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***Helicobacter pylori* infection and liver diseases: Epidemiology and insights into pathogenesis**

Okushin K *et al.* *H. pylori* and liver diseases

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**Abstract**

Both *Helicobacter pylori* (*H. pylori*) infection and liver diseases, including nonalcoholic fatty liver disease (NAFLD), viral hepatitis, and hepatocellular carcinoma (HCC), have high prevalences worldwide, and the relationship between *H. pylori* infection and liver disease has been discussed for many years. Although positive correlations between *H. pylori* and NAFLD have been identified in some clinical and experimental studies, negative correlations have also been obtained in high-quality clinical studies. Associations between *H. pylori* and the pathogenesis of chronic viral hepatitis, mainly disease progression with fibrosis, have also been suggested in some clinical studies. Concerning HCC, a possible role for *H. pylori* in hepatocarcinogenesis has been identified since *H. pylori* genes have frequently been detected in resected HCC specimens. However, no study has revealed the direct involvement of *H. pylori* in promoting the development of HCC. Although findings regarding the correlations between *H. pylori* and liver disease pathogenesis have been accumulating, the existing data do not completely lead to an unequivocal conclusion. Further high-quality clinical and experimental analyses are necessary to evaluate the efficacy of *H. pylori* eradication in ameliorating the histopathological changes observed in each liver disease.

**Key words:** *Helicobacter pylori*; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Viral hepatitis; Hepatitis C virus; Hepatitis B virus; Hepatocellular carcinoma

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**Core tip:** Both *Helicobacter pylori* (*H. pylori*) infection and liver diseases have high prevalences worldwide, and their relationship has been discussed for a long time. In this review, we comprehensively summarize positive and negative correlations suggested in clinical and experimental studies, and conclude that existing data cannot fully lead us to make a decision. We also point out the necessity of further analyses evaluating the efficacy of *H. pylori* eradication on histopathological changes in each liver disease. We believe this paper would help readers to gain a better understanding of the relationship between *H. pylori* and liver diseases.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) is one of the most well-known microbes in the world. Warren and Marshall reported the possible virulence of *H. pylori* in patients with gastritis, gastric ulcer, and duodenal ulcer in 1984[1]. Approximately 50% of the global population is estimated to be infected with *H. pylori*[2], and chronic infection with *H. pylori* is one cause of chronic atrophic gastritis, peptic ulcer diseases, and gastric cancer[3,4]. Recently, findings concerning the influence of *H. pylori* on various extra-alimentary organs have accumulated[5-12]. Among these putative extra-alimentary disorders caused by *H. pylori*, the relationship with metabolic disorders remains controversial[13-23].

Liver diseases, including nonalcoholic fatty liver disease (NAFLD), chronic viral hepatitis, and hepatocellular carcinoma (HCC), also have high prevalences worldwide. Consequently, the relationship between *H. pylori* and liver diseases has been discussed and still remains controversial[10]. Although the presence of *H. pylori* or *Helicobacter* species has been observed in liver samples from patients with various liver diseases[24-30] and findings regarding possible roles for *H. pylori* in the pathogenesis of liver diseases have been accumulating, few studies have reported a direct contribution of *H. pylori* to the pathogenesis of liver diseases. Additionally, negative correlations have been identified in high-quality clinical studies[31-34].

Currently, *H. pylori* is efficiently eradicated by various short-term treatments with combinations of antibiotics[35]. On the other hand, despite the remarkable progress in research and therapy, curative treatments have not yet been established for almost all liver diseases. Therefore, a discussion of whether *H. pylori* has a possible role in the pathogenesis of liver diseases and a clarification of the efficacy of *H. pylori* eradication in treating liver diseases are important. In this review, we present current insights into the relationship between *H. pylori* and liver diseases, such as NAFLD, chronic viral hepatitis, and HCC.

***H. PYLORI* AND NAFLD**

NAFLD is an emerging liver disease worldwide, including in Asian countries[31,36,37]. NAFLD is a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). The latter is progressive and considered a causative factor of cirrhosis, HCC, and systemic metabolic disorders[38-40].

