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CLINICAL STUDIES

Cryptogenic pyogenic liver abscess as a sign of colorectal cancer: a population-based 5-year follow-up study

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Abstract

Background/aims: No large-scale population-based study has ever been conducted to examine the relationship between cryptogenic pyogenic liver abscesses (PLA) and the subsequent risk of colorectal cancer. This study aimed to estimate the risk for colorectal cancer following a diagnosis of cryptogenic PLA over a 5-year period. *Methods:* The study group comprised 274 patients who visited an outpatient care centre or were hospitalized with a diagnosis of cryptogenic PLA between 2001 and 2003. The comparison group included 1370 randomly selected subjects. Cox proportional hazard regressions were performed to compare the 5-year colorectal cancer-free survival rates for these two groups. *Results:* Of the total sample, 40 patients from the study group (2.43%) had colorectal cancer during the 5-year follow-up period: 15 (5.45% of those with cryptogenic PLA) and 25 from the comparison group (1.82% of the comparison group). After adjusting for patients' age, sex, monthly income, level of urbanization and geographical location, the hazard of colorectal cancer during the 5-year period was 3.36 times greater for patients with cryptogenic PLA than for the comparison group [95% confidence interval (CI) = 1.72–6.56, $P < 0.001$]. The adjusted hazard of colorectal cancer during the 5-year follow-up period was 5.54 times higher for cryptogetic PLA patients with diabetes (95% CI = 2.11–14.56, $P < 0.001$) than the comparison group and 2.64 times higher among PLA patients without diabetes (95% CI = 1.19–5.85, $P < 0.05$). *Conclusions:* We conclude that cryptogenic PLA is an alarm that may signal colorectal cancer, especially among female patients with diabetes.

The aetiology and pathogenesis of liver abscesses have changed drastically in recent years (1, 2). In the beginning, pyogenic liver abscess (PLA) was most often associated with hepatobiliary tract diseases or intra-abdominal infections, including cholecystitis, suppurative cholangitis, suppurative pylephlebitis, appendicitis, diverticulitis and peritonitis (1–5). Some PLAs were idiopathic – namely, cryptogenic abscesses. In many reports, cryptogenic PLA has been regarded as the first manifestation of silent colorectal cancers and colonic tubulovillous adenomas (5–13). If a patient has a previous colon lesion (e.g. advanced colon polyp or colon cancer), then bacteria may move from the mucosal defect into the portal system and result in cryptogenic PLA.

In addition, multiple liver abscesses caused by anaerobic bacteria such as peptostreptococcus or streptococcus spp., clostridium septicum or bacteroides fragilis are the presenting forms of unsuspected colorectal cancer without liver metastases (13–19). Furthermore, there have been a growing number of reports about the relationship between diabetes mellitus and liver abscesses (20, 21). Recent evidence indicates that metabolic abnormalities such as impaired glucose tolerance and diabetes mellitus are also associated with increased incidence of colonic adenoma and cancer (22, 23). More recently, occult colonic cancer and tubulovillous adenomas have been reported in *K. pneumoniae* liver abscesses (7, 12, 24, 25). However, to our knowledge, no large-scale population-based study has ever been conducted to examine the relationship between cryptogenic PLA and the subsequent risk of colorectal cancer.

Using a nationwide population-based dataset in Taiwan, this study aims to estimate the risk of colorectal cancer following a diagnosis of cryptogenic PLA over a 5-year follow-up period. The annual incidence of PLA has increased steadily in Taiwan from 11.15/100 000 individuals in 1996 to 17.59/100 000 individuals in 2004 (24). According to the 2006 cancer report released by the Taiwan Department of Health, the incidence of colorectal cancer was 32.17/100 000 for females and 42.71/100 000

for males. Colorectal cancer has become one of the five most common cancers, and is also the third most common cause of cancer-related death in Taiwan (26). The high relative incidences of both PLA and colorectal cancer in Taiwan provide a unique opportunity to examine the association between these two conditions while adjusting for clinical and sociodemographical factors. We hypothesize that the risk of colorectal cancer is increased following a diagnosis of cryptogenic PLA.

