Systematic Review and Meta-Analysis

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Mesenteric panniculitis does not confer an increased risk for cancers

A systematic review and meta-analysis

Ikram Hussain, MBBS, MRCP[a,*], Saba Ishrat, MBBS, FRCS[b], Veeraraghavan Meyyur Aravamudan, MBBS, MRCP[c], Shahab R. Khan, MBBS[d], Babu P. Mohan, MD[e], Rahul Lohan, MBBS, FRCR[f], Muhammad Bilal Abid, MD, MRCP[g], Tiing Leong Ang, MBBS, FRCP[h]

Abstract

Background: Mesenteric panniculitis (MP) is a non-specific, localized inflammation at the mesentery of small intestines which often gets detected on computed tomography. An association with malignant neoplasms remains unclear. We performed a systematic review and meta-analysis to examine the association of malignancy with MP.

Methods: MEDLINE, EMBASE, Web of Science, and Cochrane databases were searched for articles published from inception to 2020 that evaluated the association of malignant neoplasms with MP in comparison with control groups. Using random-effects method, a summary odds ratio (OR) estimate with 95% confidence intervals for malignant neoplasms in MP was estimated.

Results: Four case-control studies reporting data on 415 MP patients against 1132 matched-controls met inclusion criteria and were analyzed. The pooled OR for finding a malignant neoplasm in patients with MP was 0.907 (95% CI: 0.688–1.196; $P = .489$). The heterogeneity was mild and non-significant. Also, there was no heightened risk of any specific type of malignancy with MP. Three more case-series with unmatched-control groups (MP: 282, unmatched-controls: 17,691) were included in a separate analysis where the pooled OR of finding a malignant neoplasm was 2.963 (95% CI: 1.434–6.121; $P = .003$). There was substantial heterogeneity in this group.

Conclusion: This meta-analysis of matched controlled studies proves absence of any significant association of malignant neoplasms with MP. Our study also demonstrates that the putative association of malignancy with MP is mainly driven by uncontrolled studies or case-series.

Abbreviations: CT = computed tomography, MP = mesenteric panniculitis, OR = odds ratio.

Keywords: malignancy, mesenteric panniculitis, meta-analysis, misty mesentery, systematic review

1. Introduction

Mesenteric panniculitis (MP) is a non-neoplastic, localized fibro-inflammatory condition which affects the adipose tissue of the small bowel mesentery.[1] The condition generally gets incidentally detected on a cross-sectional imaging of the abdomen where its diagnosis is made based upon a variety of radiological features.[2] Besides being asymptomatic at times, the condition can produce a variety of systemic (e.g., fever, malaise, loss of weight, or appetite) and/or abdominal symptoms (e.g., diarrhoea, pain).[3] Importantly, its etiology and pathogenesis

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[a] Division of Gastroenterology, Department of Medicine, Woodlands Health Campus, Singapore, [b] Singapore National Eye Centre, Singapore, [c] Department of Medicine, Woodlands Health Campus, Singapore, [d] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [e] Division of Gastroenterology, Hepatology and Nutrition, University of Utah, UT, [f] Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Singapore, [g] Divisions of Infectious Diseases & Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI, [h] Department of Gastroenterology and Hepatology, Changi General Hospital, SingHealth, Singapore.

[*] Correspondence: Ikram Hussain, Division of Gastroenterology, Department of Medicine, Level 5, Tower E, 2 Yishun Central 2, 768024, Singapore (e-mail: ikram_hussain@whc.sg).

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remain unknown though several etiologies (e.g., autoimmune, paraneoplastic phenomenon, aberrant fibroinflammatory reaction, etc) have been postulated and are consequently searched for. Several studies[4–6] have also proposed an association between MP and an underlying malignancy (e.g., non-Hodgkin lymphoma, carcinomas of large bowel, genitourinary malignancies, etc).

Since the year 1974 when Kipfer et al reported 30% cases of malignancy in their cohort of patients with MP, many other authors have similarly published a range of malignant lesions in patients with MP[6–9] This has led some to speculate a paraneoplastic pathogenesis for MP. However as is the case with retrospective case-series, these studies suffer from numerous biases as MP usually occurs in relatively older populations where the detection of concomitant malignancy might be due to aging or from the fact that these point estimates were not compared against any other group. In the first case-control study to assess such association, Gögebakan et al[10] apparently found that the risk of malignancy was not different in patients with MP when compared with another matched cohort of patients undergoing computed tomography (CT). The only systematic review by Halligan et al,[11] which aimed to determine the pooled estimate of prevalence of malignancy in patients with MP, failed to undertake a meta-analysis. In line with the authors' conclusion, an association of MP with malignancy remained uncertain. In this study, we decided to undertake a different methodological approach, as will be discussed later, while conducting systematic review and meta-analysis to estimate the odds of having a malignant neoplasm in patients who get diagnosed with MP.

