REVIEW

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Association between *Helicobacter pylori* and Hepatobiliary Cancer: A Meta-analysis and Systematic Review

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Abstract

Objective: *Helicobacter pylori* infections have been suggested to be associated with several extra gastric maladies, including hepatobiliary cancer (HBC). However, reports on the relationship between *H. pylori* infection and HBC showed variable and contrasting findings. This study aimed to address these contrasting findings and clarify the effect of *H. pylori* infections on HBC. Thus, we performed a systematic literature review of published related studies and a meta-analysis of eight eligible publications. **Methods:** Related studies were searched in various database websites namely PubMed, ScienceDirect, Google Scholar, and Cochrane Library. Eligible studies were collated, and data were extracted. The odds ratio (OR) and 95% confidence interval (CI) were computed and interpreted using Review Manager 5.4. **Results:** Our overall analysis showed a significant association between *H. pylori* infection and HBC risk. Post-outlier analysis revealed homogeneous data (I^2 = 0%, p = 0.82) and significant association (OR: 2.63, 95% CI: 1.62-4.28, P < 0.0001). Subgroup analysis based on the method of diagnosis (PCR OR: 2.46, 95% CI: 1.37–4.42, P = 0.003; ELISA OR: 2.40, 95% CI = 0.99 – 5.85, P = 0.05) showed almost similar associations and odds ratios, but only the PCR group (I^2 = 0%, P = 0.72) showed homogeneity. Subgroup analysis based on specimen types revealed consistent results for liver tissue (I^2 = 0%, P = 0.82) and bile (I^2= 0%, P = 0.76) samples, showing low heterogeneity. In contrast, serum samples (OR: 2.40, 95% CI = 0.99 – 5.85, P = 0.05) displayed a potential but statistically nonsignificant association, while bile samples demonstrated a significant association (OR: 3.65, 95% CI: 1.56-8.52, P = 0.003). **Conclusion:** Overall, the present study suggests that *H. pylori* infection is associated with increased susceptibility to HBC development, with an increased effect found in bile and serum samples as specimens of choice for diagnosing *H. pylori*.

Keywords: Hepatobiliary cancer- *Helicobacter pylori*- hepatocellular carcinoma- biliary tract cancers- gallbladder cancer

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Introduction

Helicobacter pylori is a pathogenic bacterium that infects the lining of the stomach and is implicated in some liver diseases such as liver fibrosis, cirrhosis, non-alcoholic fatty liver disease and steatohepatitis [1]. It is also a well-established principal trigger for the development of gastric cancer [2]. Recently, studies have reported *H. pylori* as a type I carcinogen for gastric cancers, chronic gastritis, gastroduodenal ulcers, and biliary tract cancers [3-4].

Hepatobiliary cancers (HBC) which include hepatocellular carcinoma and biliary cancers (bile duct cancer or cholangiocarcinoma and gallbladder cancer) are malignancies that occur in the liver and/or in the intra- and extrahepatic bile ducts [5]. Diagnosis of HBC would generally be conducted either through blood tests, sonography, CT scans, magnetic resonance imaging, angiograms, and biopsy. However, early warning signs for HBC are asymptomatic in nature and thus further understanding of the biology of the disease is warranted [6-8].

HBCs are among the leading causes of cancer-related mortalities which may be partly due to its unclear underlying carcinogenetic mechanisms and complex epidemiological status [5, 9-10]. Several risk factors for HBC such as cholestasis, sclerosing cholangitis, chronic inflammation, type 2 diabetes, tobacco consumption, exposure to certain chemicals, consumption of aflatoxin-containing food, and obesity have been demonstrated [11-15]. The involvement of *H. pylori* remains among

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the least explored and scientifically intriguing risk factor [16]. Although studies have demonstrated that *H. pylori* infection might be causative to HBC pathologies, their cause-effect relationship is still inconsistent [7, 17-18]. Thus, to address these contrasting findings and to clarify the effect of *H. pylori* infections on HBC which eventually leads to better diagnosis and prognosis, we performed a systematic literature review of related studies and performed a meta-analysis on eight eligible studies.