Materials and methods

Database

In this study, we used the 'Longitudinal Health Insurance Database 2001' (LHID2001), a nationwide population-based dataset released by the Taiwan National Health Research Institute (NHRI) in 2006. Taiwan launched a single-payer National Health Insurance Program in 1995 to provide affordable healthcare for all the island's residents. As of 2007, 22.60 million of Taiwan's 22.96 million people were enrolled in this programme. The LHID2001 includes all original medical claims data as well as a registry of 1 000 000 beneficiaries, randomly sampled from all enrollees included in the National Health Insurance (NHI) programme. The Taiwan NHRI reports that no statistically significant differences were found in the distributions of age, gender or healthcare costs between the sample group of the LHID and all enrollees. Therefore, the LHID2001 provides an exceptional opportunity to examine the risk of colorectal cancer following PLA.

As the dataset used for this study includes de-identified secondary data released to the public for research purposes, this study was exempt from a full review by the Institutional Review Board.

Study sample

For the study group, we selected patients who visited outpatient care centres or were hospitalized with a principal diagnosis of liver abscess (ICD-9-CM code 572.0) between 1 January 2001 and 31 December 2003 ($n = 325$). We excluded patients who were below 18 years of age in order to limit our sample to the adult population ($n = 16$). In addition, we excluded patients who had any type of cancer (ICD-9-CM codes 140–239) ($n = 19$) or PLA diagnosed before 2001 ($n = 11$). We also excluded patients with a history of cholangitis, common bile duct stones, pancreatitis or inflammatory bowel disease before 2001 ($n = 5$). Finally, a total of 274 patients with cryptogenic PLA were included in the study group. We assigned the first ambulatory care visit or hospitalization in which they received a principal diagnosis of cryptogenic PLA as the index ambulatory care visit.

The comparison group for this study was extracted from the remaining beneficiaries of the LHID2001. We excluded patients who had PLA during the period from 2001 to 2008. Using the SAS program, we randomly selected 1370 enrollees from the registry of beneficiaries (five for every patient with PLA) matched with the study group in terms of age (< 45, 45–54, 55–64, 65–74 and > 74 years), sex and the year of index ambulatory care visit. We assigned their first ambulatory care visit in the index year as the index ambulatory care visit. We excluded patients who had any type of cancer before their index ambulatory care visit. Finally, 1644 patients were included in our study. Each patient was individually tracked for five years following their index ambulatory care visit to identify all those who developed colorectal cancer (ICD-9-CM codes 153 or 154) during the follow-up period.

Statistical analysis

We used the SAS statistical package (SAS System for Windows, Version 8.2) to perform all analyses in this study. Pearson's χ^2 tests were carried out to examine differences in the distributions of socio-demographic characteristics [age, sex, monthly income, level of urbanization and the geographical location of the community in which the patient resided (Northern, Central, Eastern and Southern Taiwan)] between the study and the comparison groups. Monthly income was categorized into four groups: 0, NT$1-NT$15 840, NT$15 841-NT$25 000 and $\geq$NT$25 001 (US$1.00 = NT$ 33.00 in 2003). For this study, urbanization levels in Taiwan were classified into five strata, with level 1 referring to the 'most urbanized' and level 5 referring to the 'least urbanized' communities, in accordance with prior studies in Taiwan (27).

The 5-year colorectal cancer-free survival rate was computed using the Kaplan–Meier method, and the difference in the risk of colorectal cancer between the two groups was estimated by a log-rank test. In addition, stratified Cox proportional hazard regressions (stratified on age group, sex and year of index hospitalization) were carried out to calculate the hazard of colorectal cancer for these two groups, after adjusting for monthly income, level of urbanization and the geographical location of the sampled patients. The sampled patients were censored if individuals died from non-colorectal cancer causes during the 5-year follow-up period (246 patients had already died, comprising 71 from the study group and 175 from the comparison group). We have tested our data and found that the data meet the proportionality assumption (survival curves for two strata (patients with cryptogenic PLA and patients in the comparison group) have hazard functions that are proportional over time). The differences were considered significant if a two-sided P value was less than or equal to 0.05.