2. Methods

This systematic review was performed as per guidance given in the Cochrane Handbook for Systematic Reviews for Interventions[12] and was reported according the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[13] Approval from our institutional review board was not necessary for the purpose of this systematic review.

2.1. Literature search

Two authors (SI and VMA) undertook independent comprehensive search for articles from several databases and conference proceedings (MEDLINE, EMBASE, Web of Science, and Cochrane databases). The articles were searched from inception of these databases till March 2020. Both medical subject headings and free texts, along with their various combinations, were used in the search strategy. The key words included "peritoneal panniculitis," "panniculitis," "mesenteric panniculitis," "retractile mesenteritis," "neoplasm," "lymphoma," "malignancy," "cancer," "tumour." No restrictions were applied for the literature search.

Two authors (SI and VMA) independently reviewed the titles and abstracts of extracted studies. In this primary search, only studies which appeared to match the pre-determined inclusion and exclusion criteria (as detailed later) were extracted. The full texts of the extracted studies were read to determine relevancy to the current study. In case of any difference in opinions pertaining to the inclusion of a study, this was discussed with a third author, who was the senior author (IH) who made the final decision after discussion. Finally, the lists of references of the selected studies were manually scrutinized for any additional relevant study.

2.2. Selection of studies

In this systematic review, we included studies when the following criteria were met: if the studies identified patients with MP based on pre-specified radiological criteria, if the numbers of patients with malignancies (either already known or diagnosed at the time of CT or diagnosed within a specified follow-up period) were reported, if the studies either reported numbers of malignant lesions in the control group or when such numbers could be deduced from the patients who underwent CT but did not have diagnosis of MP. We did not include studies published only in abstract forms or in conference proceedings. If there was suggestion of multiple publications from the same or overlapping group of patients (e.g., studies arising from the same hospital database), we decided to include the data only from the most comprehensive study.

We used the following exclusion criteria: if a study did not have estimation of malignancy in a control group, or if a study included <10 patients.

2.3. Abstraction of data

The data from the included studies were independently extracted and collated on a standardized form by 2 authors (SK and SI). Another author (IH) examined the data for any error and finally, 2 authors (IH and SI) independently scored the quality of studies. The following data was collated from each study: the year of publication, the country of study, type of study, time period of study, location of the study (i.e., hospital based or population based), the source of data (e.g., hospital diagnostic indices, radiological database, etc), the number of patients screened, radiological criterial for identification of MP, the number of patients identified with MP, gender of patients with MP, age of patients with MP, type of control arm (matched or unmatched), methodology for matching of controls, number of total patients with malignancies in each arm and number of respective types of malignancies in patients with MP. For some studies which reported the data for malignant lesions in patients who were screened for but were not found to have mesenteric panniculitis, we collated the data from this group of the study after calculation.

2.4. Assessment of quality of the included studies

We used the Newcastle-Ottawa scale[14] to rate quality of individual studies. This well-established scale assesses each case-control study across 3 categories: selection (4 questions), comparability (1 questions) and exposure (3 questions). Although each study is reported separately on 3 separate categories, final score ranging between 0 and 8 for each study. Scores of ≥ 7, 5–6, and ≤ 4 translate into "high-quality," "medium-quality," and "low-quality," respectively. Moreover, an extra item was added to assess radiological methodology for diagnosis of MP, for following features in the study: well described criteria for diagnosis of MP; >1 independent readers; and reporting good inter-assessor concordance.

2.5. Aim

Our primary aim was to determine the odds ratio (OR) of having a diagnosis of malignancy in patients who were diagnosed with MP when compared with a group of matched controls. As secondary outcomes, we decided to estimate the same OR in studies where controls were not matched and then in all studies combined together.

