification* as follows:

Gr I: small esophageal varices which flatten with insufflation or minimally protrude into the esophageal lumen,

Gr II: moderate sized varices with minimal obscuring of the gastroesophageal junction,

Gr III: large varices showing luminal prolapse substantially obscuring the gastroesophageal junction and.

Gr IV: very large esophageal varices completely obscure the gastroesophageal junction and do not flatten on insufflations.

Correlation of noninvasive parameters like platelet count, serum bilirubin, PT, PT INR, portal vein diameter, spleen bipolar diameter, and Child-Pugh class was seen with the presence of gastroesophageal varices. After that, those noninvasive parameters, which had a statistically significant correlation with the presence of varices, were further evaluated for correlation with the grading of varices. Demographic, clinical, and laboratory parameters of patients were also evaluated.

Statistical analysis-

The sampling for the study was purposive sampling (consecutive scheme).

Sample size: The formula used for the calculation of sample size was.

$n = (Z\ \alpha)^2\ P\ (1\text{-}P)/E^2$.

Here n is the sample size.

Z α Confidence level at 95% = 1.96.

E is for Error [allowable error (E) of 10%].

P is for Prevalence = 20%.

Sample size = $n = (1.96)^2\ (20)(80)/100 = 61.46$.

Thus, the minimum sample size required was 62.

For statistical analysis, the data was entered in MS Excel Software version 20 and analyzed using SPSS IBM Comp. Version 21. Descriptive analysis of the data was performed presenting the results as frequency, percentage for qualitative variables, mean, and standard deviation for age. The relation between qualitative variables was evaluated by the Chi-square test and Fisher's Exact test if needed. The descriptive data was expressed in proportions, mean, and frequency tables. The Pearson correlation coefficient "r" was used to see any correlation between variables. The categorical data were analyzed using the Chi-square test. The quantitative data was analyzed using independent student's *t*-test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined. *P* value less than 0.05 was considered statistically significant.

Results

A total of 70 cases of liver cirrhosis were included in the study. The mean age of cases was 51.61 ± 13.54 years. Incidence of cirrhosis was maximum in the age group of 51–60 years (32.86%) followed by 31–40 years (21.43%) [Table 1]. Among 70 cirrhotic patients, 60 (85.71%) were males and 10 (14.29%) were females with male–female ratio of 6:1.

Underlying etiological factors were evaluated among 70 cirrhotic patients. Alcoholism was present in 78.57% (n = 55) patients and 21.43% of patients were nonalcoholic. From the total studied patients, 5 (7.14%) were positive for HBsAg and no one was found positive for the anti-HCV antibody.

Among 70 cirrhotic patients, endoscopically 61 (87.14%) subjects were found to have varices and 9 (12.86%) subjects had no varices. Among 61 patients having varices, grade I, II, III, and IV varices were present in 21 (30.00%), 24 (34.29%), 9 (12.86%), and 7 (10.00%) individuals, respectively. Other relevant findings on endoscopy beside varices were also noted [Figure 1].

The relationship between noninvasive parameters like platelet count, portal vein diameter, serum bilirubin, spleen bipolar

Table 1: Age-wise distribution of cases

Age in years	No. of patients	Percentage
1–10	0	0%
11–20	0	0%
21–30	3	4.29%
31–40	15	21.43%
41–50	12	17.14%
51–60	23	32.86%
61–70	9	12.86%
71–80	8	11.43%
Total	70	100.00%
Mean±SD	51.61±13.54	

Table 2: Correlation of baseline characteristics of patients studied based on the presence and absence of varices

	Varices		*P*
	Present	Absent	
Platelet count	70295.08±20267.66/µl	124222.22±20535.20/µl	0.001**
Portal vein diameter	13.53±0.90 mm	11.02±0.79 mm	0.001**
Serum bilirubin	12.69±10.34 mg/dl	7.00±9.27 mg/dl	0.001**
Spleen bipolar diameter	128.67±21.33 mm	110±22.92 mm	0.033*
PT	27.63±13.23 sec	23.24±6.69 sec	0.014*
PT INR	2.00±0.66	1.85±0.58	0.147

