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## **Preoperative Antiviral Therapy and Microvascular Invasion in Hepatitis B Virus-Related Hepatocellular Carcinoma: A Meta-Analysis**

### **Abstract**

Microvascular invasion (MVI) is an important predictor of metastatic tumor recurrence and is associated with adverse outcomes and poor prognosis in Hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) patients. The association between varying regimens of anti-viral drugs with the incidence of MVI in HBV-related HCC has been demonstrated, however, no meta-analysis of the available data has been conducted. Therefore, the current study sought to evaluate the association of preoperative antiviral therapy with incidence of microvascular invasion in HCC hepatitis virus patients. A systematic search of the literature was performed in MEDLINE/PubMed, Web of Science (WoS), and Scopus, up to January 2020. A random-effects model was used to estimate pooled odds ratios (ORs). Overall, six studies, with 4,988 patients, met our inclusion criteria. The pooled OR of MVI in the patients who had preoperative antiviral therapy versus the patients who did not have antiviral therapy was; OR: 0.60, 95% Confidence Interval (CI): 0.49-0.73;  $I^2=25\%$ . In this study, a significant reduction in the OR of MVI was evident in patients who had antiviral therapy.

**Keywords:** Anti-viral therapy; Hepatitis B; Hepatocellular Carcinoma; microvascular invasion

## 1. Introduction

Hepatocellular carcinoma (HCC) is, reportedly, the fifth most prevalent cancer, and one of the largest contributors to cancer-related mortality, globally (McGlynn and London, 2011; Rahmani et al., 2020). The incidence of HCC is heterogenous and studies have estimated the age-standardized incidence rates per 100,000 people was the highest in Egypt (32.2), Gambia (23.9), Eastern Asia (17.7), and South-East Asia (13.3) (Yang et al., 2019).

Potential curative treatments consist of partial hepatectomy or liver transplantation (Bruix et al., 2014; Kachare et al., 2015; Wang et al., 2020); however, surgical outcomes and long-term prognosis are poor, primarily attributed to high rates of tumour recurrence (Poon et al., 2000). Early recurrence of HCC, characterised by recurrence  $<2$  y post-surgical intervention, is attributable to over 60% of HCC recurrence (Wu et al., 2009), and interestingly, early recurrence is reportedly related to the presence of microvascular invasion (MVI) (Zhang et al., 2018), which represents a histopathological feature of microscopic metastasis (Rodriguez-Peralvarez et al., 2013; Yang et al., 2012b). Indeed, empirical data suggests a significant association between hepatitis virus-related HCC and MVI (Bui-Nguyen et al., 2010; Ryu et al., 2008). In addition, it has been speculated that a hepatitis-

related virus might augment angiogenic processes and disrupt the immune responses against tumour cells escaped from the primary tumour-site, thereby resulting in vascular metastasis (Yang et al., 2012a). Microvascular invasion has been repeatedly established as an independent risk factor for early HCC recurrence following surgical treatment, and it has been reported that the recurrence-free survival rates are significantly lower in patients with, versus without, MVI, 32.7 vs. 75.9%, respectively (Sumie et al., 2014).

Problematically, patients with hepatitis-related HCC are at an increased risk of MVI, as compared to patients with HCC formed of alternative aetiologies (Sasaki et al., 2017). Moreover, Lei et al reported that serum levels of hepatitis-related viruses may influence the extent of MVI (Lidor et al., 2015). The recent introduction of novel antiviral treatments that directly target Hepatitis C Virus (HCV) replication has yielded decreases in HCC occurrence, and even recurrence of HCC in those patients with a past history of liver cancer (Conti et al., 2016)

Although the current evidence base suggests a potential association of preoperative antiviral therapy with MVI formation in hepatitis-related HCC; currently, clinical consensus has been lacking, with no summative assessment having been conducted. Thus, the current study sought to evaluate the association between preoperative antiviral therapy and incidence of MVI in HCC hepatitis virus patients.

## 2. Materials and methods

### 2.1. Search in literature

The present study was conducted in accordance with the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015). A literature search with Medical Subject Headings (MeSH) and non-MeSH terms (supplementary Table 1) was performed, without language, location, and time restrictions, in PubMed/MEDLINE, Scopus, and Web of Science databases, up to January 2020. Furthermore, we scrutinized the respective studies reference lists to search for additional papers.

