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Meta-Analysis

Prevalence of colorectal cancer in cryptogenic pyogenic liver abscess patients. Do they need screening colonoscopy? A systematic review and meta-analysis

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ABSTRACT

Background: Cryptogenic pyogenic liver abscess (PLA) could result due to compromised colonic mucosal barrier in patients with colorectal cancer (CRC). Association of PLA and CRC is unclear. Evidence is weak and limited to small sized studies. As a result, the need for colonoscopy in PLA patients is debatable.
Methods: We conducted a comprehensive search of multiple electronic databases and conference proceedings (from inception through January 2019) to identify studies that reported on the prevalence of CRC in PLA patients. Our goals were to evaluate the pooled rate of CRC in patients with cryptogenic PLA.
Results: 12 studies were included in the analysis. 18,607 patients were diagnosed with PLA in study group and 60,130 patients were in control group. 63% were males in the age range of 56–94 years. 90.5% of the colonic lesions were left sided and 93.1% were positive for *Klebsiella pneumoniae*. The pooled rate of prevalence of CRC was 7.9% (95% CI (confidence interval) 5–12.1, $I^2 = 92.4$, relative risk = 6.6) in patients with PLA, as compared to 1.2% (95% CI 0.3–5.7, $I^2 = 93.4$) in control, with statistical significance ($p = 0.001$ respectively).
Conclusion: Our study, albeit limited by heterogeneity, demonstrates that patients with cryptogenic PLA are at a 7-fold risk of having CRC. A screening colonoscopy may be considered in population with cryptogenic PLA, especially if positive for *K. pneumoniae*. Well-conducted studies are needed to answer this question.

1. Introduction

Pyogenic liver abscess (PLA) is a serious condition frequently seen in malnourished and immune-compromised patients. PLA is most often caused by pathogens entering the liver due to loco-regional spread. Ascending cholangitis and appendicitis are well-established etiologies that result in portal vein seeding of the microbes [1]. The frequency of PLA due to cholangitis and/or appendicitis has significantly decreased with the use of effective diagnostic imaging and early administration of appropriate antibiotics with more invasive treatment as needed [1,2]. However, a recent US-population based study revealed that the incidence of PLA has increased more than 2-fold during the past 35 years [2].

A considerable proportion of PLA patients do not have a definite source of infection: this subset of patients are referred to as having cryptogenic PLA. While the precise mechanism behind cryptogenic PLA is not well known, one of the possible routes of infection in such patients could be disruption of colonic mucosal barrier with resultant translocation of the bacteria via the portal vein. Colorectal cancer (CRC) is potential cause of such a disruption and prior data

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suggest that PLA formation could be an early manifestation of CRC [1,3].

Debate exists whether a screening colonoscopy is warranted in patients with cryptogenic PLA. The association of PLA with CRC is unclear given the results of the available literature on the subject. We conducted this systematic review and meta-analysis to calculate the pooled rates of prevalence of CRC in patients diagnosed with PLA, and sought to find evidence to support and/or refute the need for a screening colonoscopy in this patient population.

2. Methods

2.1. Search strategy

We conducted a comprehensive search of several databases and conference proceedings including PubMed, EMBASE, Google-Scholar, Scopus, LILACS, and Web of Science databases (earliest inception to January 2019). We followed the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4], by using predefined protocol, to identify studies reporting on the prevalence of colonic neoplasms in patients with cryptogenic PLA. An experienced medical librarian helped with the literature search.

Key words used in the literature search included a combination of 'pyogenic liver abscess', 'liver abscess', 'cryptogenic liver abscess', and 'colorectal cancer', 'colorectal neoplasia', 'colorectal adenoma'. The search was restricted to studies in human subjects and published in English language in peer-reviewed journals. Two authors (B.M, V.M.) independently reviewed the title and abstract of studies identified in primary search and excluded studies that did not address the research question, based on pre-specified exclusion and inclusion criteria. The full text of remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus, and in discussion with a co-author.

The bibliographic section of the selected articles, as well as the systematic and narrative articles on the topic were manually searched for additional relevant articles.

2.2. Study selection

In this meta-analysis, we included studies that reported on the prevalence of colorectal neoplasia in patients diagnosed with PLA. Studies irrespective of prospective or retrospective design, the methodology of cancer detection (computed tomography colonography, surgery, and/or colonoscopy), country of study, and abstract/manuscript status, were included as long as they provided adequate data needed for the analysis.

The following were our exclusion criteria: (1) single patient case reports, (2) cancer of other GI site with no information on colorectal neoplasia, (3) studies in pediatric (<18 years) population, and (4) studies not published in English language.