The initial description of NASH pathogenesis, which was previously defined as the “two-hit” theory, was presented by Day *et al*[41] in 1998 and has been discussed by other researchers. In addition to a “first-hit” of hepatic steatosis, a “second-hit,” such as gut-derived endotoxins, proinflammatory cytokines, dysregulation of adipokines, oxidative stress, endoplasmic reticulum stress, and lipotoxicity, is necessary for NASH development. Considering the complicated mechanisms of NAFLD, however, the “two-hit” theory had been thought to be insufficient, and instead, the “multiple-parallel hits” hypothesis was proposed by Tilg *et al*[42]. According to this hypothesis, inflammatory mediators derived from various tissues, including the gut and adipose tissue, play a central role in the inflammatory cascade. However, the detailed pathogenesis largely remains unclear.

The relationship between *H. pylori* and NAFLD in the context of gastrointestinal tract inflammation has been long discussed but remains controversial (Table 1)[10,31-34,43-51]. Some cross-sectional or retrospective studies have not identified correlations between NAFLD and *H. pylori*[31-34]. Previously, we examined the associations of causative background factors with NAFLD by analyzing 13737 subjects in a cross-sectional study in Japan, but no correlations were observed between NAFLD and *H. pylori,* regardless of gender[31]. On the other hand, opposite results have also been reported[45-48]. In a meta-analysis, Wijarnpreecha *et al*[49] found a significantly increased risk of NAFLD among patients with *H. pylori* infection, with pooled odds ratios of 1.21 (95%CI: 1.07-1.37).

To the best of our knowledge, only two randomized prospective studies have attempted to reveal the direct correlation between *H. pylori* eradication and NAFLD. As shown in the study by Jamali *et al*[50], eradication does not exert significant effects on the liver fat content, liver function tests, lipid profiles, and homeostasis model assessment of insulin resistance (HOMA-IR) index in patients with NAFLD, although one limitation of this study was that it was conducted on dyspeptic patients with NAFLD. Polyzos *et al*[51] performed a small-scale prospective study of *H. pylori* eradication in patients with biopsy-proven NASH. In this study, eradication had no long-term effect on hepatic steatosis but showed a trend toward improving the noninvasive NAFLD fibrosis score[52]. Namely, in the *H. pylori*-eradicated group, the fibrosis scores decreased from -0.34 at baseline to -0.24 at month 12 (*P* = 0.116), whereas the scores increased in the control group from -0.38 at baseline to -0.56 at month 12 (*P* = 0.249). Larger-scale randomized prospective studies focusing on *H. pylori* eradication are needed.

NAFLD is closely related to metabolic syndrome. The relationship between *H. pylori* and metabolic syndrome has also been discussed for many years. Recently, Refaeli *et al*[53] analyzed 147936 individuals aged 25-95 years who performed the urea breath test during 2002-2012 using a large computerized database of a health maintenance organization in Israel. In this study, the prevalences of *H. pylori* infection and metabolic syndrome were 52.0% and 11.4%, respectively. Compared to noninfected patients, *H. pylori*-infected patients exhibited an increased likelihood of developing metabolic syndrome (adjusted OR: 1.15, 95%CI: 1.10-1.19). Similar results have been obtained in a meta-analysis[54], middle-sized community-based studies[55,56], and hospital-based studies[17,57,58]. On the other hand, Takeoka *et al*[59] reported unique controversial results focusing on the quantification of *H. pylori*-specific IgG concentrations. Namely, the subjects were stratified into 4 groups according to the concentration of *H. pylori*-specific IgG as follows: *H. pylori* seronegative (< 10 U/mL), low *H. pylori*-specific IgG levels (10-30 U/mL), moderate *H. pylori*-specific IgG levels (30-50 U/mL), or high *H. pylori* -specific IgG levels (> 50 U/mL). After stratification, patients with low IgG levels had the lowest risk of metabolic syndrome, after adjusting for age, sex, smoking, drinking, and physical activity status. Using patients with the low IgG levels as the reference, patients with negative, moderate, and high IgG levels had ORs (95%CIs) of 2.15 (1.06-4.16), 3.69 (1.12-16.7), and 4.05 (1.05-26.8), respectively. Indeed, *H. pylori*-specific IgG levels do not always reflect disease severity; further discussion is needed to determine why the group with low IgG levels, but not negative for IgG, exhibited the lowest risk of metabolic syndrome. Another cross-sectional study in Japan, which analyzed 7394 cases, evaluated the correlations between *H. pylori* infection with the development of metabolic syndrome and each parameter[17]. In this study, *H. pylori* seropositivity was a significant and independent predictor of metabolic syndrome (OR: 1.39, 95%CI: 1.18-1.62, *P* < 0.001), as determined by a multivariate logistic regression analysis. Furthermore, according to the multivariate linear regression analysis, *H. pylori* seropositivity was significantly correlated with metabolic syndrome-related variables, such as higher systolic blood pressure (β coefficient = 1.03, *P* = 0.014), a lower high-density lipoprotein (HDL) cholesterol level (β coefficient = -2.00, *P* < 0.001), and a higher LDL cholesterol level (β coefficient = 2.21, *P* = 0.005). In addition, successful eradication of *H. pylori* significantly improves disturbances in these metabolic parameters[60-63]. However, some reports contradict an association between *H. pylori* and these metabolic risk factors[64-68]. Therefore, we are not able to reach a definitive conclusion, and the effect of *H. pylori* on metabolic factors may depend on the subjects examined, due to differences in factors such as country of residence, dietary habits, culture, and fitness habits.