2.5.1. Statistical analysis. For each study, the data for the malignancies in patients with MP was extracted as OR. Given the expected heterogeneity in the effect-sizes, we decided to perform the meta-analysis using random-effects model[15] based upon the method described DerSimonian and Laird.[16] The heterogeneity among the studies was assessed using 2 methods[17]: Cochran *Q* statistic which takes into account the overall variance of effect sizes, with subsequent assessment of statistical significance of such heterogeneity (as the tests for heterogeneity have low power, a *P*-value of <.10 was taken as suggestive of significant heterogeneity); the inconsistency index (I^2) which depicts the proportion of true heterogeneity among studies from the overall heterogeneity (conventionally, the I^2 values of <30%, 30% to 59%, 60% to 75%, and >75% are considered to represent low, moderate, substantial, and considerable heterogeneity, respectively). A priori decision was taken to also conduct separate meta-analyses of studies which explicitly had matched controls (matched studies) in their designs and for studies where such control arms (unmatched studies) was deduced from their texts. Due to the varied (and sometimes unreported) data, we decided not to conduct meta-analysis on individual types of malignancies (e.g., hematological malignancies, solid neoplasms, etc). The publication bias was ascertained quantitatively using Egger regression test and qualitatively using funnel plots.

All analyses were performed using Comprehensive Meta-analysis (CMA) software, version 3 (Biostat Inc., Englewood, NJ).

3. Results

3.1. Results of literature search

The preliminary search using the above-mentioned strategy yielded a total of 5709 articles, from which 42 studies were selected for review of the full text (see Fig. 1 for PRISMA

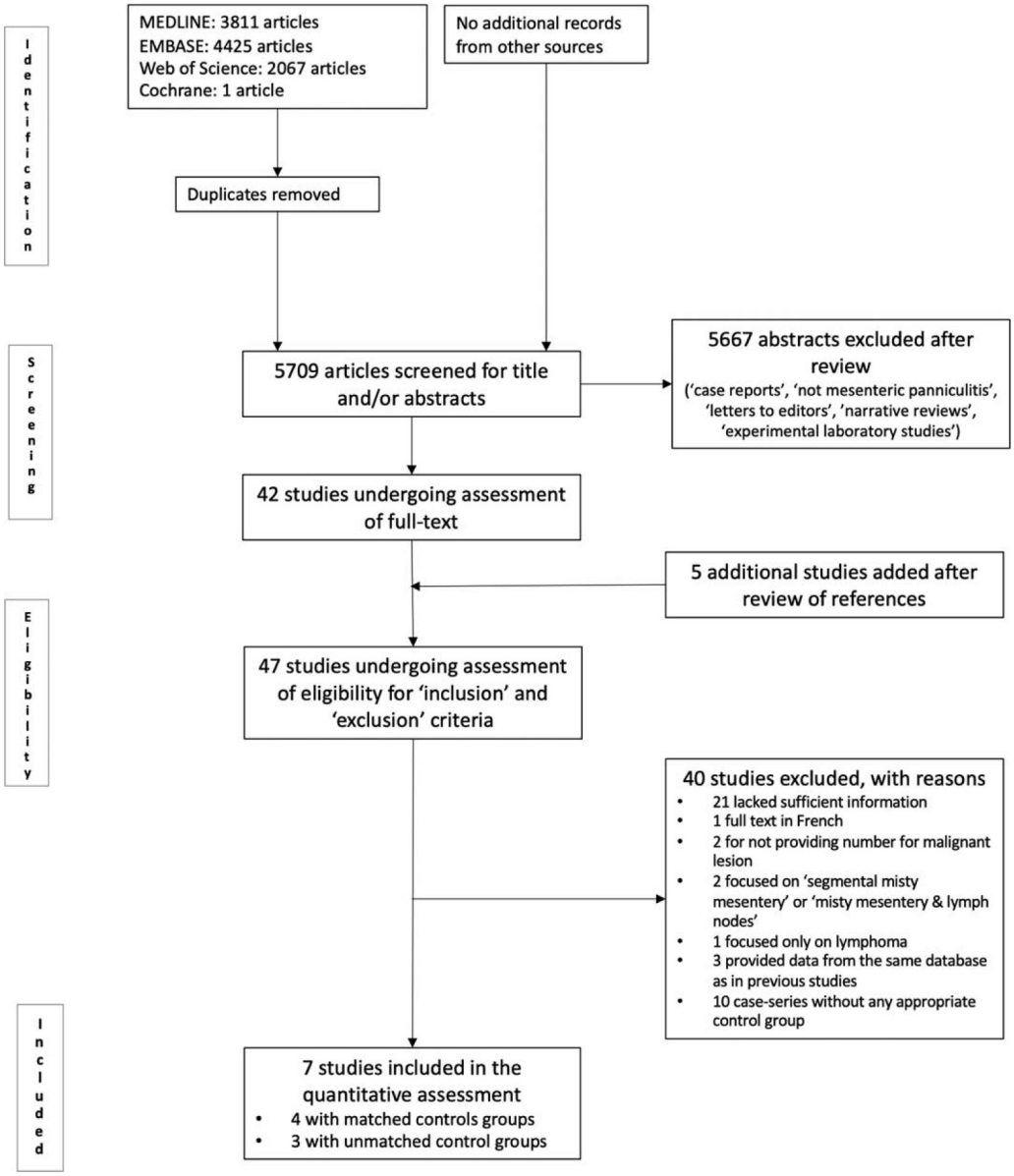

Figure 1. PRISMA flow chart of included studies. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