In case of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were included.

2.3. Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form independently by at least two authors (V.M., S.K.), two authors (B.M., S.C.) independently cross-checked the data for errors, and two authors (B.M., S.K.) did the quality scoring independently.

In the situation of randomized trials, and case-control studies, the data collection was done as number of reported events (n) out of total number of patients (N) from each study. The collected data was treated akin to cohort studies and therefore we used the Newcastle-Ottawa scale for cohort studies to assess the quality of studies [5]. This quality score consisted of 8 questions: representative of the average adult in the community (1 point for population-based studies, 0.5 point for multi-center studies, 0 point for a single-center hospital-based study); cohort size (1 point for >40 patients, 0.5 point for 39–20, and 0 point for <20 patients); information on technical and clinical success (1 point if reported, 0.5 point if derived from percentage value, 0 point if not reported); outcome not present at start of study (1 point if not present, 0 point if present); factors comparable between other stents (1 point if yes, 0 point if no); adequate clinical assessment (1 point if yes, and 0 point if no); follow-up time (1 point if yes, 0 point if not mentioned); and adequacy of follow-up (1 point if all patients were accounted for, 0.5 point if <50% patients lost to follow up, 0 point if >50% patients lost to follow up). A score of ≥7, 4.1 to 6.9, and ≤4 were considered suggestive of high-quality, medium-quality and low-quality study, respectively.

2.4. Outcomes assessed

1 Pooled rate of prevalence of CRC in PLA vs control.

2.5. Statistical analysis

Meta-analysis was done using the random-effects model to calculate the pooled estimates following the methods suggested by DerSimonian and Laird [6]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [7]. We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity, 95% prediction interval (PI), which deals with the dispersion of the effects [8,9], and the I^2 statistics [10,11]. In this, values of <30%, 30%–60%, 61%–75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [12]. Publication bias was ascertained by funnel plot and quantitatively by the Egger test [13]. When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's 'Trim and Fill' test was used to ascertain the impact of the bias [14]. Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there were no bias. The impact was reported as minimal if both versions were estimated to be same, modest if effect size changed substantially but the final finding would still remain the same, and severe if basic final conclusion of the analysis is threatened by the bias [15].

All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

3. Results

3.1. Search results and population characteristics

From an initial total of 132 studies, 54 records were screened and 45 full-length articles were assessed. 12 studies were included in the final analysis [3,16–26].

The schematic diagram of study selection is illustrated in Supplementary Fig. S1. Baseline study and population characteristics are summarized in Table 1.

Included patients were between 56 to 94 years, with a mean age of 67 years. The majority of patients were male (63%). Left sided colon lesions (90.5%) were more common than right, and *Klebsiella pneumoniae* (93.1%) was the most common organism cultured from PLA patients.

Table 1
Study and patient characteristics.

Name of study	Study design	Age	Sex (M/F)	Total PLA	Total N (PLA patients with evaluation for colorectal neoplasm)	Colorectal cancer	Follow up time	Colon site	Most common organism
Chen et al. [16]	Retrospective, 2004–2008, single center, Taiwan.	57.5 (41–76)	NR	425	170	3	5 years	NR	9 *Klebsiella*, 1 *E. coli*
Heo et al. [17]	Prospective, January 2014–October 2015, multicenter, Korea.	62 (20–94)	64/37	101	62	0	NR	NR	63 *Klebsiella*, 3 *Streptococcus*, 1 *E. coli*
Hiraoka et al. [18]	Retrospective, single center, 1990–2005, Japan	67.4 ± 14	20/21	41	41	3	NR	3 left	3 *Klebsiella*
Huang et al. [19]	Retrospective, January 2000 and December 2009, single center, Taiwan.	56.6 ± 13.2	1506/788	2294	2294	54	11 years	54 left	1194 *Klebsiella*
Jang et al. [20]	Retrospective, July 2005 and July 2012, single center, Korea	57.8 ± 14.1	47/21	68	68 (CT colonography group)	8	40 ± 20.3	NR	72 *Klebsiella*, 8 *Bacteroides*, 2 *E. coli*
		59.2 ± 13	28/13	41	41 (colonoscopy group)	6	47.5 ± 31.2		
Jeong et al. [21]	Retrospective, May 2003 and May 2010, single center, South Korea.	60.7 ± 12.8	120/110	230	37	8	38.7 ± 32.3M	4 right, 4 left	73 *Klebsiella*, 29 *E. coli*
Koo et al. [22]	Retrospective, single center, January 2001 and April 2010, Korea	63.49 (27–94)	103/60	268	163	12	NR	4 right, 16 left	85 *Klebsiella*, 14 *E. coli*
Lai et al. [3]	Retrospective, population based, 2000– 2007, Taiwan	1487 < 40 yrs, 2386 40–49 yrs, 3539 50–59 yrs, 7278 > 60 yrs	9251/5439	14,690	14,690	510	NR	NR	NR
		5948 < 40 yrs, 9544 40–49 yrs, 14,156 50–59 yrs, 29,112 > 6 yrs	37,004/21,756	NA	Control 58,760	484			
Lai and Lin [23]	Retrospective, single center, January 2001–December 2003, Taiwan	53.6 (17.1)	152/122 760/610	274 NA	274 Control 1370	15 25	5 years	NR	17 *Klebsiella*, 6 *Streptococcus*, 3 *E. coli*
Mezhir et al. [24]	Retrospective, single center, January 1998–May 2009, USA (United States of America)	30 pts >60 yrs	33/25	58	58	7	NR	NR	20 *Streptococcus*, 13 *E. coli*, 12 *Klebsiella*
Mohse et al. [25]	Retrospective, single center, April 1988–December 1999, UK	64yrs	37/28	65	65	16	10 years	NR	11 *E. coli*, 3 *Pseudomonas*, 1 *Klebsiella*
Yeh et al. [26]	Retrospective, single center, January 1980–December 1993, Taiwan	56.4 ± 2.8	29/23	52	52	6	NR	NR	NR

