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Review

Hepatitis C virus in MALT-lymphoma of the ocular adnexa

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ABSTRACT

Objective: Hepatitis C virus (HCV) has been proposed as a possible etiologic factor in ocular adnexal marginal zone lymphoma (OAML). We aimed to assess the prevalence of HCV infection in patients with OAML through a systematic review and meta-analysis.
Methods: Electronic databases were searched from their inception to August 2019 for studies assessing HCV seroprevalence in patients with OAML. Pooled prevalence of HCV infection was calculated with 95 % confidence interval (CI). Statistical heterogeneity among studies was quantified *via* the inconsistency index (I^2). Funnel plot symmetry was used to assess the risk of bias across studies.
Results: Nine studies with 360 patients were included. Overall pooled prevalence of HCV in OAML was 12.7 %, with low statistical heterogeneity (I^2 = 17.4 %) and with asymmetrical funnel plot. The studies clustered into two groups: 5 studies (3 from Italy and 2 multicenter with a major Italian contribution) showed a higher HCV prevalence in OAML (15.6 %), while the other 4 (from countries other than Italy) showed a lower prevalence (4.7 %); in both subgroups, statistical heterogeneity was null (I^2 = 0%) and funnel plot was symmetrical.
Conclusion: HCV might be a significant etiologic factor of OAML in Italy.

1. Introduction

Ocular adnexal MALT lymphoma (OAML) is the most common type of lymphoma of the ocular adnexa, accounting for 60–80 % of cases [1–3].

Etiopathogenesis of MALT lymphomas has been shown to be related to chronic stimulation of B-cell promoted by autoimmune disorders [4–6] or infectious agent [7–9]. In the case of OAML, great interest has been given in the study of infectious agents that may be involved in lymphomagenesis, including *Chlamydiaceae*, human hepatitis viruses and *Helicobacter pylori* [10–16]. However, unlike gastric MALT lymphoma (in which *H. pylori* is the main etiologic factor), no univocal factors have been identified for OAML; furthermore, the involvement of certain infectious agents seems to be affected by strong geographical variations [8,17–19].

In this review, we focused on Hepatitis C Virus (HCV), which has been suggested as a possible etiologic factor for OAML [16,20–27]. We aimed to determine the prevalence of HCV infection in patients with OAML.

2. Materials and methods

Methods of this review were based on methods of our previous studies [28–31]. Three authors (AT, SV and MM) independently performed electronic search, study selection, data extraction, risk of bias assessment and data analysis. In the case of disagreement, all authors consulted to achieve a solution. This study was reported following the PRISMA statement [32].

2.1. Search strategy and study selection

Web of Sciences, Scopus, MEDLINE, OVID and Google Scholar were searched from the inception of each database to August 2019. The following text words were used in different combinations: marginal, lymphoma, MALT, mucosa-associated, ocular adnexa*, conjunctiva, orbit, eyelid, Hepatitis C, HCV, virus. All studies assessing the prevalence of HCV infection in patients with OAML were included. The following exclusion criteria were defined *a priori*: HCV not assessed, data not extractable, case reports, reviews.

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2.2. Data extraction

No data were modified during the extraction process. Main extracted data were the total number of patients with OAML and the number of patients with HCV infection. Further data extracted were country, period of enrollment, methods for patient selection, methods for HCV detection.

2.3. Risk of bias within studies assessment

The QUADAS-2 [33] was adapted to our data as previously described [34–36]. Four domains were assessed in each study: 1) "Patient selection" (i.e. if patients were consecutively selected, or at least period of enrollment and inclusion criteria and were reported.); 2) "Index test" (i.e. if methods for determining HCV infection were adequate); 3) "Reference standard" (i.e. if OAML histological specimens were reviewed to confirm the diagnosis); 4) "Flow" (i.e. if all patients with OAMLs were assessed for HCV infection). The risk of bias in each domain was categorized as "low", "high" or "unclear", as previously described [37–39]. Concerns about applicability of the domains 1, 2 and 3 were also assessed. Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used to graphically report the risk of bias within studies.