Materials and Methods

Literature Search Strategy

Related literature that reported the association between *Helicobacter pylori* and hepatobiliary cancer was acquired from four databases, namely PubMed, ScienceDirect, Google Scholar, and Cochrane Library, as of September 2, 2022. The keywords that were used for the literature search were divided into two components with their corresponding synonyms: *H. pylori* (e.g., *Helicobacter pylori*) and hepatobiliary cancer (e.g., liver cancer, liver carcinoma, hepatocellular carcinoma, HCC, fibrolamellar carcinoma, bile duct cancer, cholangiocarcinoma, angiosarcoma, hepatoblastoma, malignant neoplastic disease of the liver, malignant hepatoma, hepatocarcinoma, intrahepatic cholangiocarcinoma). There were no restrictions applied on the publication date of the studies. However, studies published in the from 2000 to present were chosen to maintain relevance.

Study Assessment and Eligibility Criteria

First, a preliminary screening was performed so that only the titles and abstracts of the acquired studies were qualified for full-text evaluation. From the 3,503 records, duplicate and unrelated studies were excluded, resulting in 877 records. The following inclusion criteria were used to evaluate further the relevant articles that made it through the initial screening. These are whether they included (1) *H. pylori* and (2) HBC. These studies were conducted as either cohort or case-control designs, in which patients with confirmed HBC were assigned to the case group, while cancer-free individuals comprised the control group. This meta-analysis did not include research on animal models, review articles, clinical trials, indexes, brief reports, or case reports. Non-English publications and those lacking English translation were excluded, reducing the initial records to 40. After evaluating the full-text articles, those that did not meet the eligibility criteria or had incomplete data were further excluded, resulting in 14 remaining records. Additional publications identified from the references of the selected studies were screened and evaluated, but none met the criteria, leaving a final set of 8 records.

Data Extraction

Data extraction was performed on the eligible studies, and the following information was recorded: first author's last name, publication year, place of publication, sample type (e.g., serum, bile, liver tissue, breath, stool, or other liver specimens), analysis method for *H. pylori* presence or absence, control group description in each article, total number or percentage of patients with and without *H. pylori* and hepatobiliary cancer, and control group data for patients without hepatobiliary cancer. The mentioned data were extracted by J.G.P., K.B.R., J.R.R., A.R.A., M.I.D., and J.N.P., and were agreed upon by J.G.P. and J.R.R., and further verified by J.G.P., K.B.R., J.R.R., A.R.A., M.I.D., J.N.P., J.A.M., R.E.T., and P.M.A. collectively. The data were then tabulated to be properly presented in this review.

Quality Assessment of Eligible Studies

The studies were reviewed based on the title and abstract of the records identified to select all the potentially relevant studies. The full text of selected studies that met the eligibility criteria was then evaluated using Newcastle-Ottawa Scale (NOS) to assess the quality and compare methodological data across the selected studies. The NOS has eight items divided into three domains, with a maximum score of nine. A study with a score of 7-9 has high quality, a score of 4-6 has high risk, and a score of 0-3 has a very high risk of bias [19].

Meta-analysis Protocol

Review Manager 5.4.1 and Meta-Essentials were used to conduct the statistical analysis [20-21]. The protocol used for this meta-analysis was based on the procedure of Gaab et al. [22] with modifications to fit the study. Using the resultant pooled odds ratios (OR) and 95% confidence intervals (CI), which were then evaluated using either a fixed-effects model or a random-effects model, the link between *H. pylori* and HBC was assessed. The model employed depended on heterogeneity, which was determined by the calculated P value and I^2 statistics. An I^2 value of 0% to 40% was interpreted as homogeneous; 30% to 60%, moderate heterogeneity; 50%, substantial heterogeneity; and 75%, considerable heterogeneity. When there was heterogeneity, a fixed-effects model was applied, and when there was none, a random-effects model was used. All the ORs and 95% CIs had two-sided P values with a significance level of ≤ 0.05. However, due to the low power of the test, the P value for heterogeneity testing was set at <0.10 [23]. Sensitivity analysis, which involved systematically removing one study at a time from consideration, was performed to assess the robustness of the overall summary effects.