Since obesity is closely linked to NAFLD, a relationship between *H. pylori* and obesity has also been hypothesized. A meta-analysis by Lender, *et al*[69]concluded that the rates of obesity and overweight were inversely and significantly correlated with the prevalence of *H. pylori* infection (r = 0.29, *P* < 0.001). However, this meta-analysis only selected studies conducted in developed countries (GDP > 25000 US $/person/year). Contradictory results were obtained in rather large-scale studies performed in other countries, such as China[70,71]. The reason for this discrepancy remains to be elucidated, but the difference in dietary habits and culture is probably responsible. In addition, the subjects’ appetites and actual food intake levels will presumably be changed after successful eradication of *H. pylori* and may affect body weight. To determine whether the presence of *H. pylori* itself triggers body weight gain, detailed studies without exogenous factors are necessary to determine whether an *H. pylori* infection itself triggers body weight gain. Nwokolo *et al*[72] presented interesting data in a study examining this point. In a small-scale pilot trial, plasma ghrelin, leptin, and gastrin levels were measured before and after the cure of *H. pylori* in 10 subjects. After *H. pylori* cure, plasma ghrelin levels increased significantly by 75% (*P* = 0.002). On the other hand, leptin and gastrin levels have decreased by 11% and 30%, respectively, although the differences were not significant. Ghrelin is known to stimulate appetite and induce a positive energy balance, leading to body weight gain[73]; therefore, an increase in plasma ghrelin levels might be associated with the development of obesity following the eradication of *H. pylori.*

One of the important manifestations of NAFLD is insulin resistance (IR)[74]. Higher HOMA-IR scores were recorded for *H. pylori*-infected patients[55,75-78], while opposite results have also been obtained in other studies[19,79]. Cytokine production was suggested as a mechanism by which *H. pylori* induced IR. *H. pylori* infection stimulates the release of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 and IL-8[80,81]. TNF-α induces IR by suppressing insulin-induced tyrosine phosphorylation of insulin receptor and its substrate, insulin receptor substrate (IRS)-1, in a hepatoma cell line[82]. In fact, neutralization of increased TNF-α levels in obese fa/fa rats significantly increases the peripheral uptake of glucose in response to insulin[83]. Adiponectin and fetuin-A are also regarded as key factors contributing to IR. Adiponectin, an adipocyte-derived hormone, antagonizes excess lipid storage in the liver and protects against inflammation and fibrosis[84].According to Ando *et al*[85], successful eradication of *H. pylori* significantly increases total adiponectin levels from 5.61 μg/mL to 6.16 μg /mL (*P* < 0.0001) as well as the levels of each multimer form (high-, middle-, and low-molecular-weight) of adiponectin. Fetuin-A, a glycoprotein produced by the liver, is correlated with impaired insulin sensitivity, glucose metabolism and the onset of diabetes mellitus[86,87]. *H. pylori*-positive subjects have higher fetuin-A levels and HOMA-IR scores than *H. pylori*-negative subjects. In a cross-sectional study, the mean fetuin-A values were 0.77 g/L and 0.58 g/L in *H. pylori*-positive and *H. pylori*-negative subjects, respectively. Mean HOMA-IR scores were 3.1 and 2.2 in *H. pylori*-positive and *H. pylori*-negative subjects, respectively. In addition, a significant positive correlation between fetuin-A and HOMA-IR was observed after adjusting for other factors (adjusted coefficient β = 0.23, *P* < 0.01)[88]. Based on these results, levels of inflammatory cytokines, adiponectin and fetuin-A may be associated with *H. pylori*-related IR, although that relationship has not been completely acknowledged.