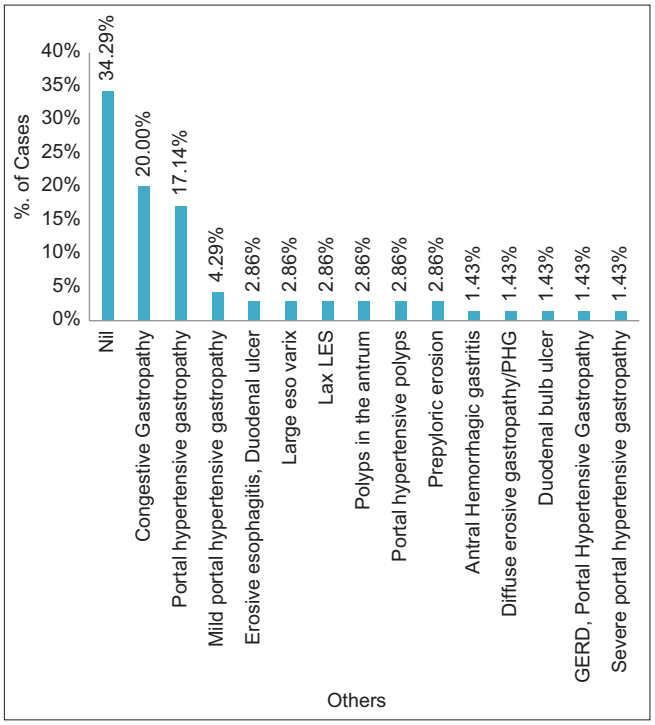

Figure 1: Other relevant findings beside varices noted on endoscopy

diameter, PT, PT INR, and presence of varices was studied. Out of these noninvasive parameters, platelet count, portal vein diameter, serum bilirubin, spleen bipolar diameter, and PT had a statistically significant correlation with the presence of varices [Table 2].

There was no statistically significant ($P = 0.36$) correlation between the Child-Pugh class and the presence of varices [Table 3].

In the study serum bilirubin, platelet count, portal vein diameter, spleen bipolar diameter, and PT values had statistically significant correlation with presence of varices, and these noninvasive parameters were further evaluated for correlation with the grading of varices.

On comparison, it was found that platelet count was in decreasing trend with increment of variceal grading. There was statistically significant correlation of platelet count with grading of varices ($P < 0.001$) [Table 4].

There was a statistically significant correlation of portal vein diameter with grading of varices ($P < 0.001$) [Table 5]. There was also a statistically significant correlation of total bilirubin with grading of varices ($P = 0.035$) [Table 6].

There was no statistically significant correlation of spleen bipolar diameter with grading of varices ($P = 0.473$) [Table 7]. There was also no statistically significant correlation of PT with grading of varices ($P > 0.05$) [Table 8].

For the presence of varices, platelet count <100000/µl had a sensitivity of 100%, specificity of 100%, PPV 100%, and NPV 100%. Platelet counts ≤80000/µl had a sensitivity of 67.21%, specificity of 100%, PPV of 100%, and NPV of 31.03%.

Portal vein diameter >13 mm had a sensitivity of 77.5%, specificity of 100%, PPV of 100%, and NPV of 39.13% for the presence of varices. Serum bilirubin >3 mg/dl had a sensitivity of 57.38%, specificity of 22.22%, PPV of 83.33%, and NPV of 7.14% for the presence of varices. Spleen size >13 cm had a sensitivity of 100%, specificity of 100%, PPV of 100%, and NPV of 100% for the presence of varices. Child-Pugh score (B + C) had a sensitivity of 96.72%, specificity of 0%, PPV of 86.76%, and NPV of 0% for the presence of varices. PT INR ≥2.2 had a sensitivity of 21.31%, specificity of 55.56%, PPV of 76.47%, and NPV of 9.43%. PT >18 had a sensitivity of 80.33%, specificity of 11.11%, PPV of 85.96%, and NPV of 7.69% [Table 9].