Results

Search Result

In this meta-analysis, 3,503 studies were initially acquired from PubMed, ScienceDirect, Google Scholar, and Cochrane Library (Figure 1). After removing duplicate studies, only 877 articles were further evaluated. Screening the title further excluded 837 studies. The remaining 40 studies were subjected to an in-depth review of the abstract and excluded 26 studies in the process. From this number, 14 studies were assessed for eligibility, with eight studies qualified and six unqualified due to incomplete data. Only eight articles were included in this study, namely those of Boonyanugomol et al. [11], Boonyanugomol et al. [12], Esmat et al. [13], Fotouhi et al. [24], Ito et al. [25], Leone et al. [26], Makkar et al. [27], and Ponzetto et al. [28].

Characteristics of the Included Studies

Table 1 provides an overview of the included studies' characteristics. Of the eight studies, one followed a cohort design, while the remaining seven were case-control studies. Geographically, the studies were distributed across various regions, with two conducted in Italy, two in Thailand, and one each in Germany, Ethiopia, Egypt, and Iran. The articles were published between 2003 and 2020, of which two were published in the past decade. The NOS scoring indicated that the included studies were of high quality, with a mean and standard deviation of 6.30 ± 1.27 and a median of 6.

Overall Analysis and Post-outlier Analysis for the Association of H. pylori with HBC

Eight studies were included in the overall analysis of the association between Hp and HBC (Figure 1). A random-effects model analysis (Figure 2) was used and showed significant association (OR = 2.41, 95% CI = 1.39-4.16, P = 0.002) yet displayed heterogeneity (I^2 = 72%, P = 0.0001) in the overall analysis. This prompted us to identify the source by visual examination of the funnel plot (Figure 2). The studies of Makkar et al. [27] and Ponzetto et al. [28] were found to be the outliers and were removed.