2.4. Data analysis

In each primary study, the prevalence of HCV infection in patients with OAML was calculated as the number of patients with OAML and HCV infection divided by the total number of patients with OAML. Pooled prevalence was obtained by using the random effect model of DerSimonian-Laird. Both primary results and pooled estimates were reported on forest plots with 95 % confidence interval (CI).

Higgin's inconsistency index (I^2) was used to quantify the statistical heterogeneity among studies as follows: null (I^2 = 0%), minimal ($0 < I^2 \leq 25$ %), low (25 % $< I^2 \leq 50$ %), moderate (50 % $< I^2 \leq 75$ %) or high ($I^2 > 75$ %), as previously described [40–42]. In the case of statistical heterogeneity among studies ($I^2 \geq 0$%), causes of heterogeneity were assessed by performing a subgroup analysis.

Results were reported on funnel plots (standard error by logarithm of prevalence) in order to assess the risk of bias across studies.

Comprehensive Meta-Analysis (Biostat,14 North Dean Street, Englewood, NJ 07631, USA was used for data analysis.

3. Results

3.1. Study selection and characteristics

At the end of the study selection process (reported in Supplementary Fig. 1), nine studies with 360 patients with OAML were included [16,20–27]. Three studies were from Italy, two were form Austria, one from Japan and three were multicenter. Characteristics of the included studies are reported in Table 1.

3.2. Risk of bias assessment

For the "patient selection" domain, seven studies were considered at low risk of bias (they clearly stated that patients were consecutive and/or reported at least inclusion criteria and period of enrollment), and two studies at unclear risk. Concerns about applicability of this domain were unclear for one study, which only included relapsed and/or refractory lymphomas.

For the "index test" domain, three studies were considered at low risk of bias (HCV infection confirmed by RNA assessment) and six studies at unclear risk. No concerns about applicability were raised.

For the "reference standard" domain, six studies were considered at low risk of bias (histological slides were reviewed by expert pathologists) and three studies at unclear risk. No concerns about applicability were raised.

For the "flow" domain, eight studies were considered at low risk of bias (all included patients were assessed for HCV infection) and unclear for one study. No concerns about applicability were raised.

Results of the risk of bias assessment are shown in Supplementary Fig. 2.

3.3. Meta-analysis

Overall, the pooled prevalence of HCV in patients with OAML was 12.7 % (95 % CI, 9 %–17.6 %) (Fig. 1). There was low statistical heterogeneity among studies (I^2 = 17.442 %). The funnel plot showed asymmetrical distribution of the results across studies, which were disposed into two clusters (Fig. 4).

The first cluster was composed of 5 studies, out of which 3 were from Italy and 2 were multicenter, with a major Italian contribution. In this subgroup, the pooled prevalence of HCV in patients with OAML was 15.6 % (95 % CI, 11.6 %–20.7 %) (Fig. 2), with no statistical heterogeneity among studies (I^2 = 0%) and without significant risk of bias across studies (Fig. 4).

The second cluster was composed of 4 studies, out of which two were form Austria, one from Japan, and one multicenter involving UK and USA. In this subgroup, the pooled prevalence of HCV in patients with OAML was 4.7 % (95 % CI, 2 %–10.8 %) (Fig. 3), with no statistical heterogeneity among studies (I^2 = 0%) and without significant risk of bias across studies (Fig. 4).