Recently, the gut microbiota has been the focus of studies on the pathogenesis of various diseases and has also been suggested to play key roles in NAFLD pathogenesis[89,90]. Cytotoxin-associated gene A antigen (CagA), the known virulence factor of *H. pylori*, has been reported to alter the gut microbiota, resulting in the exacerbation of cell proliferation and immune phenotypes[91]. Furthermore, increased mucosal permeability of the intestine induced by *H. pylori* infection was reported[92]. These alterations in the gut environment, such as the microbiota and mucosal barrier, by *H. pylori* may influence the pathogenesis of NAFLD.

In summary, positive correlations between *H. pylori* and NAFLD have been reported in some clinical and experimental studies, but other studies have presented contradictory data. Further analyses focusing on the effect of *H. pylori* eradication on histopathological changes in patients with biopsy-proven NAFLD are necessary.

***H. PYLORI* AND CHRONIC VIRAL HEPATITIS OR CIRRHOSIS**

The involvement of *H. pylori* in the pathogenesis of chronic viral hepatitis has been speculated (Table 2). Esmat *et al*[30] evaluated the presence of the *H. pylori* CagA gene in liver samples from patients with hepatitis C virus (HCV)-related chronic hepatitis or cirrhosis by the polymerase chain reaction (PCR). In this study, the *H. pylori* gene was detected in 28.2% cases of late fibrosis (F3 + F4) and 5.9% cases of early fibrosis (F1 + F2) (*p* = 0.0001) by PCR. The influence of *H. pylori* on the progression of HCV-related liver diseases has also been examined. Anti-*H. pylori* antibody positivity was significantly and independently associated with cirrhosis in patients with HCV-related chronic hepatitis or cirrhosis in multivariate analyses (OR: 2.42, 95%CI: 1.06-5.53, *P* = 0.037)[93]. Rocha *et al*[94]*.* examined liver tissues from *H. pylori*-infected patients and revealed that the *Helicobacter* 16S rDNA was only detected in 4.2% of liver samples from control patients and in 3.5% of samples from patients with noncirrhotic chronic hepatitis C. The *Helicobacter* 16S rDNA was detected in 68.0% of liver samples from patients with HCV-positive cirrhosis without HCC as well as in 61.3% of patients with HCC. In a meta-analysis, Wang *et al*[95] analyzed the prevalence of *H. pylori* infection in a total of 1,449 patients with chronic hepatitis C and 2377 control cases. The prevalence of *H. pylori* was significantly higher in patients with chronic hepatitis C than in those without chronic hepatitis C (pooled odds ratio 2.93). In a subgroup analysis, the odds ratios were 4.48 for HCV-related cirrhosis and 5.45 for HCC. These results suggest an association between *Helicobacter* species and HCV-related disease progression, but these findings only show the presence of *H. pylori,* not its pathogenicity in the liver. *H. pylori* may putatively flow into the liver *via* the portal vein and be caught and eliminated by intrahepatic immune cells such as Kupffer cells in the normal liver. Since the number of these cells decreases with the progression of fibrosis, *H. pylori* is speculated to be present in the liver as a result of immune escape. Accordingly, the prevalence of *H. pylori* might simply be high in patients with cirrhosis compared with that in control or noncirrhotic patients. Additional in-depth studies are required to confirm the actual involvement of *H. pylori* in the progression of liver fibrosis.