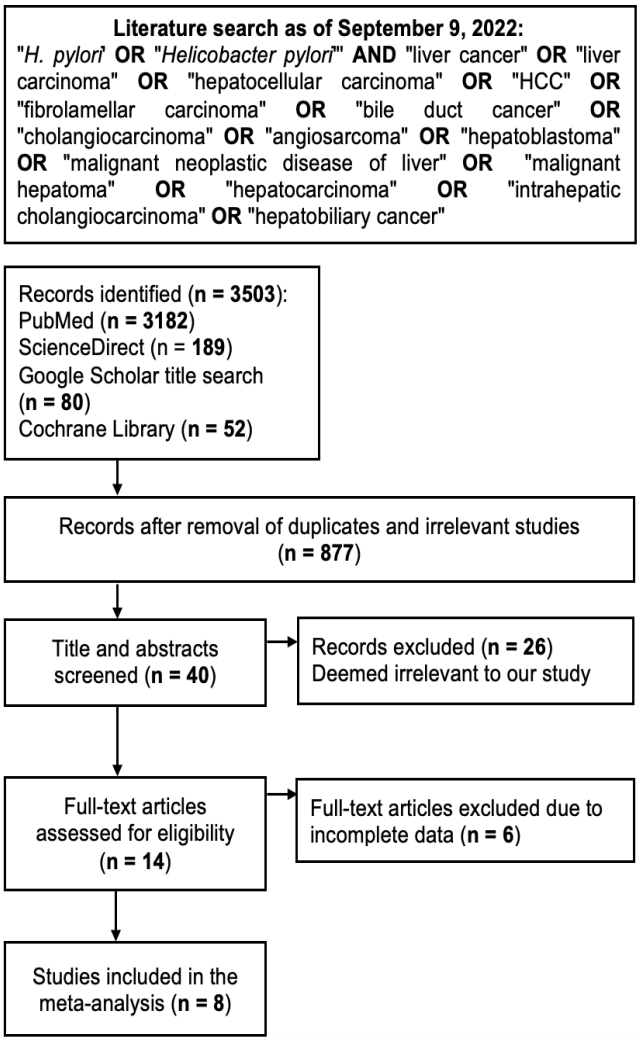


Figure 1. PRISMA Flow Diagram for the Selection of Included Studies

Table 1. Characteristics of the Included Studies

Article No.	First Author	Year of Publication	Country	Sample	Method	Source of Control	Hp+		Hp-		Newcastle-Ottawa Scale
							HBC	Control	HBC	Control	
1	Makkar	2020	Germany	Non-fasting serum	Multiplex serology	Participants without HBC	274	484	258	577	8
2	Ponzetto	2017	Italy	Serum	ELISA	Patients without HCC	183	227	37	182	8
3	Leone	2003	Italy	Serum	ELISA	Patients without HCC	36	25	10	21	6
4	Boonyanugomol	2012	Thailand	Bile	PCR	Patients without CCA	80	4	58	12	5
5	Ito	2003	Japan	Liver tissue	PCR	HCC-free individuals	13	10	10	10	5
6	Boonyanugomol	2011	Thailand	Bile	PCR	Patients without CCA	17	5	16	15	7
7	Esmat	2011	Egypt	Liver tissue	PCR	Patients without HCC	13	11	3	6	6
8	Fotouhi	2011	Iran	Liver tissue	PCR	Patients without HCC	7	3	22	19	5

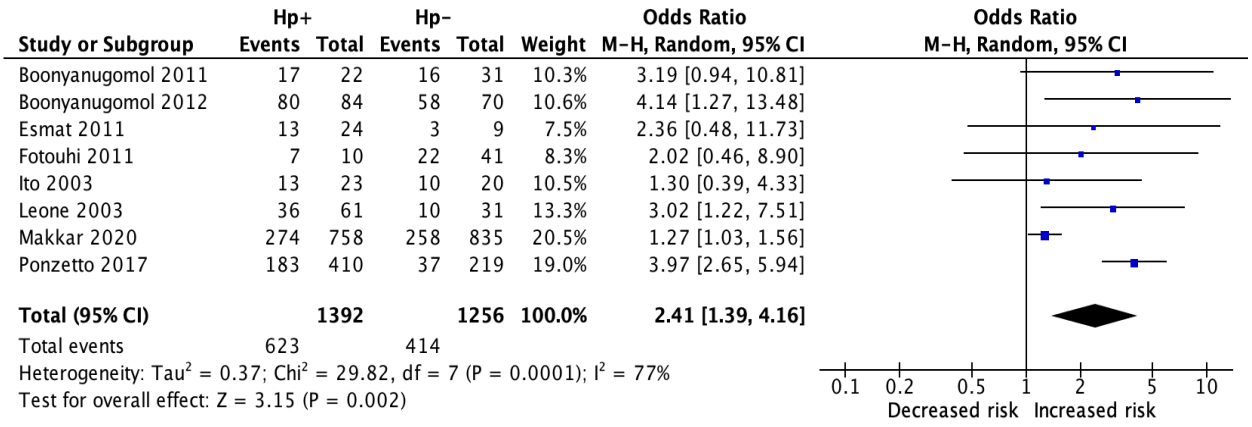


Figure 2. Overall Association of the Presence of *H. pylori* with the Development of Hepatobiliary Cancer. CI and degrees of freedom are presented above.

Re-analysis was done, and we obtained homogenous ($I^2 = 0\%$, p = 0.82) and significant results (OR: 2.63, 95% CI: 1.62-4.28, P < 0.0001) (Figure 3).