flowchart). An additional 5 studies were manually added after screening of the references of the 42 studies. After careful application of the pre-defined criteria, 7 studies were included in the final meta-analysis of concomitant malignancy. Four studies had pre-defined control groups who were matched for various confounders. Among these 4, the study by Gögebakan et al[10] controlled for age, gender, year of CT, protocol of CT, diameter of abdomen, and comorbidities; 2 studies[18,19] only matched controls for age and gender; while 1 study[20] matched for age, gender, and comorbidities. Three more studies[5,8,21] could provide data for the estimation of prevalence of malignancy in all patients who were screened for MP and for the patients who were actually diagnosed with MP, thereby allowing estimation of OR of finding malignancy in the MP. These 3 studies were not explicitly designed to be case-control studies and were therefore also separately treated in the subgroup of "unmatched" studies. The report by Khasminsky et al[22] was also case-controlled, but had an opposite question to compare the prevalence of MP in patients with lymphoma, and therefore was not relevant to current study.

3.2. Population characteristics

The period of diagnoses of MP in the selected studies ranged from January 1995 to December 2014. These 4 matched-control studies had 415 patients with MP against 1132 patients in control arms. The 3 studies with unmatched control arms had 282 patients with MP against 17,691 patients in control arms. Overall, there were 697 cases of MP in all studies. Among all patients with MP, the mean age ranged between 63.7 and 69.9 years and 61% were men (425 men, 272 women). All studies used CT scans of the abdomen with pre-specified respective criteria to diagnose MP. Table 1 (and Table S1, Supplemental Digital Content, http://links.lww.com/MD/G675) summarized the population characteristics of included studies.

3.3. Quality of included studies

Geographically, 5 studies originated from Europe, 1 study was from the United States, and 1 study was from Jordan. With no population-based study, all studies captured diagnoses of MP from the radiological databases of their respective centers. When assessed with New-Castle Ottawa scale (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G676), 3 studies were estimated to be of high quality, 1 of medium-quality and 3 were of low quality. The 3 "low quality" studies were expected to have low scores on Newcastle-Ottawa scale as these were not actually intended to be case-control studies but were treated like this for the current study.

3.4. Methodology to identify malignancy

The information for the diagnosis of any malignancy was retrospectively assessed from the patients' records. Out of 7 studies, only 4 studies[10,18–20] screened patients' future records for collection of information about malignancy (for next 4–5 years). In the light of lack of established protocols, the search for underlying malignancy rested upon physicians' judgments supported by patients' clinical features.

3.5. Odds of having malignancy in patients with the MP in studies with matched controls

Based on the 4 studies with matched controls (MP: 415; controls: 1132), the pooled estimate of OR was 0.907 (95% CI: 0.688–1.196; $P = .489$) for finding a malignant neoplasm (Fig. 2). Moreover, the effect sizes among these 3 studies had "low" inconsistency ($I^2 = 28.23$), this heterogeneity was not statistically significant (Cochran Q-value: 4.18, $P = .243$). When individual sub-types of malignancies (gastro-intestinal, lung, hematological, genitourinary, and breast malignancies) were compared, no increased risk of any specific malignancies with MP was identified (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G672).

3.6. Odds of having malignancy in patients with the MP in studies with unmatched controls

Among these 3 studies where there were no matched controls, we treated the patients who did not have MP from the original screened radiological database as controls. The pooled estimate of OR (MP: 282, unmatched controls: 17,691) among these studies was 2.963 and was statistically significant (95% CI: 1.434–6.121; $P = .003$) (Fig. 3). Also, there was substantial inconsistency among the effect sizes ($I^2 = 85.85$) with statistically significant heterogeneity (Cochran Q-value: 14.13; $P < .001$).

3.7. Odds of having malignancy in patients with the MP among all studies

When all 7 studies were combined (MP: 697, controls: 18,223), the OR for finding a malignancy was 1.506 but this was not statistically significant (95% CI: 0.817–2.77, $P = .19$) (Fig. 4).

Table 1

Characteristics of included studies.