Table 3: Correlation between Child-Pugh class and presence of varices

Esophageal varices	A		B		C	
	No.	%	No.	%	No.	%
Absent	0	0.00%	1	5.00%	8	16.67%
Present	2	100.00%	19	95.00%	40	83.33%

P=0.36 (Not Significant)

Table 4: Correlation of platelet count with grading of varices

Varices Grading	Mean (per ml)	SD
Absent	124222.22	20535.20
I	74952.38	17249.57
II	69833.33	20217.66
III	63444.44	21178.47
IV	66714.29	28087.45

P≤0.001 (Highly significant)

Table 5: Correlation of portal vein diameter with grading of varices

Varices Grading	Mean (mm)	SD
Absent	10.02	0.80
I	13.45	0.98
II	13.68	0.86
III	13.74	0.65
IV	13.01	1.06

P≤0.001 (Highly significant)

Table 6: Correlation of total bilirubin with grading of varices

Varices Grading	Mean (mg/dl)	SD
Absent	3.84	5.04
I	3.84	1.34
II	9.59	10.54
III	12.69	10.34
IV	11.67	15.61

P=0.035 (Significant)

Table 7: Correlation of spleen bipolar diameter with grading of varices

Varices Grading	Mean (mm)	SD
Absent	121.00	32.92
I	110.86	32.29
II	120.33	30.68
III	118.89	33.71
IV	136.14	25.22

P=0.473 (Not Significant)

Discussion

In this study, the mean age of 70 liver cirrhosis patients was 51.6 ± 13.54 years. In our study, approximately 75% of patients were below 60 years. A similar presentation was there in a study by Muhammad *et al.* who studied 739 patients with a mean age of 45.81 ± 15.13 years.[19] Chalasani *et al.* studied 346 patients with a mean age of 49.7 ± 10.9 years.[20] In a study by Afsar *et al.*, a total of 110 patients were included in the study, and the mean age of the patients was 59.89 ± 9.01 years.[21] In a study by Kumar *et al.*, the mean age of presentation was 53.40 ± 6.2 years.[22] In Dewan KR *et al.*, patients had ages ranging from 14 to 88 years and the mean being 48.76 + 17.19 years.[23]

By comparison of results between various studies, it is highlighted that the presence of liver cirrhosis is evident in younger age.

Table 8: Correlation of PT with grading of varices

Varices Grading	Mean (seconds)	SD
Absent	21.61	4.53
I	22.67	4.47
II	23.50	6.83
III	23.83	8.03
IV	27.63	13.23

P=0.501 (Not Significant)

Table 9: Sensitivity and specificity of various parameters in predicting varices

Parameters	Sensitivity	Specificity	PPV	NPV
Platelet count ≤100000	100%	100%	100%	100%
Platelet count ≤80000	67.21%	100%	100%	31.03%
Portal vein diameter >13 mm	77.5%	100%	100%	39.13%
S. Bilirubin >3 mg/dl	57.38%	22.22%	83.33%	7.14%
Spleen size >13 cm	100%	100%	100%	100%
Child-Pugh score (B + C)	96.72%	0%	86.76%	0%
INR >2.2	21.31%	55.56%	76.47%	9.43%
PT >18	80.33%	11.11%	85.96%	7.69%

Person in this age group usually have many dependents that indicate liver cirrhosis have a greater social impact. Every effort should be made to control preventable causes of liver cirrhosis specially alcohol intake.

In this study, among 70 cirrhotic patients, 60 (85.71%) were males and 10 (14.29%) were females with male–female ratio of 6:1. Similar presentation was there in a study by Muhammad *et al.* (2012) who studied 739 patients with 481 (65.1%) males.[19] Mark DP *et al.* reported male–female ratio of 2.5:1.[24] A study by Dewan KR *et al.* also had male predominance (75%).[23]

In the study by Kumar *et al.*, out of 50 patients, 12 were females (24%) and 38 patients were males (76%).[22] in this study outoff 101 patients 87 were males.[16] In the study by Afsar *et al.*, a total of 110 patients were included in the study and among them 55.5% (n = 61) were males and 44.5% (n = 49) were females.[21]

Various studies are showing that liver cirrhosis is more evident in males than females. Further studies should be done on the genetic, pathological, and social basis for the lower occurrence of liver cirrhosis in females. A higher tendency of alcohol intake in males may be one of the responsible reasons for the higher occurrence in males.