Subgroup Analyses based on Diagnostic Methods and Specimen Types

Subgroup analyses were conducted to assess the impact of diagnostic methods (Figure 4a) and specimen types (Figure 4b) on the strength of the association. PCR studies displayed greater homogeneity ($I^2 = 0\%$, P = 0.72) compared to ELISA studies ($I^2 = 92\%$, P < 0.00001). Both PCR (OR: 2.46, 95% CI: 1.37–4.42, P = 0.003) and ELISA studies (OR: 2.40, 95% CI = 0.99 – 5.85, P = 0.05) revealed significant associations, with a slightly higher odds ratio observed in the PCR subgroup. Furthermore, studies that utilized liver ($I^2 = 0\%$, P = 0.82) and bile ($I^2 = 0\%$, P = 0.76) samples exhibited homogeneity. Notably, significant associations were observed solely in bile and serum (or ELISA) samples (OR: 2.40, 95% CI = 0.99 – 5.85, P = 0.05), with bile samples displaying a relatively higher odds ratio (OR: 3.65, 95% CI: 1.56-8.52, P = 0.003). Overall, these findings suggest that the presence of *H. pylori* may be associated with an increased risk of HBC. However, the choice of diagnostic specimen types and methods for detecting *H. pylori* infection could be critical in establishing this association.

Discussion

Overall Association between H. pylori Infection and Hepatobiliary Cancers

H. pylori is a naturally occurring bacterium in the oral microbiota, and part of the gut microbiota in the absence of inflammation [29]. The oral-gut axis connects gut organs together through this transmission route from mouth to stomach [30-31]. In *H. pylori*-related HBCs, hepatobiliary system colonization starts with bacterial translocation from the gastric region through the portal vein or directly through the bile duct [32-33]. The presence of *H. pylori* in individuals with HBC supports the hypothesis that the former has a role in the development of the latter. However, inconsistent associations between *H. pylori* and HBC have been reported. In the present paper, we performed meta-analysis of eight papers and quantified the association of *H. pylori* and HBC risk to clarify the role of the bacterial infection in HBC carcinogenesis. In our overall meta-analysis, we strengthened the claim that a significant association exists between *H. pylori* and HBC susceptibility with strong statistical power.

Immunologic mechanisms have been mostly proposed to explain this association. It has been implicated that synthesis of inflammatory cytokines and promotion of cell inflammation, which are innate immune mechanisms against *H. pylori* infection, might result in HBC. Increased