Clinical findings suggesting relationships between *H. pylori* and hepatitis B virus (HBV)-related liver diseases have also been reported[96-100]. A higher prevalence of *H. pylori* infection in HBV-infected patients has been reported in several studies[96-98], but these findings may just reflect the hygienic environments in childhood. Actually, Wang *et al*[99] reported that the prevalence of *H. pylori* infection in asymptomatic HBV carriers was 38.67% in Shandong Province, China, which was not different than that in the normal adult population recruited from the same region (35.94%, *P* = 0.352). Possible associations between the progression of HBV-related liver disease and liver-related complications, such as variceal bleeding, ascites, and encephalopathy, have also been reported[97]. In a meta-analysis of a Chinese population, the prevalence of *H. pylori* infection among patients with HBV-related liver diseases increased as the disease severity increased[100]. Namely, the *H. pylori*-positive rate in patients with chronic hepatitis B patients but not cirrhosis or HCC was 2.44-fold higher than that in healthy controls (pooled OR: 2.44, 95%CI: 1.85–3.24; *P* < 0.01). Furthermore, the *H. pylori*-positive rate in patients with HBV-induced cirrhosis was 4.28-fold higher (pooled OR: 4.28, 95%CI: 2.99-6.13, *P* < 0.01) than that in healthy controls, while it was 6.02-fold higher (pooled OR: 6.02, 95%CI: 4.33-8.37, *P* = 0.821) in patients with HBV-related HCC. Therefore, the presence of *H pylori* may accelerate the progression of HBV-related liver pathogenesis, but the precise pathogenicity in the liver remains to be elucidated.

In summary, although *H. pylori* infection and chronic viral hepatitis seem to be associated in limited situations, further studies are necessary to obtain a final conclusion since researchers have not yet clearly determined whether *H. pylori* itself directly contributes to the progression of viral hepatitis.

***H. PYLORI* AND HEPATOCARCINOGENESIS**

Several clinical studies have reported an association between *H. pylori* and HCC (Table 2). *H. pylori* and similar species were detected in liver samples from patients with HCC[24-27]. Additionally, a positive association between *H. pylori* and the risk of HCC was reported in a meta-analysis[101]. The overall prevalence of *H pylori* in the liver was 53.3% (129 of 242) in patients with HCC and 10.4% (29 of 280) in controls, and the odds ratio for the association between *H. pylori* infection and the risk of HCC was 13.63 (95%CI: 7.90-23.49). These observations, however, only showed the presence of *H. pylori* in liver tissues. HCC is usually accompanied by liver fibrosis, and in these circumstances, the intrahepatic immune status and hemodynamics may be changed to permit the inflow of *H. pylori* and escape from immunity in the liver, as noted above. Therefore, the presence of *H. pylori* only in HCC tissues does not provide strong support for an association with HCC.

Some *in vitro* studies have presented the possible mechanism underlying the association between *H. pylori* and hepatocarcinogenesis. As shown in the study by Zhang *et al*[102], *H. pylori* causes pathological effects on HepG2 hepatoma cells by upregulating the expression of some proteins related to gene transcription and signal transduction. Virulent type *H. pylori* cause cell cycle arrest and apoptosis of Huh7 cells, another hepatoma cell line[103]. According to Liu *et al*[104], histidine-rich protein (Hpn), a small histidine-rich cytoplasmic protein from *H. pylori*, induces apoptosis by suppressing ubiquitin-specific peptidase 5 (USP5) expressions and activating the P14-P53 signaling pathway. However, these data are only indirect findings obtained from *in vitro* studies using cancer cell lines. Indeed, to the best of our knowledge, direct evidence for the tumorigenic effect of *H. pylori* on the liver has not been obtained. Ki *et al*[105] postulated that *H. pylori* infection might promote the transforming growth factor (TGF)-β1-dependent oncogenic pathway, disturbing the balance between hepatocyte apoptosis and proliferation in a murine model of CCl4-induced fibrosis, but in this study, the development of HCC itself was not observed. Furthermore, in transgenic mice expressing HCV proteins, *H. pylori* infection did not promote the development of HCC[106]. Based on these findings, *H. pylori* infection is currently presumed to be unlikely to contribute to HCC development.

In summary, although *H. pylori* genes are frequently detected in HCC samples, possible correlations between *H. pylori* and hepatocarcinogenesis seem to be doubtful. Further studies showing the direct contribution *in vivo* using infectious animal models or mice transgenic for *H. pylori* genes are necessary to confirm this relationship.