4. Discussion

This study showed that the prevalence of HCV infection in OAML was 12.7 %, but that high geographical differences were present;

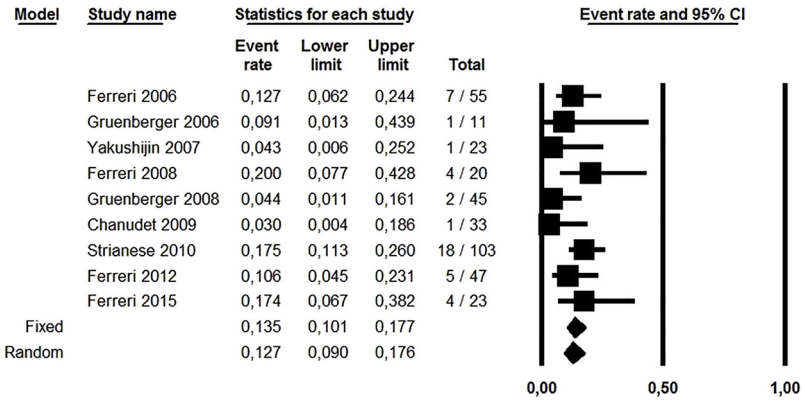

Fig. 1. Forest plot reporting the pooled seroprevalence of HCV in patients with MALT-lymphoma of the ocular adnexa.

Table 1
Characteristics of the included studies.

STUDY	COUNTRY	PERIOD OF ENROLLMENT	SAMPLE SIZE	HCV-POSITIVE
Ferreri 2006	Italy	1990-2004	55	7 (12.7 %)
Gruenberger 2006	Austria	unclear	11	1 (9.1 %)
Yakushijin 2007	Japan	1996-2004	23	1 (4.3 %)
Ferreri 2008	Italy	2006-2007	20	4 (20 %)
Gruenberger 2008	Austria	2000-2006	45	2 (4.4 %)
Chanudet 2009	USA, UK	unclear	33	1 (3%)
Strianese 2010	Italy	1992-2006	103	18 (17.5 %)
Ferreri 2012	Italy, Chile, Spain, Switzerland	2006-2010	47	5 (10.6 %)
Ferreri 2015	Italy, Austria	2012-2013	23	4 (17.4 %)

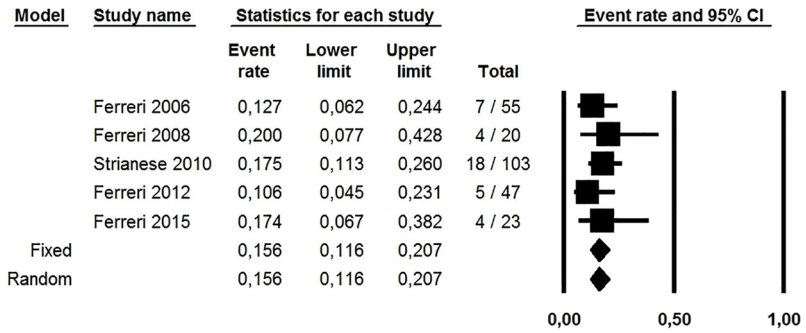

Fig. 2. Forest plot reporting the pooled seroprevalence of HCV in patients with MALT-lymphoma of the ocular adnexa in studies from Italy and in multicenter studies with major Italian contribution.

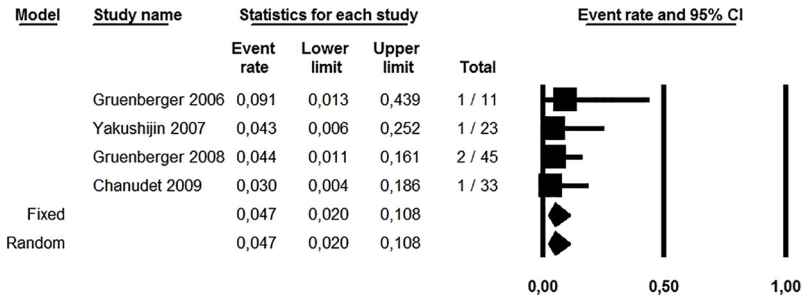

Fig. 3. Forest plot reporting the pooled seroprevalence of HCV in patients with MALT-lymphoma of the ocular adnexa in studies from countries other than Italy (Austria, Japan, UK, USA).

indeed, the prevalence was 15.6 % in studies from Italy and multicenter studies with major Italian contribution, and 4.7 % in studies from countries other than Italy (Austria, Japan, UK, USA). To the best of our knowledge, this is the first meta-analysis assessing this topic.