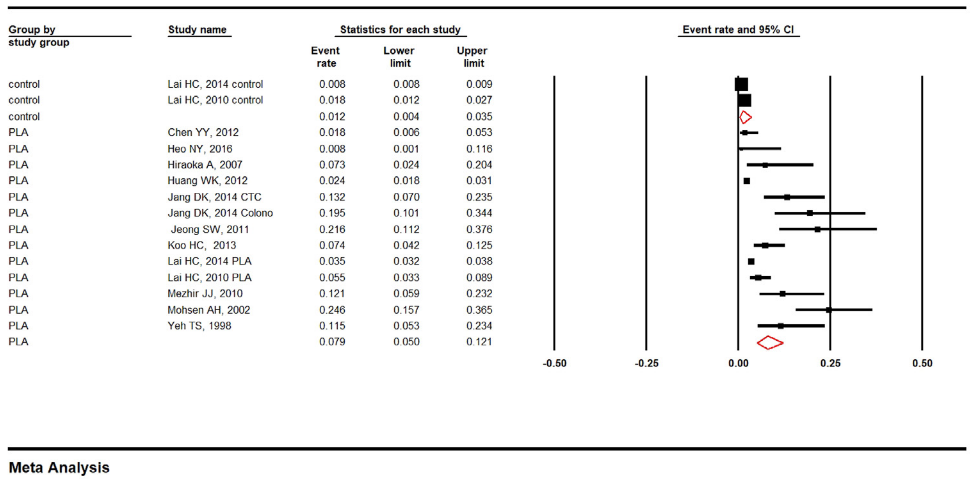

Fig. 1. Forest plot.

From the 12 studies included for analysis, a total of 18,607 PLA patients were reported, of which 17,906 PLA patients underwent screening for colorectal neoplasm. A total of 713 cases of colorectal lesions were found, of which 648 were diagnosed with CRC. 60,130 patients were used as control group, of which 509 patients were diagnosed with CRC.

3.2. Characteristics and quality of included studies

Of the 12 studies, one was population based [3], one was prospectively conducted [17], and the rest were retrospective in nature. All studies were based out of East Asian countries except two, one from USA [24] and one from UK (United Kingdom) [25]. Based on the New-Castle Ottawa scoring system to assess the quality of studies, eight studies were considered of high quality [3,16,17,19–21,23,25] and the rest were of medium quality. There were no low quality studies in this analysis. The detailed assessment of study quality is given in Supplementary Table S1.

3.2.1. Definitions and procedure descriptions

A diagnosis of PLA was made based on the presence of clinical signs of fever with or without chills, abdominal pain, abdominal tenderness, and nausea and/or vomiting, along with imaging findings. Computed tomography and/or ultrasonography was the preferred imaging technique used to evaluate a PLA.

In the majority of PLA cases, colonoscopy was the preferred modality to ascertain the presence or absence of CRC. In the study by Jang et al., 68 patients underwent a CT colonography to evaluate the colon [20]. Colonoscopy procedure was performed under sedation-analgesia with the help of an anesthetist.