Author, year	Country	Time period	Patients undergoing screening of CT records	No. of malignancies/No. of mesenteric panniculitis	No. of malignancies/No. of controls	Variables for which control groups were matched*
O. Gogebakan, 2013[10]	Germany	Jan 2010–Oct 2012	13,458	39/77	93/152	1, 2, 3, 4, 5, 6
N.V. Putte-Katier, 2014[18]	The Netherlands	Jan 2006–Jan 2007	3820	53/94	94/188	1, 2
L. Protin-Catteau, 2016[19]	France	Jan 2008–Aug 2008	3054	58/96	114/192	1, 2
M Deskalogiannaki, 2000[8]	Greece	Jan 1995–Mar 1998	7620	34/49	3983/7571	None
F. Scheer, 2016[5]	Germany	Jan 2010–Dec 2013	5595	107/143	1867/5452	None
W.S. Mahafza, 2017[21]	Jordan	Jan 2012–Dec 2014	4758	28/90	827/4668	None
S.G. Marcus, 2018[20]	USA	Jan 2001–Dec 2010	NR	76/148	343/600	1, 2, 6

CT = computed tomography, NR = not reported.

* Variables for which controls were matched for: (1) age, (2) gender, (3) year of CT, (4) protocol for CT, (5) abdominal diameter, (6) co-morbid illnesses.

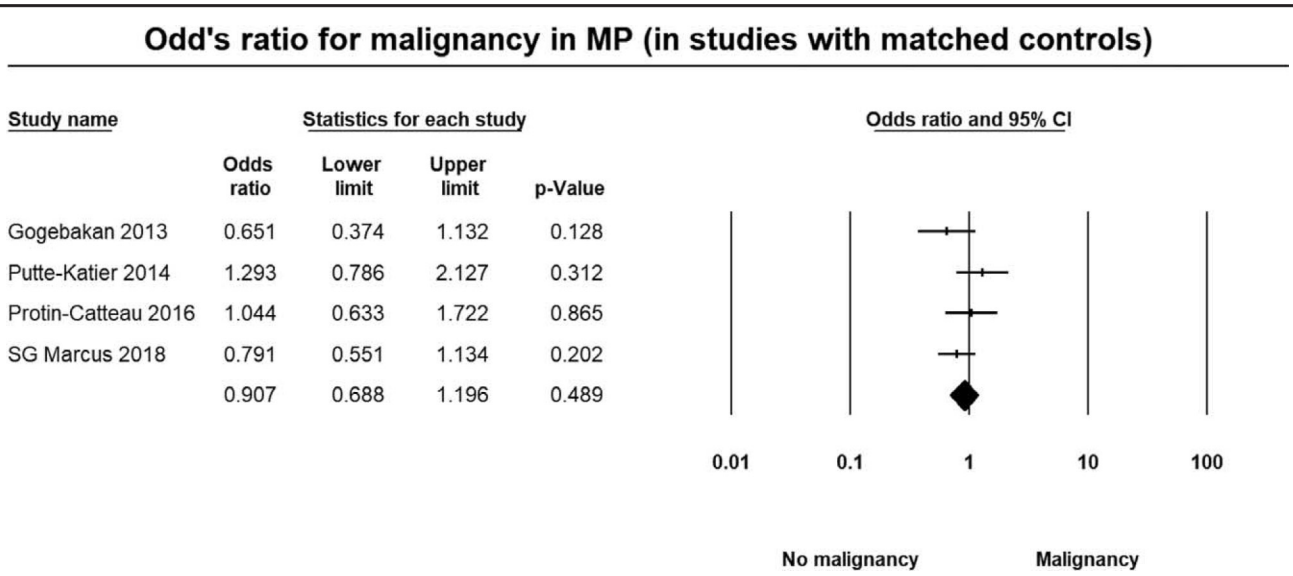

Figure 2. Pooled estimate of odds ratio (OR) of malignancy in mesenteric panniculitis in studies with matched controls. The overall OR was 0.91 (95% CI: 0.688–1.196; $P = .489$).

As expected from the crude visualization of the effect sizes between studies with "matched" and "unmatched" controls, there appeared to be substantial and significant heterogeneity (Cochran Q-value: 72.92, $P < .001$; $I^2 = 91.77$). The difference between the estimates of these 2 groups was also statistically significant, again suggesting that the inclination towards finding a positive odds for malignancy in MP was being driven by studies with "unmatched" controls ($P = .003$). See Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G673.

3.8. Publication bias

For the 4 studies with matched controls, the visual inspection of Funnel plot did not reveal any publication bias which was confirmed quantitatively by the Egger test (P-value [2-tailed test]: .184). See Figure S3, Supplemental Digital Content, http://links.lww.com/MD/G674.