Results

Of the total sample of 1644 patients, the mean age was 53.6 years, with a standard deviation of 17.1 years. Table 1 shows the distribution of the sociodemographic

Table 1. Patients with cryptogenic pyogenic liver abscess and comparison group in relation to sociodemographical characteristics and comorbid conditions in Taiwan, 2001–2003 ($n = 1644$)

	Patients with cryptogenic pyogenic liver abscess ($n = 274$)		Comparison group ($n = 1370$)		
Variables	Number	%	Number	%	*P* value
Gender					1.000
Male	152	55.5	760	55.5	
Female	122	44.5	610	44.5	
Age					1.000
< 45	74	27.0	370	27.0	
45–54	60	21.9	300	21.9	
55–64	54	19.7	270	19.7	
65–74	54	19.7	270	19.7	
> 74	32	11.7	160	11.7	
Monthly income					0.652
0	147	53.7	743	54.2	
NT$1–15 840	23	8.4	132	9.6	
NT$15 841–25 000	79	28.8	352	25.7	
≥NT$25 001	25	9.1	143	10.4	
Urbanization level					0.028
1	45	16.4	245	17.9	
2	40	14.6	251	18.3	
3	21	7.7	137	10.0	
4	32	11.7	93	6.8	
5	136	49.6	644	47.0	
Geographical region					0.239
Northern	178	65.0	929	67.8	
Central	49	17.9	186	13.6	
Southern	45	16.4	235	17.2	
Eastern	2	0.7	20	1.5	
Diabetes					< 0.001
Yes	57	20.8	117	8.5	
No	217	79.2	1253	91.5	
Hyperlipidaemia					0.948
Yes	8	2.9	41	2.9	
No	266	97.1	1329	97.1	
Hypertension					0.464
Yes	51	18.6	230	16.8	
No	223	81.4	1140	83.2	
Coronary heart disease					0.162
Yes	20	7.3	71	5.2	
No	254	92.7	1299	94.8	
Heart failure					0.203
Yes	5	1.8	13	1.0	
No	269	98.2	1357	99.0	
Cerebrovascular disease					1.000
Yes	9	3.3	45	3.3	
No	265	96.7	1325	96.7	
Renal disease					0.009
Yes	10	3.7	19	1.4	
No	96.4	264	1351	98.6	
Diabetes with ophthalmic manifestations					0.654
Yes	1	0.4	3	0.2	
No	273	99.6	1367	99.8	

characteristics and comorbidities between patients with and without cryptogenic PLA. The majority of the patients were male (55.5%), and almost a half (48.9%) were below 54 years of age. After matching patients by age and gender, a significant difference was observed between these two groups in the level of urbanization of the community where the patient resided ($P = 0.028$). In addition, patients with cryptogenic PLA were more likely to have diabetes ($P < 0.001$) and renal disease ($P = 0.009$) than patients without cryptogenic PLA.

Table 2 presents the distribution of colorectal cancer during the 5-year follow-up period for patients with and without cryptogenic PLA. Of the total sample, 40 patients from the study group (2.43%) developed colorectal cancer during the 5-year period, 15 (5.45% of the patients with cryptogenic PLA), and 25 from the comparison group (1.82% of patients without cryptogenic PLA). The log-rank test revealed a significant difference in the 5-year colorectal cancer-free survival rates between patients with and without cryptogenic PLA ($P < 0.001$). Figure 1 displays the results of the Kaplan–Meier survival analysis.

Table 2 also shows the crude and adjusted hazard ratios (HRs) of colorectal cancer within the 5-year period following the index ambulatory care visits. The crude HR for colorectal cancer for patients with cryptogenic PLA was 3.12 [95% confidence interval (CI) = 1.62–5.99, $P < 0.001$] as compared with patients without cryptogenic PLA. Similarly, stratified Cox proportional hazard regressions (stratified on age group, sex and year of index hospitalization) showed that after adjusting for patients' monthly income, the level of urbanization and the geographical location of the patient's community, the HR for colorectal cancer for patients with cryptogenic PLA was 3.36 times as high as the comparison group in the 5-year follow-up period (95% CI = 1.72–6.56, $P < 0.001$). In addition, among cryptogenic PLA patients with and without diabetes, the adjusted hazard of colorectal cancer during the 5-year follow-up period was 5.54 (95% CI = 2.11–14.56, $P < 0.001$) and 2.64 (95% CI = 1.19–5.85, $P < 0.05$) times higher, respectively, than that in the comparison group.