In this study, possible etiological factors of liver cirrhosis were also evaluated like alcoholism and viral infections. Among 70 patients studied, the cause of cirrhosis was found to be alcoholism in 78.57%. In the current study, five patients (7.14%) were found positive for HBsAg and none for anti-HCV antibody.

In a study by Mark DP, 30 out of 100 patients (30%) took alcohol.[19] In the study by Kumar *et al.*, among the study population alcohol was the cause of cirrhosis in 64% patients and 18% patients were HBsAg positive.[22] In a study by Prakruthi J, among the study population 14% patients had a history of consumption of ayurvedic medicine.[25] In a study of Cherian *et al.*, the etiology included alcohol (42.4%) followed by hepatitis B virus (15.3%) infection.[15] In a study by Chalasani *et al.*, among 346 patients the etiology included alcohol in 22% and hepatitis B virus in 5%.[20] In various studies, alcohol consumption was found as a prominent etiological factor. Knowledge about prevalence of various etiological factors can be used for preventive strategies.

A total of 70 cases of liver cirrhosis were included in this study. Among 70 cirrhotic patients, endoscopically 61 (87.14%) subjects were found to have varices and 9 (12.86%) subjects had no varices. On endoscopic examination, grades I, II, III, and IV varices were present in 21 (30.00%), 24 (34.29%), 9 (12.86%), and 7 (10.00%) individuals, respectively.

Higher grades of varices had a tendency to bleed which can be life-threatening. The occurrence of variceal bleeding can be prevented; it is important to recognize patients who are having varices and those who are at a higher risk of developing variceal bleeding and likely to benefit from interventions. Therefore, various parameters which can noninvasively predict the presence and grading of esophageal varices have been identified in this study.

In this study, the correlation between noninvasive parameters like platelet count, portal vein diameter, serum bilirubin, spleen bipolar diameter, PT, PT INR, and presence of varices was studied. Out of these platelet counts, portal vein diameter, serum bilirubin, spleen bipolar diameter, and PT had statistically significant correlations with the presence of varices.

Cherian *et al.* in their study found that the platelet count, portal vein diameter, spleen bipolar diameter, PT, and Child-Pugh score had statistically significant correlations with presence of varices.[15] Muhammad *et al.* found that spleen bipolar diameter, platelet count, and portal vein diameter had statistically significant correlation with the presence of varices.[19]

The study by Thomopoulos KC *et al.* found that spleen bipolar diameter, platelet count, and portal vein diameter had a statistically significant correlation with the presence of varices.[26] In a study by Jeon SW *et al.*, on univariate analysis serum albumin, total bilirubin, PT, platelet count, spleen size, velocity of portal vein, and portal vein diameter were found significant. On multivariate analysis, independent variables were platelet count and diameter of spleen. Endoscopic screening for varices was recommended in cirrhotic patients with splenomegaly.[27] Madhotra *et al.* also concluded that thrombocytopenia and splenomegaly are independent predictors of large varices in cirrhosis.[13]

In the current study, platelet count ($P < 0.001$), portal vein diameter ($P < 0.001$), and serum bilirubin ($P = 0.035$) also had a statistically significant correlation with the grading of varices.