The association of chronic HCV infection with malignancies is well documented. The clearest example is hepatocellular carcinoma, for which HCV is a major etiologic factor [43]. However, the involvement of HCV has also been advocated for lymphomas of several organs, including spleen, liver, stomach and salivary glands [44]. Several studies have shown that HCV-positive patients bear a risk of lymphoma more than two times higher than the general population [44]. In particular, HCV is associated with non-Hodgkin B-cell lymphoma; the strongest association has been shown for marginal-zone lymphoma and lymphoplasmacytic lymphoma, while a weaker association has been found for follicular lymphoma, chronic lymphocytic leukemia and diffuse large B-cell lymphoma [45]. Mechanisms for lymphomagenesis may include both chronic B-cell stimulation (similarly to *H. pylori*) and direct transformations through intracellular viral proteins (similarly to Epstein-Barr Virus) [44]; given that HCV may causes orbital inflammatory manifestation, it is likely that HCV may lead to the development of ocular adnexa lymphoma through chronic inflammation [46]. Furthermore, Hosry et al. showed that, among patients with diffuse large B-cell lymphoma, HCV-positive patients were younger and more likely to have advanced disease and showed worse survival [47]. On this account, patients with HCV infection may need to be assessed for the presence of lymphoma in order to obtain an early diagnosis and treatment [48].

In this review, we found that the prevalence of HCV in patients with OAML was overall 12.7 %. Considering that this percentage is by far higher than the overall prevalence of HCV in the general population (2.5 %) [49], an etiologic role of HCV in OAML may reasonably be hypothesized. On subgroup analysis, we found that the results were strongly affected by geographical differences. In fact, the included studies clustered into two more homogeneous subgroup: a subgroup of studies from Italy and multicenter studies with major Italian contribution, in which HCV prevalence in OAML was higher (15.6 %), and a subgroup of studies from other countries, in which the prevalence was lower (4.7 %). These results were strengthened by the absence of statistical heterogeneity and of publication bias in the two subgroups. Therefore, as observed for *C. psittaci* [8], it seems that the involvement of HCV in OAML may depend on geographical factors. Since the general HCV prevalence in Italian population is about 2% [49], the result found supports an etiopathogenetic role for HCV in OAML in Italy. Interestingly, even in the non-Italian subgroup, the prevalence found was higher than the general prevalence of HCV in the world population [49], supporting that patients with HCV infections still are at higher