The crude and adjusted HRs for colorectal cancer stratified by patient sex and age are presented in Table 3. Among male and female patients, the adjusted hazard of colorectal cancer during the 5-year follow-up period was 2.82 (95% CI = 1.14–6.99, $P = 0.024$) and 4.08 times greater (95% CI = 1.42–11.73, $P = 0.009$), respectively, for those with cryptogenic PLA than for those in the comparison group. Furthermore, we analysed the risk of colorectal cancer for patients with cryptogenic PLA by age group (< 65 vs. ≥65). We found that the adjusted HR for colorectal cancer during the 5-year period was 3.09 (95% CI = 1.31–7.33, $P = 0.019$) and 3.70 times higher (95% CI = 1.21–11.27, $P = 0.001$) for cryptogenic PLA patients ≥65 years old and < 65 years old, respectively, than that for the same age categories in the comparison group.

Table 2. Crude and adjusted hazard ratio for colorectal cancer during the 5-year follow-up period for patients in Taiwan with cryptogenic pyogenic liver abscess and patients in the comparison group ($n = 1644$)

Presence of Colorectal Cancer	Total sample		Comparison		Cryptogenic pyogenic liver abscess (all)		Cryptogenic pyogenic liver abscess, (with comorbid diabetes)		Cryptogenic pyogenic liver abscess, (without comorbid diabetes)	
	No.	%	No.	%	No.	%	No.	%	No.	%
5-year follow-up period										
Yes	40	2.43	25	1.82	15	5.45	6	10.53	9	4.15
No	1604	97.57	1345	98.18	259	94.53	51	89.47	208	95.85
Crude HR (95% CI)	–		1.00		3.12*** (1.62–5.99)		6.33*** (2.49–16.11)		2.33* (1.07–5.06)	
Adjusted† HR (95% CI)	–		1.00		3.36*** (1.72–6.56)		5.54*** (2.11–14.56)		2.64* (1.19–5.85)	

†Stratified Cox proportional hazard regression was used to stratify by age group and year of index hospitalization and to adjust for monthly income and urbanization level.

*$P < 0.05$.

***$P < 0.001$.

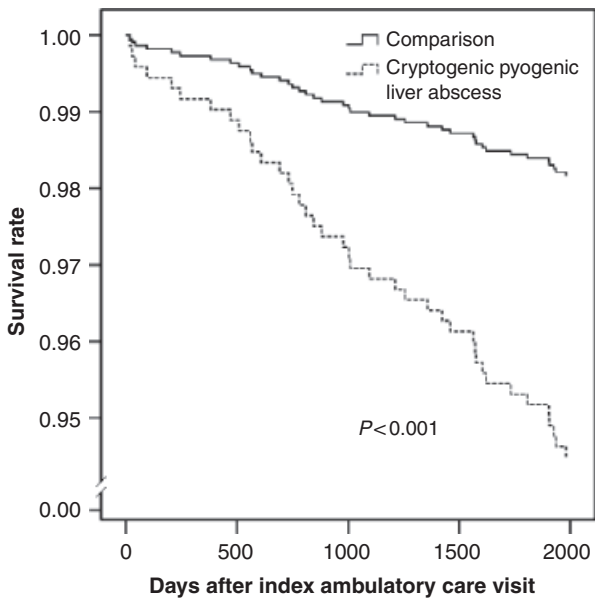

Fig. 1. Colorectal cancer-free survival rates for patients with cryptogenic pyogenic liver abscess and the comparison group in Taiwan, 2001–2003.

Table 4 shows the distribution of concurrent micro-organism diagnoses among patients with cryptogenic PLA according to colorectal cancer. We also found that there was no significant relationship between whether patients had bacteraemia or septicaemia and the risk of colorectal cancer during the 5-year follow-up period among patients with cryptogenic PLA (3.3 vs. 6.0%; $P = 0.393$ respectively).

Discussion

To our knowledge, this is the first attempt to investigate the risk of colorectal cancer following cryptogenic PLA using a nationwide population-based dataset. We found that 5.45% of patients with cryptogetnic PLA, and 1.82% of patients without, developed colorectal cancer during the 5-year follow-up period. The likelihood of developing colorectal cancer was 3.36 times greater among cryptogenic PLA patients than for patients without the condition, during the 5-year follow-up period. Furthermore, cryptogenic PLA patients with diabetes (adjusted HR, 5.54; 95% CI = 2.11–14.56, $P < 0.001$) were also at a higher risk of developing colorectal cancer than such patients without diabetes, relative to the comparison group (adjusted HR, 2.64:95% CI = 1.19–5.85, $P < 0.001$). These findings support our hypothesis that the risk of colorectal cancer is increased following a diagnosis of cryptogenic PLA.