### 2.2. Inclusion and exclusion criteria

We included Studies that had a Randomized Controlled Trial (RCT), retrospective, or prospective design and compared MVI risk in anti-viral treatment and non-treatments as an outcome, with appropriate items such as hazard ratio, risk ratio, or odds ratio. Other studies, such as review, case report, ecological, editorials, and non-human studies were excluded. In instances of multi-report studies, the longest follow-up period reported was used for inclusion in this meta-analysis. Screening of searched studies was performed in three steps: 1- removal of duplicate studies; 2- removal of non-related studies during title and/or abstract screening; and 3- removal of non-related studies during full text evaluation. All steps were performed by two researchers, independently.

### 2.3. Data extraction and quality assessment

Data extraction was completed by two authors independently, and in instances of disagreement, consensus was achieved through discussion with a senior author. In instances of missing data, we contacted the corresponding authors of included studies. The quality of studies was examined using the Newcastle-Ottawa Quality Assessment Scale (NOS), used for observational studies (19).

### 2.4. Statistical analysis

A random effects model was used to pool results (Jackson et al., 2010). The group of non-antiviral treatment patients was considered as reference category. In order to conduct analysis, the full adjusted model data were extracted from primary studies. The  $I^2$  statistic (cut point: 50%) and Cochran Q test (P heterogeneity (cut-point: 0.10)) were used to evaluate the heterogeneity of results. Funnel plot, Egger's asymmetry test, Egger's asymmetry plot, and Begg's tests, respectively, were conducted to assess potential publication bias, whilst trim and fill analysis was conducted to adjust results for publication bias. The effect of each study, individually, on pooled results was calculated by sensitivity analysis. STATA 14.0 software used to conduct all statistical analyses.

## 3. Results

### 3.1. Literature search

The literature process is demonstrated in Fig. 1. Accordingly, 201 articles were retrieved in the initial search. Fifty-two duplicated records were removed, and 128 articles were excluded following title and abstract screening. Twenty-one studies were screened in the full text evaluation, and according to our inclusion criteria, 15 irrelevant records were excluded. Finally, six studies met our inclusion criteria and were, therefore, included in this meta-analysis (Huang et al., 2017; Lei et al., 2016; Li et al., 2018b; Liu et al., 2019; Qu et al., 2019; Wei et al., 2017).

### 3.2. Study characteristics and quality assessment

Included studies were published from 2016 to 2019, and Table 1 details characteristics of all included studies. One study had a prospective design (Lei et al., 2016), and all others had a retrospective design (Huang et al., 2017; Li et al., 2018b; Liu et al., 2019; Qu et al., 2019; Wei et al., 2017). In total, of 4,988 participants, ranging from 349 to 2,362, 1,005 participants had antiviral treatment, and 2,069 participants showed MVI. The average age of participants was 52.6 years and all studies contained both genders. For quality assessment of studies, the NOS tool was used, and two studies showed high quality (Lei et al., 2016; Li et al., 2018b). Moreover, the quality assessment of studies detailed in Supplemental Table 2.

### 3.3. Meta-analysis results

Six articles with 4,988 patients reported relevant outcomes. The pooled Odds Ratio (OR) (95% Confidence Interval (CI)) of MVI in the patients who had preoperative antiviral therapy, versus the patients who did not have preoperative antiviral therapy, was OR: 0.60, 95% CI: 0.49-0.73 (Fig. 2). Indeed, HBV-Related HCC patients who had treatment with antiviral regimes had a 40% lower risk of MVI. Our analysis indicated no significant heterogeneity among the included studies ( $P=0.24$ ,  $I^2=25\%$ ).

#### 3.4. Publication bias and Sensitivity analysis

Funnel plots and Egger plots showed an asymmetry and indicated publication bias among the included studies (Fig. 3A and 3B, respectively). Begg's and Egger's tests, respectively, confirmed this publication bias (Begg's  $P=0.03$  and Egger's regression test  $P=0.02$ ). The 'trim and fill' analysis method was used to adjust publication bias among results, and its details are provided in Supplemental table 3. Furthermore, sensitivity analysis for each of the included studies showed no significant differences, beyond the 95% CI limits of calculated pooled standard errors (SEM), for the included studies (Fig 4).