4. Discussion

As far as we are aware, this study is the first meta-analysis to study an association of malignant neoplasms in patients who are diagnosed with MP on CT examinations. From a total of 4 studies (415 patients with MP) which explored this issue after matching the patients with controls for a variety of confounding factors, we found that the odds of finding a concomitant (or in near future) malignancy was not any different than the odds in a matched control population.

Since the year 1924 when Jura[23] published the first description of condition as "sclerosing mesenteritis," the disease

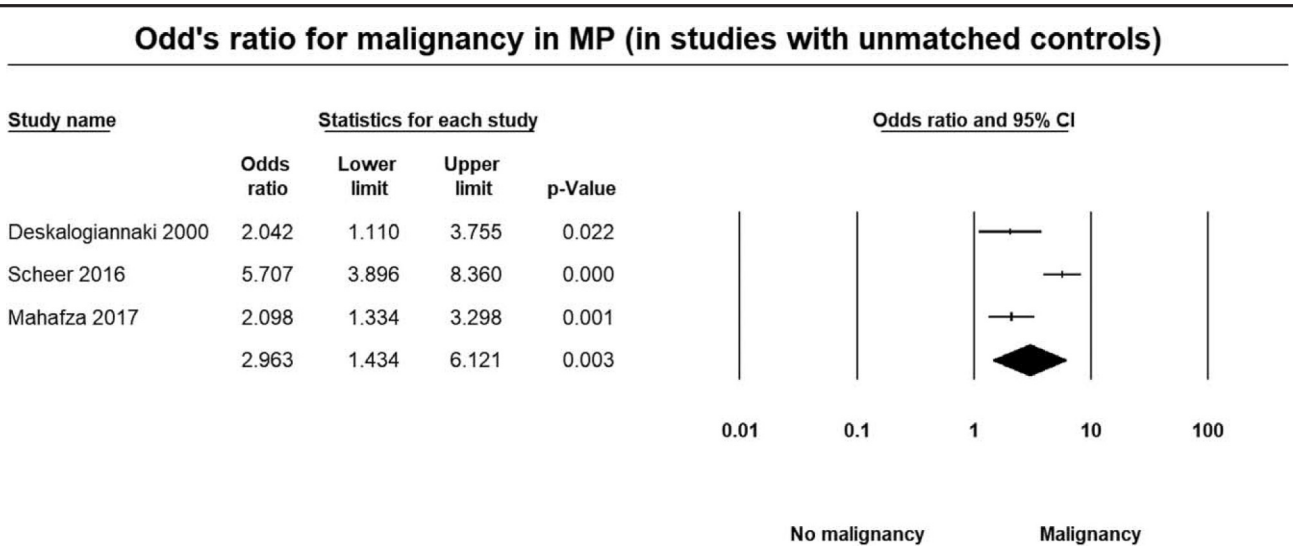

Figure 3. Pooled estimate of odds ratio (OR) of malignancy in mesenteric panniculitis in studies with unmatched controls. The overall OR was 2.96 (95% CI: 1.434–6.121; $P = .003$).