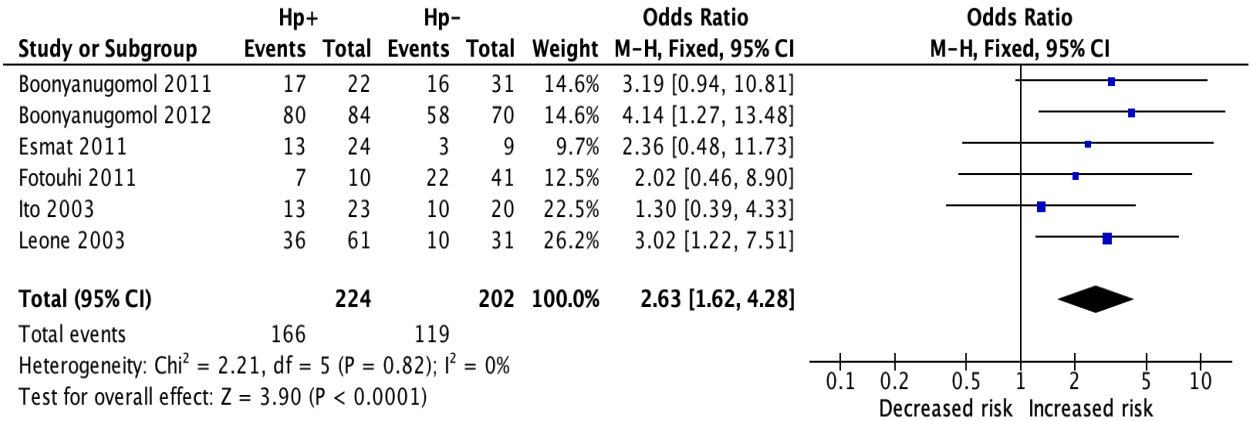
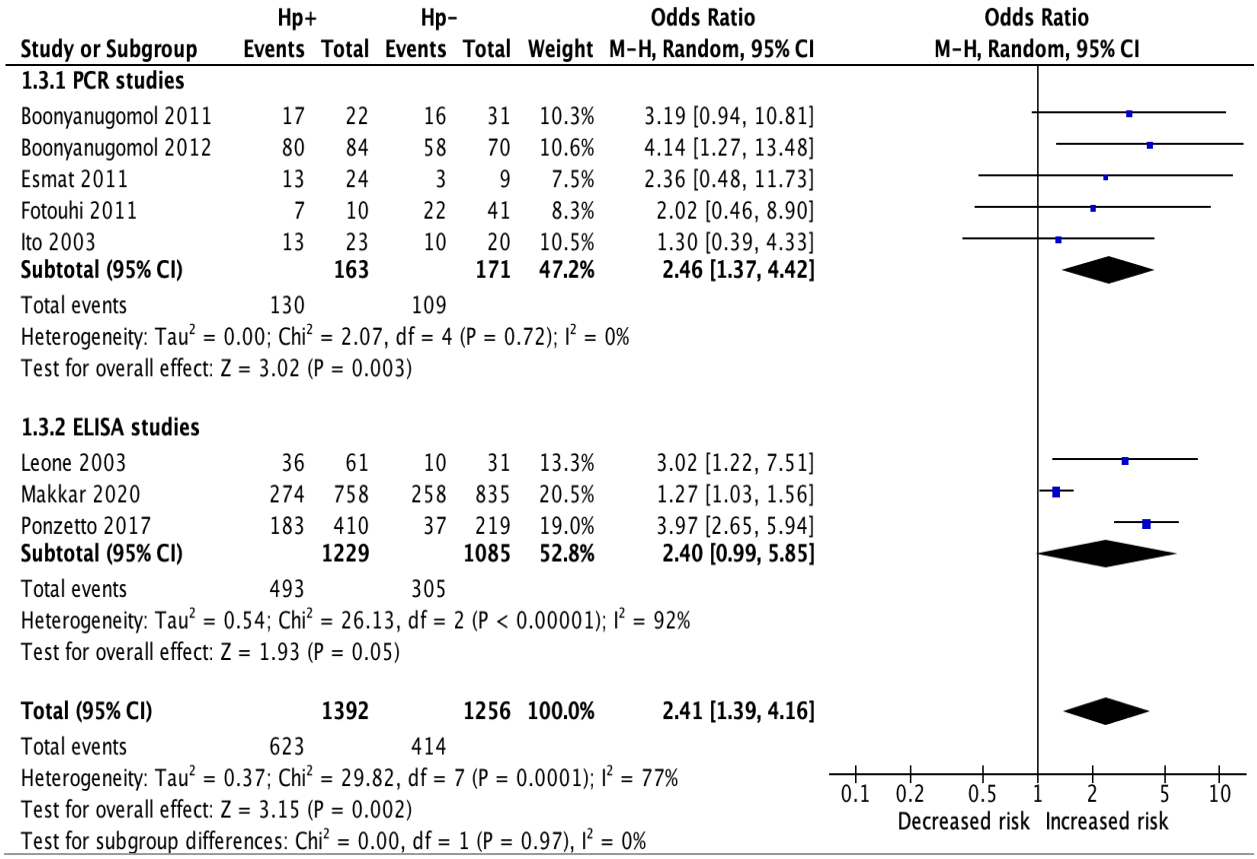


Figure 3. Post-Outlier Analysis for Association of Hp Presence with HBC. CI and Degrees of Freedom are Presented Above.