#### 4. Discussion

Microvascular invasion is regarded as an important predictor of metastatic tumour recurrence and is associated with adverse outcomes and poor prognosis in HBV-related HCC patients. Concordantly, studies have shown that the HBV-related HCC patients were more likely to develop MVI than HCC with other



aetiologies (Omichi et al., 2015; Zhang et al., 2019). A high preoperative HBV viral DNA load in these patients was reported to be an independent risk factor of MVI. The results from the accumulated data demonstrate an important association between the use of preoperative antivirals in HBV-related HCC patients and the incidence of MVI formation and early HCC tumour recurrence (Akateh et al., 2019; Elshaarawy et al., 2019; Ke et al., 2019). Moreover, HCC patients following an antiviral treatment regimen for more than 90 days before surgery was associated with reduced incidence of MVI (Li et al., 2018). Indeed, this can also influence early tumour recurrence in partial hepatectomy for HBV-related HCC.

This study systematically reviewed the published literature of preoperative antiviral therapy for HBV-related HCC, and sought to evaluate the association on the incidence of MVI. In total, six cohort studies fulfilled our criteria, where all the studies included HBV positive HCC patients, used antiviral treatment, and showed MVI. Accordingly, the pooled estimates indicated that preoperative antiviral therapy offers potential benefits in reducing the risk of MVI in the HBV-related HCC patients by 40%. However, there is no conclusive evidence on the duration of the preoperative antiviral therapy that can optimally benefit in reducing the incidence of MVI and HBV-related HCC tumour recurrence. The length of anti-viral therapy in most of the included studies was 3 months (Huang et al., 2017; Wei et al., 2017); indeed, findings from Li et al.

demonstrated that antiviral treatment for HBV, for more than 90 days pre-resection, was associated with a reduced risk of MVI (OR, 0.75, 95%CI: 0.57-0.99) (Lei et al., 2016). Therefore, it appears that anti-viral treatment after the tumour may be more likely to be successful in preventing MVI formation and a worsening prognosis.

Some empirical evidence suggests that antiviral treatment can protect against tumour recurrence. Indeed, Huang et al. conducted a RCT on patients with HCC, highlighting that patients who received antiviral therapy showed reduced tumour recurrence and improved survival (Huang et al., 2018). However, caution should be taken while treating HCV patients with a history of HBV, as it is associated with HBV reactivation in patients who are Hepatitis B surface antigen-positive (Sanaka et al., 2018). In the present study, HBV-Related HCC patients who received treatment with antiviral regimes had a 40% lower risk of MVI. Interestingly, Li et al highlighted that a high preoperative HBV-Related DNA levels were an independent risk factor of MVI (Li et al., 2018a). Indeed, the authors further demonstrated that antiviral treatment was associated with reduced MVI incidence, but only in instances where treatment commenced more 90 days prior to surgery. Taken together, these findings suggest that, with respect to MVI-positive HCC, anti-viral therapy may be associated with improved survival outcomes and prevention of MVI in HBV-related HCC patients.

## Strength and limitations

To the best of our knowledge, this study is the first meta-analysis to have evaluated the association of preoperative antiviral therapy with incidence of MVI in HBV-related HCC. The low heterogeneity observed between studies was a strength of this work, indicating veracity in our findings, and may be of use practically. However, the most important limitation of this study was the varying type of anti-viral drugs; indeed, most of the included studies did not report the effect of different anti-viral drugs separately, so we could not report the effect of each anti-viral drug on risk of MVI. In addition, the potential impact of immune status vs. MVI in HBV-related HCC patients was not considered amongst the included studies. However, it has been noted that during chronic HBV infection, adaptive immunity changes from tolerance, progressively, to immune activation, inactivation, reactivation, and, subsequently, exhaustion, which, indeed, may all represent immune pathogenic factors for the development of HCC (Chen and Tian, 2019). A further consideration that would be pragmatic to investigate is the co-infection of HBV and Hepatitis C (HCV), indeed, in this regard, it has been demonstrated that although HBV and HCV are independent risk factors of HCC, the combination of both infections can additionally modify HCC development (Tsai et al., 1997). Clearly, it is important that further work is conducted, considering the

limitations highlighted above, in addition to delineating the differences between populations.

## 5. Conclusion

In this study, a reduction in the odds of MVI was evident in patients who underwent anti-viral therapy. However, all of the studies included in this meta-analysis were observational, and thus, there is an urgent need for high-quality, large scale RCTs, in different populations, to further confirm the veracity of our results.

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