**CONCLUSION**

*H. pylori* have a high prevalence, and its roles in liver diseases, as well as its well-known contribution to the pathogenesis of gastric disorders, have been discussed. As described in this review, several correlations between *H. pylori* and liver diseases, particularly NAFLD, have been reported in some clinical and experimental studies, but these correlations remain controversial. Further analyses are required to elucidate the associations. In addition, since only a few studies have examined the effect of *H. pylori* eradication on the pathogenesis of NAFLD, histopathological confirmation that *H. pylori* eradication specifically prevents or improves disease progression is necessary. Concerning chronic viral hepatitis and HCC, some observational studies suggested positive correlations. But, we have to recognize possibilities of the publication bias and confounding factors such as hygienic environments and contaminations resulting from the presence of cirrhosis. Actually, few studies have definitively confirmed the pathogenic contribution of *H. pylori* to increase of inflammation, progression of fibrosis, or acceleration of hepatocarcinogenesis. *H. pylori* infection and liver diseases still have high prevalences worldwide and significant impact on patients’ prognosis. There is a room to discuss whether *H. pylori* are really involved in pathogenesis of each liver disease. To demonstrate the actual involvement of *H. pylori* in these processes, *H. pylori* itself or its gene product must be shown to accelerate the pathogenesis of these diseases using well-established animal models.

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Grade E (Poor): 0

**Table 1 Summary of relevant studies between *Helicobacter pylori* and nonalcoholic fatty liver disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Year** | **Country** | **Study design** | **Number of subjects** | **Conclusion** |
| Okushin *et al*[31] | 2015 | Japan | Cross-sectional study | 13737 | Negative |
| Baeg *et al*[32] | 2016 | South Korea | Cross-sectional study | 3663 | Negative |
| Fan *et al*[33] | 2018 | China | Cross-sectional study | 21456 | Negative |
| Cai *et al*[34] | 2018 | China | Cross-sectional study | 2051 | Negative |
| Polyzos *et al*[45] | 2013 | Greece | Cross-sectional study | 53 | Positive |
| Dogan *et al*[46] | 2013 | Turkey | Cross-sectional study | 174 | Positive |
| Kim *et al*[47] | 2017 | South Korea | Retrospective study | 17028 | Positive |
| Chen *et al*[48] | 2017 | China | Cross-sectional study | 2263 | Positive |
| Wijarnpreecha *et al*[49] | 2016 | Various countries | Meta-analysis | 38622 | Positive |
| Jamali *et al*[50] | 2013 | Iran | Prospective study (RCT) | 49 | Negative |
| Polyzos *et al*[51] | 2014 | Greece | Prospective study | 12 | Negative |

RCT: Randomized controlled trial.

**Table 2 Summary of relevant studies between *Helicobacter pylori* and chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Type of study** | **Number of subjects** | **Conclusion** |
| **HCV** |  |  |  |  |  |
| Esmat *et al*[30] | 2012 | Egypt | Cross-sectional study | 85 | Positive |
| Queiroz *et al*[93] | 2006 | Argentina | Cross-sectional study | 106 | Positive |
| Rocha *et al*[94] | 2005 | France | Cross-sectional study | 109 | Positive |
| Wang *et al*[95] | 2016 | Various countries | Meta-analysis | 3826 | Positive |
| **HBV** |  |  |  |  |  |
| Ponzetto *et al*[96] | 2000 | Italy | Case-control study | 355 | Positive |
| Huang *et al*[97] | 2017 | China | Cross-sectional study | 608 | Positive |
| Mohamed *et al*[98] | 2018 | Egypt | Cross-sectional study | 170 | Positive |
| Wang *et al*[99] | 2011 | China | Cross-sectional study | 1872 | Negative |
| Wang *et al*[100] | 2016 | China | Meta-analysis | 4645 | Positive |
| **HCC** |  |  |  |  |  |
| Nilsson *et al*[24] | 2001 | Sweden | Cross-sectional study | 36 | Positive |
| Pellicano *et al*[25] | 2004 | Italy | Cross-sectional study | 26 | Positive |
| Huang *et al*[26] | 2004 | China | Cross-sectional study | 36 | Positive |
| Xuan *et al*[27] | 2006 | China | Cross-sectional study | 50 | Positive |
| Xuan *et al*[101] | 2008 | Various countries | Meta-analysis | 522 | Positive |