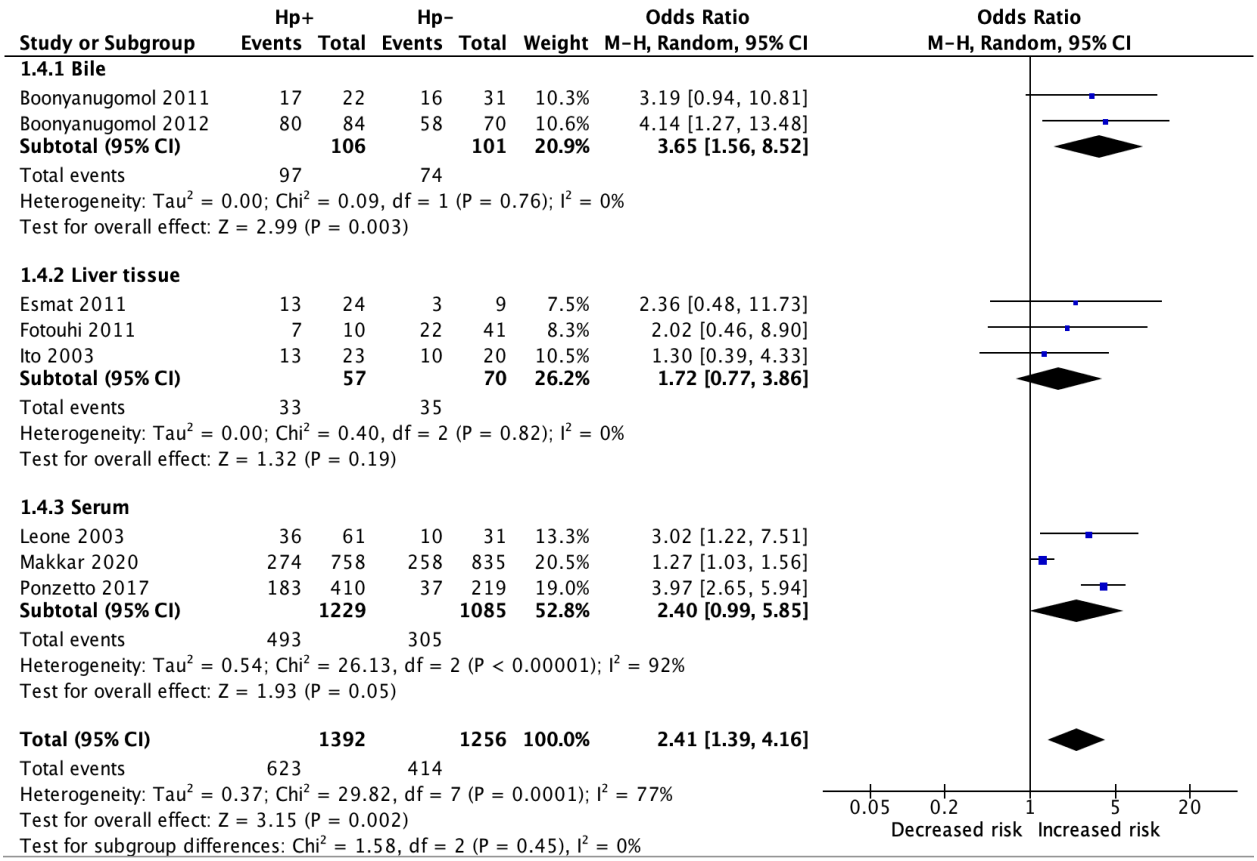


Figure 4. Subgroup Analysis of the Association of Hp Presence with HBC Development. Sugroups were formed based on method of testing used (upper figure), and type of specimen sample used (lower figure). CI and degrees of freedom are presented above.

synthesis of pleiotropic cytokines TNF-α and IL-6 may destroy normal cell adhesion thus enabling mutated epithelial cells to migrate and eventually metastasize. Proinflammatory cytokines and other signaling pathways have been shown to be activated by the Cag pathogenicity island (Cag PAI) virulence factor of *H. pylori* in a dysregulated manner [34-35]. Chronic inflammation may also result in release of nitric oxide thereby promoting oxidative DNA damage, another hallmark of cancer development. In addition to these immunologic responses, in vitro experiments have demonstrated the direct involvement of *H. pylori* in excessive cell proliferation and decreased apoptosis in mouse biliary cells although the mechanisms are still unclear [11, 36-37]. *H. pylori* was also shown to confer hepatoxicity in vitro and is associated with impaired DNA mismatch repair [25, 38].