Recent reports assert that cryptogenic PLA might be a presentation of occult or silent colorectal cancer or adenoma without any gastrointestinal symptoms on admission (5, 7, 8, 14). Studies by Cohen *et al.* (6), Nosher *et al.* (28) and Yeh *et al.* (29) revealed that 5% (1/20 patients), 6.7% (1/15 patients) and 11.5% (6/52 patients) of patients with PLA had colorectal cancer respectively. Recently, Hiraoka *et al.* reported that three of 41 patients with PLA had the condition because of colon cancer (12). Colorectal cancer or large adenomas can induce loss of integrity of the normal mucosal barrier (11, 18). The mechanism that explains how colorectal cancer or adenoma can be involved in the aetiology of cryptogenic PLA is probably that mucosal defects offer a route for bacterial invasion into the portal system, which consequently arrives at the liver (11, 18, 30). In addition, in a report from the United Kingdom, one out of four patients with a definitive diagnosis of cryptogenic PLA developed colorectal cancer during a 2-year follow-up period (10). This suggests that colorectal cancer could coexist with or pre-exist cryptogenic PLA. Our study thus confirms prior findings that cryptogenic PLA is a warning sign of colorectal cancer.

In previous reports, multiple hepatic abscesses caused by anaerobic bacteria are the presenting signs of unsuspected colon cancer without liver metastases (13, 14). Several bacteria, such as Bacteroides, anaerobic Streptococcus and *K. pneumoniae* cause PLA with an underlying

Table 3. Crude and Adjusted hazard ratios for colorectal cancer during the five-year follow-up period for patients with cryptogenic pyogenic liver abscess and patients in the comparison group, stratified by patient age and gender

	Patient sex†				Patient age‡ (years)			
	Male		Female		< 65		≥ 65	
Presence of colorectal cancer	Comparison number (%)	Cryptogenic pyogenic liver abscess number (%)	Comparison number (%)	Cryptogenic pyogenic liver abscess number (%)	Comparison number (%)	Cryptogenic pyogenic liver abscess number (%)	Comparison number (%)	Cryptogenic pyogenic liver abscess number (%)
5-year follow-up period								
Yes	16 (2.14)	8 (5.26)	9 (1.45)	7 (5.74)	8 (0.85)	6 (3.19)	17 (3.93)	9 (10.47)
No	732 (97.86)	149 (94.74)	613 (98.55)	115 (94.26)	929 (99.15)	182 (96.81)	416 (96.07)	77 (89.53)
Crude HR (95% CI)	1.00	2.54* (1.07–6.05)	1.00	4.15*** (1.51–11.36)	1.00	3.83* (1.31–11.17)	1.00	2.86* (1.23–6.65)
Adjusted HR (95% CI)	1.00	2.82* (1.14–6.99)	1.00	4.08*** (1.42–11.73)	1.00	3.70* (1.21–11.27)	1.00	3.09* (1.31–7.33)

†Hazard ratio was calculated by Stratified Cox proportional hazard regression which was stratified on age group and year of index hospitalization and adjusted for monthly income, urbanization level and geographical region.
‡Hazard ratio was calculated by Stratified Cox proportional hazard regression which was stratified on sex and year of index hospitalization and adjusted for monthly income, urbanization level and geographical region.
*$P < 0.05$.
***$P < 0.001$.

Table 4. The distribution of concurrent microorganism diagnoses according to colorectal cancer among patients with cryptogenic pyogenic liver abscess ($n = 274$)

Concurrent microorganism diagnosis (ICD-9-CM code)	*n*	Colorectal cancer Yes, *n* (%)
Streptococcus (038.0, 041.0X)	6	0
Staphylococcus (038.1X, 041.1X)	1	0
Pneumococcus (038.2, 041.2)	1	0
Escherichia (038.42, 041.4)	3	0
Klebsiella (041.3)	17	0
Proteus (041.6)	1	0
Gram-negative bacteria (038.40, 038.49, 041.85)	5	1 (20.0)
Other/unspecified bacteria (038.8, 038.9, 041.81)	25	1 (4.0)
None	215	13 (6.0)

diagnosis of colon cancer (9, 14, 15, 31, 32). In our earlier study, we described two cases, one with cryptogenic PLA and *K. pneumoniae* infection and another with diabetes and *K. pneumoniae* infection, which were found to be the presenting manifestation of colonic tubulovillous adenoma (7). These bacteria are colonizers in the human gastrointestinal tract. The defect in the mucosal barrier caused by colorectal cancer or large adenomas predispose to microbial seeding to the portal venous system and into the liver, resulting in abscess formation (11, 18).