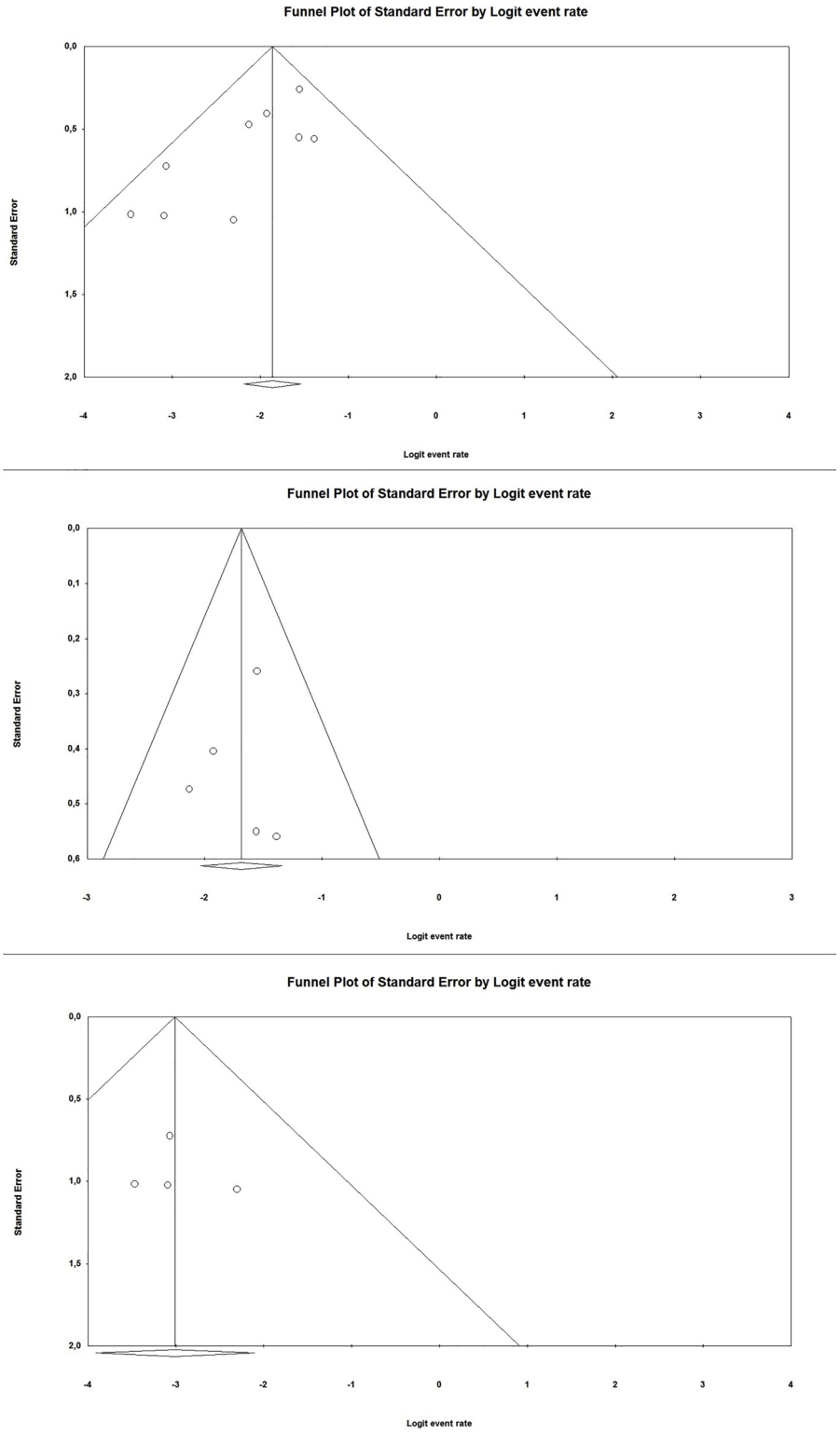

Fig. 4. Forest plots for the assessment of the risk of bias across studies (publication bias) in the overall analysis (upper panel), in Italian studies-subgroup analysis (middle panel) and in non-Italian studies-subgroup analysis (lower panel).

risk of developing OAML. The difference between the subgroups might be due to the general prevalence of HCV in Italy, which is significantly higher than the average HCV prevalence in Western Europe (2% *vs* 0.9 %) [49]. In fact, it has been shown that the association between HCV infection and lymphoma is stronger in endemic areas [44].

These findings may be highly relevant in terms of treatment, as the eradication of the infectious agent may lead to the regression of lymphoma [50]. Indeed, anti-*H. pylori* antibiotics are recommended as first-line treatment for gastric MALT-lymphoma [51]. Regarding *Chlamydia psittaci*, the usefulness of antibiotics in OAML is not completely clarified. On a hand, antibiotics have shown to be effective in a variable percentage of cases of OAML, in particular in populations where *Chlamydia* infection is endemic [8,26,27,50]. On the other hand, the use of anti-*Chlamydia* antibiotics blinded to the *Chlamydia* status was shown

not to be effective [20]. On this account, it may be hypothesized that anti-*Chlamydia* antibiotics are effective in part of *Chlamydia*-positive OAML while they are not effective in the absence of *Chlamydia* infection. Given that antibiotics have a cytotoxic effect, they may kill neoplastic cells regardless of *Chlamydia* status, resulting to be effective even in some *Chlamydia*-negative OAMLs, as it was reported in the Literature [52].