3.3. Prevalence of CRC in PLA patients

The pooled rate of prevalence of CRC in PLA patients was 7.9% (95% CI 5–12.1, $I^2 = 92.4$) as compared to 1.2% (95% CI 0.4–3.5, $I^2 = 93.4$) in controls. The difference was statistically significant, p = 0.001. (Forest plot, Fig. 1) (Relative risk = 6.6)

4. Validation of meta-analysis results

4.1. Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

4.2. Heterogeneity

Heterogeneity was noted in our analysis. We assessed dispersion of the calculated rates using the prediction interval (PI) and I^2 percentage values. The PI gives an idea of the range of the dispersion and I^2 tell us what proportion of the dispersion is true vs chance [30]. The PI for CRC was 1.3–35.5, $I^2 = 92.4$.

4.3. Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias (Egger's p-value = 0.01). Based on further statistics, no change was noticed on the overall pooled rates after adjustments for the biased studies (Supplementary Fig. S2).

5. Discussion

To the best of our knowledge, this study is the only meta-analysis reporting on the prevalence of CRC in patients with cryptogenic PLA. From a total of 12 good quality studies [3,16–26], that evaluated 78,737 participants (18,607 PLA patients and 60,130 controls), we report a pooled CRC rate of 8% in patients with cryptogenic PLA. Patients with cryptogenic PLA are at an increased risk of CRC and may be considered to undergo screening to look for malignancy.

Disruption of the mucosal barrier created by the tumor in patients CRC serves as a potential route for bacterial invasion into the portal venous system with subsequent spread to the liver [3]. Despite the growing body of evidence, there are no current guidelines suggesting the need for a screening colonoscopy in patients diagnosed with PLA and this matter remains a topic of debate. A large Taiwanese population-based study by Lai et al., reported a CRC incidence rate of 8.85 per 1000 person-years in men and 10.77 per 1000 person-years in women [3,27]. The current trend in some East Asian countries, like Taiwan, shows that patients diagnosed with PLA should be evaluated for potential occult CRC [27].

Based on our analysis, 8% of patients diagnosed with PLA did have CRC. The value was statistically significant when compared to the prevalence of CRC in patients without PLA (1.2%, p = 0.001). In terms of relative risk, the risk of having a CRC is increased approximately 7-fold in patients with PLA when compared to patients without PLA. This is the key finding of our study, and supports the need for a screening colonoscopy in patients diagnosed with PLA, especially when the source of infection is not obvious. The age range of patients included in our analysis was between 56 to 94 years. We, however, were not able to assess the effects of age as a predictive factor on the reported outcome and therefore cannot comment if a screening colonoscopy would be of use in a younger patient with PLA.

A qualitative review published on this topic reported that 80% of the cases diagnosed with PLA who had CRC were from eastern Asian countries and the most common pathogen causing PLA was *K. pneumoniae*. 41% of CRC tumors were identified in the sigmoid colon followed by 27% in the rectum [28]. Our results are comparable to this report and it is important to note that the majority of our included studies are also from eastern Asian countries. Latest global cancer statistics estimates the incidence of CRC to be more than two-folds in Caucasian population as compared to east Asian population [29]. Therefore, the applicability of this data to Caucasian population is very important.

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good quality studies with detailed extraction of data, rigorous evaluation of study quality, and statistics to establish and/or refute the validity of the results of our meta-analysis. With meta-analysis methods, the results of various study population has been combined to derive a global pooled value thereby improving the overall quality of evidence.

There were limitations to this study, most of which are inherent to any meta-analysis. Majority of the included studies were retrospective in nature and based out of single centers. Therefore, the risk of selection bias was unavoidable and the studies may not have been entirely representative of the general population and a community gastroenterology/hepatology practice. Heterogeneity with wide prediction-interval was noted. Probable reasons are due to the variability in the clinical presentation of PLA, and the variability in the guidelines used to define the performance of CRC screening.

We were unable to analyze the predictive role of patient related factors like age, presence of diabetes, and smoking history but several questions remain unanswered. We were unable to assess the risk of CRC based on the location and size of PLA, due to limited data. Is CRC and PLA a problem solely of the East Asian population? Do all patients with *K. pneumoniae* positive PLA need a colonoscopy? An 11-year follow-up study by Huang et al., showed that patients older than 60 years with a *Klebsiella* positive PLA were found to have a higher rate of CRC when compared to non-*Klebsiella* PLA patients [19].

In conclusion, our meta-analysis demonstrates that patients with cryptogenic PLA have a 7-fold risk of having CRC, when compared to people without PLA. Although limited by heterogeneity, our results seem to support the need for a screening colonoscopy in patients diagnosed with cryptogenic PLA, especially if positive for *K. pneumoniae*.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.08.016.

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