Patients with diabetes are known to show defects in neutrophil chemotaxis and phagocytosis, which are thought to be the most important predisposing factors for *K. pneumoniae*-pathogenic liver abscess (33). Our previous survey also showed that diabetes mellitus was a major risk factor for PLA in Taiwanese (21). Similarly, Thomsen *et al.* reported that 11.2% of PLA cases were accompanied by diabetes in the United States (20). In the present study, we found that about 22% of patients with PLA had diabetes. It is proven that diabetes is a risk factor for Gram-negative bacteraemia, including episodes caused by abdominal foci of infection (34). Potential biological mechanisms may include tissue hyperglycaemia and preference for some microorganisms, such as *Escherichia coli* and *K. pneumoniae* (24, 35, 36).

Many risk factors have been identified for colorectal cancer including ageing, a high-fat diet, obesity, familial polyposis syndrome and inflammatory bowel disease. Recent evidence indicates that metabolic abnormalities such as impaired glucose tolerance and diabetes mellitus are also associated with increased incidence of colonic adenoma and cancer (22, 23). One study by Seow *et al.* (37) reported that diabetes was significantly associated with colorectal cancer risk in both men [relative risk (RR) = 1.5, 95% CI = 1.2–2.1] and women (RR = 1.4, 95% CI = 1.0–1.9) in Singapore Chinese. Similarly, a study by Larsson *et al* also showed a significant risk of colorectal cancer (RR 1.49, 95% CI = 1.14–1.96) in Swedish men (38). Metabolic syndrome was found to be

associated with an increased risk of colorectal adenoma (odds ratio, 1.51, 95% CI = 1.18–1.93) in a study by Kim (39). Those studies support our finding that PLA patients with diabetes had a higher risk of developing colorectal cancer during a 5-year follow-up than patients without diabetes (adjusted HR. 5.54 vs. 2.64).

The strengths of this study include its large nationwide population-based sample, the availability of data on patients with a wide range of demographic characteristics and complete histories of medical service utilization for the sampled patients. Although we tried to overcome the inherent limitations of using administrative data, this study suffers from two limitations that should be addressed. The first is the lack of detailed information on body mass index data, smoking, alcohol use, a physically active or a sedentary lifestyle, high-fat diet and a family history of colorectal cancer, all of which have been shown to be associated with the risk of colorectal cancer. In addition, microbiological data that might be related to the risk for colorectal cancer were also unavailable in our dataset.

Secondly, there may be a surveillance bias in that patients with a cryptogenic PLA diagnosis are likely to have more frequent check-ups, and thus to have their colorectal cancer detected by a physician. Indeed, we found that 19.3% of the patients with cryptogenic PLA and 8.2% of the patients without had received endoscopic procedures or faecal testing analysis during the 5-year follow-up period respectively. Therefore, it is possible that receiving medical attention for cryptogenic PLA may contribute to the elevated odds of being diagnosed with colorectal cancer.

Conclusions

Despite the above limitations, we have found that during a 5-year follow-up period, the risk for colorectal cancer was 5.54 times higher than the comparison group among cryptogenic PLA patients and 2.64 times higher for PLA patients without diabetes. Furthermore, the odds of colorectal cancer were 4.08 times higher for females with cryptogenic PLA than the comparison group and 2.82 times higher among males with cryptogenic PLA. Our findings revealed that cryptogenic PLA is an alarm suggesting colorectal cancer, especially for those with diabetes and females. We suggest that the patients with cryptogenic PLA, an underlying cause of gastrointestinal tract, should be surveilled aggressively; we therefore recommend that diabetes patients with cryptogenic PLA undergo a survey of the colon to detect the presence of neoplasms.

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