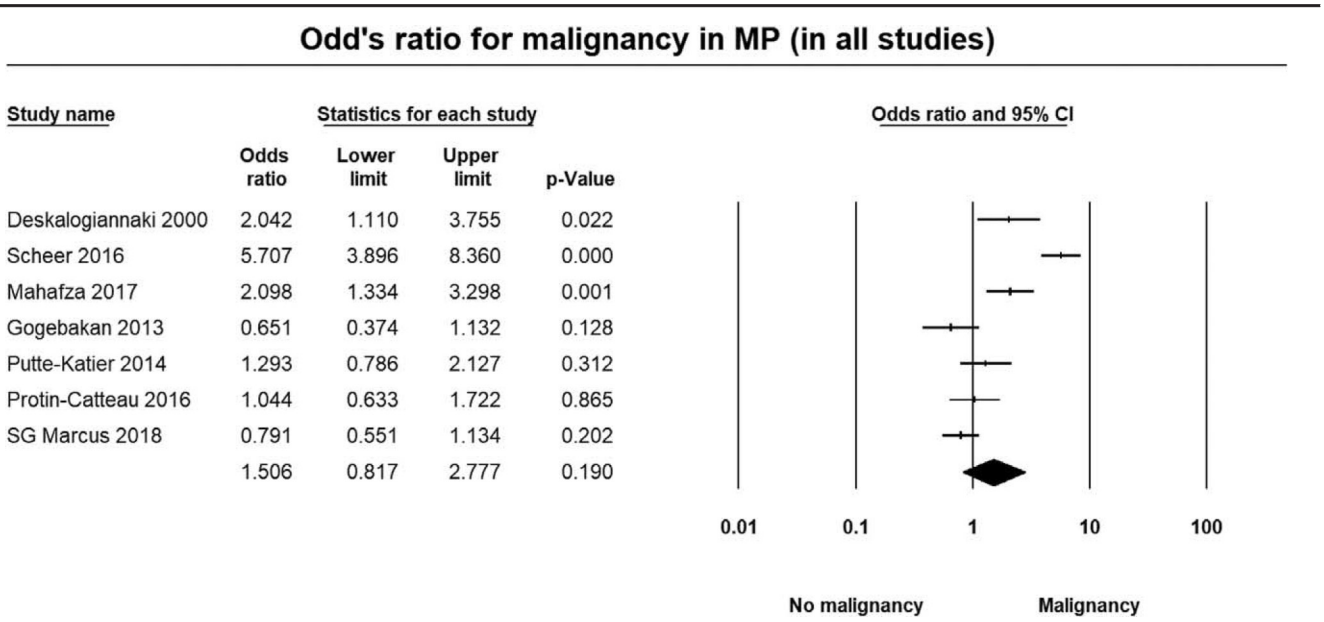

Figure 4. Odds ratio (OR) of malignancy in mesenteric panniculitis in all studies. The overall OR was 1.506 (95% CI: 0.817–2.77, $P=0.19$).

has been described by a variety of names. The MP is now considered a non-aggressive subset of sclerosing mesenteritis with non-specific, non-neoplastic, non-infiltrative tumor-like inflammatory features in the root of bowels.[1,24] In series describing its histopathology, a mix of necrosis, chronic inflammation and fibrosis of the adipose tissues of the mesentery is found; however characteristically, the mesentery remains explicitly uninvolved from any malignancy or dysplasia.[25] The population prevalence of sclerosing mesenteritis was studied in the only autopsy series which found 9 cases (1.26%) of sclerosing mesenteritis among 712 autopsies over a period of 6 months.[26] As the MP is a subset of sclerosing mesenteritis, its prevalence could only be estimated to be lower than 1.26% in the population. Having said that, the diagnosis of MP is generally an incidental radiological diagnosis when patients undergo cross-sectional examinations of their abdomen. Using a variety of pre-specified diagnostic criteria, the prevalence of MP has been reported between 0.16% and 2.50% in respective radiological databases.[6,27]

The underlying cause of MP remains largely uncertain. Despite their inherent biases, numerous case reports and case series have proposed an association of MP with a variety of etiologies: prior abdominal surgery or trauma, autoimmune illnesses, chronic infections, medications, and malignancies.[1] In an old case series, Kipfer et al[7] reported that 16 (30%) of 53 cases of mesenteric lipodystrophy had some form of malignancy, with lymphoma being the most common neoplasm. Daskalogiannaki et al[8] later reported a much higher prevalence (69.3%) of associated malignancy in 49 patients of MP which were identified from their consecutive CT database. Similarly, other authors reported have estimated higher risk of having a malignancy (range: 17.6–38%) in groups of MP which were screened from their radiological databases.[5,6,21,27,28] Consequently, several authors proposed a paraneoplastic phenomenon as an underlying pathogenesis for the development of MP. However, being retrospective and uncontrolled, such association in these studies has remained crucially fraught with inherent biases.

In the first case-control study, Gögebakan et al[10] reported that there was no heightened odds of finding a malignant lesion in MP when the cases were properly matched with a control group. In our systematic review and meta-analysis, we found the similar outcome that there was no statistical difference between odds of malignancy in MP when such cases are compared against a matched control population. Moreover and as has been the suggestion of several other authors, we also showed that such heightened association of malignancy is only found when the cases with MP are not matched against proper controls (OR of malignancy: 0.907 in "matched" vs 2.963 in "unmatched," $P=.003$). To explore the latter hypothesis (as a secondary outcome in our study) more aptly, we decided to pool such estimates only from those studies which could provide some comparative data for calculation of odds in an unmatched group instead of meta-analyzing the point-estimates of prevalence of malignancy in MP from all studies whence no comparative data could be deduced. We believe that such methodology might have made the comparison more transparent.