In HCV-positive patients with lymphoma, the etiologic treatment has shown to be effective; indeed, a recent meta-analysis showed an overall response rate of 73 % for HCV-related lymphomas treated by antiviral therapy [53]. Anti-HCV therapy includes interferon-based therapy and direct acting antivirals [54]. Interferon-alpha is a cytokine that stimulates the T-cell response against the virus; its use is associated with severe adverse effects [54]. The more recently introduced direct acting antivirals have been shown to be more effective and with less adverse effects compared to interferon-based therapy [54]. Interestingly, all oral direct-acting antiviral-based therapies have been shown to be effective in HCV-related lymphomas [48]. Anti-HCV therapy may be used alone in patients with low-grade lymphoma and in combination with chemotherapy in the case of diffuse large B-cell lymphoma, leading to an improvement of oncologic outcomes with marked reduction of the rate of recurrence after remission [45]. Therefore, anti-HCV therapy may appear as a major therapeutic option to be considered in Italian patients with OAML. In agreement, antibiotics against *C. psittaci* were shown to be an effective treatment for OAML in Italy (where the prevalence of *C. psittaci* in OAML is high) but not in countries that showed a lower prevalence [8,20,26,50]. Similarly, in other countries specific treatments might be considered in the future for infectious agents that are highly prevalent in patients with OAML; for example, a Korean study showed a high prevalence of *H. pylori* in OAML specimens, while studies from other countries did not [12,55]. Two Italian studies also reported a prevalence of Hepatitis B virus similar to that of HCV in patients with OAML [26,27]; unfortunately, data were insufficient to perform a meta-analysis, and further studies are necessary in this regard.

Interestingly, geographical differences in the general HCV prevalence are also present between different Italian regions. In fact, general HCV prevalence increases from Northern Italy to Southern Italy (1.3 % *vs* 4.6 % in a study published in 2005) [56]. However, the included studies showed that the prevalence of HCV in OAML was high both in Northern and in Southern Italy [16,22,25–27]; therefore, it is unlikely that these differences may lead to a different management.

In addition, HCV infection may also have a prognostic relevance in patients with OAML. In fact, HCV infection was found to be associated with extra-orbital spread and poorer oncologic outcomes [16,25]. In this regard, HCV status might also affect the aggressiveness of treatment in some patients with OAML.

A limitation of this review may lie in the fact that not all studies specified whether HCV seropositivity was confirmed by RNA assessment. Since serology tests are sensitive but not highly specific (specificity around 85 % [57]), the prevalence of HCV infection might be overestimated in some study. However, since our reference was the seroprevalence of HCV in the general population, we believe that our conclusion (i.e. the association of HCV with OAML) cannot be significantly affected by such limitation. Furthermore, it should be remarked that the general HCV prevalence is progressively decreasing in Italy, with the highest prevalence in elder patients [58,59]. This trend is due to the improvement of sanitary conditions [58]. It may be hypothesized that the prevalence of HCV in patients with OAML is decreasing along with the decrease in the national population. Further studies are necessary to assess this point.

5. Conclusions

Patients with HCV infection seem to be at increased risk of developing OAML. However, the prevalence of HCV in patients with OAML is highly variable, constituting a possible major etiologic factor in Italy, with a minor role in other countries such as Austria and Japan. Further studies are necessary to clarify whether anti-HCV therapy can be used as a major therapeutic option in HCV-positive patients with OAML, and whether the prevalence of HCV in OAML is decreasing along with the improvement of sanitary conditions in endemic areas.

Funding

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Ethical approval

Not required due to the study design (systematic review and meta-analysis).

Declaration of Competing Interest

The authors declare no conflict of interest.

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.prp.2020.152864.

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