In a study by Kumar *et al.*, 17 (73.91%) patients with clinically palpable spleen had large varices. A significant association was found between splenomegaly, portal vein diameter, and large varices.[22] In a study by Afsar *et al.*, a significant inverse correlation was found between platelet count and grades of esophageal varices; lower platelet count was associated with high varices.[21]

Chalasani *et al.* had large esophageal varices in 20% patients. The study found splenomegaly and low platelet count as independent predictors of large esophageal varices.[20]

Zaman *et al.* found that platelet count <88,000 was the only parameter associated with large varices.[28] Sarwar *et al.* included 101 patients and found that patients with platelet count <88,000 and portal vein diameter >11 mm are more likely to have high grade varices.[29] El-Din *et al.* also concluded that there was a significant negative correlation between platelet count and grading of varices.[30]

Monitoring of these noninvasive parameters can help in monitoring of variceal growth to a higher grade and to prevent bleeding by timely intervention.

In this study, sensitivity, specificity, PPV, and NPV were evaluated for various cut-off values of noninvasive parameters for the presence of varices [Table 9].

In a study by Cherian *et al.,* platelet count <90,000 had a sensitivity of 59.3%, specificity of 64.2%, PPV of 47.5%, and NPV of 74.2%. Spleen diameter ≥160 mm had a sensitivity of 66.7%, specificity of 54.7%, PPV of 44.6%, and NPV of 75%.[15]

Muhammad *et al.* showed platelet count <150,000/μl had sensitivity, specificity, PPV, and NPV of 76.6%, 52.0%, 63.9%, and 66.7%, respectively, and for platelet count <50,000/μl had 30.1%, 98.9%, 96.7%, and 56.0%, respectively. In their study, portal vein >13 mm had a sensitivity and specificity of 64.5% and 51.7% for predicting varices. PT and spleen bipolar diameter were not affected with varices grading.[19]

In a study by Prakruthi *et al.,* portal vein >13 mm had a sensitivity and specificity of 64.5% and 51.7%, for predicting varices. With the increase in the size of spleen, the specificity of predicting varices in cirrhosis increased but sensitivity decreased. Serum bilirubin >3 mg/dl ($P < 0.001$) had sensitivity, specificity, PPV, and NPV of 33.4%, 78.9%, 63.7%, and 51.6%, respectively. INR >2.2 ($P < 0.001$) had sensitivity, specificity, PPV, and NPV for varices in cirrhosis of 60.4%, 91.7%, 89.0%, and 67.6%, respectively.[25]

EL-Din *et al.* also concluded that the cutoff value of platelet count as a predictor for the presence of varices was less than or equal to 130000, with a sensitivity of 95% and specificity of 95%. The cutoff value as a predictor for the presence of large varices was less than or equal to 80000, with a sensitivity of 91.2% and a specificity of 86.7%.[30]

In a study by Prihatini J *et al.*, the cutoff value of platelet count 82,000/ul (90.9% sensitivity and 41.7% specificity), portal vein diameter 1.15 cm (75% sensitivity and 54.5% specificity), and splenic size 10.3 cm (83.3% sensitivity and 63.6% specificity) can be used to predict varices in cirrhosis patients. They concluded that platelet count, portal vein diameter, and splenic measurement can be used as noninvasive parameters to detect esophageal varices in cirrhotic patients.[31]

According to Fagundes *et al.*, only splenomegaly had good sensitivity (97.7%) and NPV (91.7%). The study suggested that this can be used as a screening test for varices.[32]

Various studies are showing favorable results that various noninvasive parameters can be used to predict the presence and grading of esophageal varices. These parameters can also be used for monitoring of varices. By using noninvasive parameters, patients benefit by decreasing requirement of repeated endoscopic evaluation which is an unpleasant procedure and availability is also limited. Variability in results of different studies indicates the need for further studies to establish cutoff values and schedule of monitoring of these noninvasive parameters.

Conclusion

Liver cirrhosis is more evident in younger age groups and more evident in males. Every effort should be made to control preventable causes of liver cirrhosis like alcoholism.

The platelet count, portal vein diameter, serum bilirubin, spleen bipolar diameter, and PT had a statistically significant correlation with the presence of varices. Platelet count, portal vein diameter, and serum bilirubin also had a statistically significant correlation with the grading of varices.

By using noninvasive parameters, patients can benefit by decreasing requirement of repeated endoscopic evaluation which is an unpleasant procedure and availability is also limited.

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Conflicts of interest

There are no conflicts of interest.

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