There are several mentionable strengths in our study: systematic strategy for search of the literature with well-defined criteria for inclusion and exclusion; appropriate exclusion of redundant and non-informative studies, scrutiny of studies for their pre-specified criteria for diagnosis of MP, meticulous extraction of data (both explicit as well as deduced from the studies), careful evaluation for quality of studies, and appropriate quantitative statistical assessment. Unlike a previous systematic review with indeterminate conclusion pertaining an association of malignancy with MP, our study unequivocally showed absence of an increased odds of having a malignant neoplasm in patients with MP.[11] Halligan et al[11] pooled 14 studies of varying methodologies (case-series and case-control studies) and described a narrative review in a systematic method, primarily aiming to determine the pooled estimate of malignant neoplasms among MP at cross-sectional imaging. According to the authors, their attempt to undertake a meta-analysis was "frustrated." We believe that our differing and explicit

conclusion could be achieved due to a dissimilar methodology. Firstly, our data was abstracted from 4 large bibliographic databases as compared with the single database used by Halligan et al.[11] Secondly and more importantly, we only included studies where an OR for malignancy could be estimated unlike descriptive case series included in the previous systematic review, thereby allowing a meta-analysis. Thirdly, our primary aim was a comparative estimate (i.e., to calculate the OR) as compared with the linear pooled-estimate of the proportion of malignancy in MP. We believe that a comparative estimate provided a better assessment of any association of malignancy among patients with MP. On the other hand, it is obvious that our methodology resulted in fewer studies as compared with the previous systematic review. However, the resultant exclusion of descriptive case-series based upon current methodology led to low (and insignificant) heterogeneity among the effect sizes. We believe that the power of our meta-analysis might have been adequate to reject any association of malignancy with MP. Further controlled studies with much larger sample size (or/and with large ORs to suggest association of malignancy with MP) will be needed to refute our findings.

We also acknowledge several limitations in our study, many of which will be inherent for any meta-analysis: all studies were based upon single institutions, with data derived from their respective radiological databases. Nevertheless, and as stated before, the diagnosis of MP is generally a hospital-based diagnosis when such condition is incidentally noticed on a cross-sectional imaging. Except when evaluated with the autopsy-based studies, examination of population-based prevalence of MP, along with its putative association with malignancy, will be a daunting task. All studies were retrospective in nature with their intrinsic biases (e.g., selection bias, recall bias, reporting bias). From our scrutiny of the studies, we believe that the primary authors made efforts to alleviate such biases wherever possible. As the aim was only to look for an association, our study does not comment upon a paraneoplastic pathogenetic hypothesis for mesenteric panniculitis, as majority of the patients with MP were already known to have an underlying malignancy, this study solely aimed to look for an association of malignancy with MP rather than claiming that the detection of MP heightens or lowers the risk of malignancy in itself. The possibility of spectrum bias could not be negated as the controls were taken from hospital-based group (i.e., not otherwise healthy cohort) rather than from an otherwise healthy population. But from a pragmatic standpoint, this might have been the closest cohort of control that could be compared with answer our primary question. We state that our findings should be taken in context and it still remains unproven whether there is an actual difference in the association of malignancy in the MP when such patients are actually compared with a healthy group from community. In the absence of a gold standard for the diagnosis of MP, it is often both detected and established based upon a cross-sectional imaging. In other words, we acknowledge the possibility of spectrum bias while defining the population for this systematic review. But from a clinical viewpoint, MP is often a radiological diagnosis, and with unsubstantiated histological confirmation, which embarks physicians or radiologists to screen for a malignant cause.

As alluded in the previous paragraph, there remains a lack of an internationally accepted radiological definition of MP. In 2011, Coulier et al[2] enlisted criteria thereby assisting the radiological diagnosis of MP and most studies have utilized such criteria since then. In fact 5 of 7 studies included in this review utilized Coulier criteria for diagnosis of MP (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G675). It is possible that variations in incidence pattern and etiologies in older studies might have been contributed by the absence of uniform diagnostic criteria.[8] It is believed that in future a concerted effort to develop and adopt universally accepted criteria may demystify the "misty mesentery."

5. Conclusion

In conclusion, our systematic review with meta-analysis demonstrates that there is no statistically significant association of malignancy in patients with MP when compared with a controlled group of hospital-based patients who undergo computed tomographic scans for other reasons. We re-emphasize that these results should be used in context given the possibility of residual confounding. Future studies with more rigorous controls may strengthen or refute our findings.

Author contributions

All authors vouch for accountability for the content of the work. All authors contributed in conception, design, editing and final approval of the studies. Following authors provided additional specific contributions.

Ikram Hussain: Literature search, statistical analysis, interpretation of data and drafting of article.

Saba Ishrat: Collection of data, statistical analysis and interpretation.

Veeraraghavan Meyyur Aravamudan: Literature search, collection of data.

Shahab R. Khan: Collection of data and synthesis.

Babu P. Mohan: Statistical analysis and interpretation of data.

Rahul Lohan, Tiing Leong Ang: Critical revision of article for important intellectual content.

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