Diagnostic Method for H. pylori Infection

Stratified analyses were also conducted to probe the putative involvement of *H. pylori* diagnostic and detection methods in establishing the relationship between the pathogen and HBC. A significant association was noted for both PCR and ELISA studies although a slightly better OR value was noted for PCR. For PCR studies, primers were used to confirm the presence of *H. pylori*. For the ELISA subgroup, anti-*H. pylori* antibodies were detected by ELISA and multiplex serology techniques. While both are considered accurate and standardized molecular tools for detecting *H. pylori*, studies have reported potential sources of inconsistencies for ELISA-based diagnosis of *H. pylori* due to the ability of the pathogen to evade antibody detection through its CagA protein. *H. pylori* possesses a virulent determinant called the Cag PAI, and this 40 kb DNA insertion element encodes an estimate of 32 genes including the CagA gene [39-43]. The primers and antibodies detect the expression products of CagA gene, the CagA protein. In the context of *H. pylori* detection, studies have reported that approximately 60% of *H. pylori* strains contain the Cag PAI. Almost all Eastern *H. pylori* strains have this virulent determinant, while only 30-40% Western strains exhibit such determinant [40, 43-44]. In terms of specificity, ELISA-based detection of *H. pylori* is considered limited due to potential cross reactivity between Helicobacter and Campylobacter species. Although these factors may have slightly decreased the statistical power of ELISA studies, significant associations were still noted thereby strengthening its accuracy as a diagnostic method.

In terms of the diagnostic specimen type for *H. pylori* (bile, liver, and serum samples), we reported significant association between risk of developing HBC and *H. pylori* infection when bile and serum samples were utilized. For the liver samples, earlier studies reported that *H. pylori* might not be detected in metastatic liver tumors due to presence of resident macrophages that may have phagocytosed the bacteria which might explain the insignificant result [25, 45]. Meanwhile, the presence of *H. pylori* in bile samples of HBC patients might be due to bile duct obstruction observed in cholangitis wherein pathogens ascend to the hepatobiliary system from the duodenum [46]. Another potential explanation might be that bacterial influx, including *H. pylori*, into the biliary tract occurs due to an increase in pressure within the biliary system during bile duct obstruction [47]. Lastly, in serum samples, anti-*H. pylori* antibodies are detected as described in the ELISA subgroup above. The sensitivity of using serum samples depends on the kit but in our analysis, the relevance of serology in detecting *H. pylori* and establishing association between the pathogen and HBC risk is strengthened [48-49].

Strengths and Limitations of the Study

A significant strength of this study lies in its substantial sample size, which comprises eight eligible studies, encompassing a total of 1037 cases and 1611 controls. A larger sample size bolsters the statistical power of our analysis, enabling us to detect more subtle associations and providing greater confidence in the results. Our study also adheres to a meticulous quality assessment process using the Newcastle-Ottawa Scale (NOS). The NOS provides a structured and systematic framework for evaluating the quality of non-randomized studies in meta-analyses, ensuring that only high-quality studies are included in our analysis. Additionally, we conducted subgroup analyses based on diagnostic methods and specimen types. This approach facilitates a comprehensive exploration of the factors that may influence the association between *H. pylori* and hepatobiliary cancer, enhancing the depth and specificity of our findings. Lastly, our post-outlier analysis revealed homogeneous data, indicating that the removal of outliers did not significantly impact the overall results. This homogeneity underscores the robustness and stability of our findings, further strengthening the validity of our conclusions.

Moreover, studies included in our meta-analysis were published between 2003 and 2021. Even if the last search was on September 2022, no additional studies have been published regarding the association between *H. pylori* infection and HBC risk within that time frame. In June 2023, there has been a published review paper discussing the link between *H. pylori* infection and biliary tract diseases including biliary tract cancer (BTC). The study highlighted the purported etiologic role of *H. pylori* in BTC but did not provide statistical power to quantify the association [49].

Meanwhile, several limitations merit consideration. The potential for publication bias must be acknowledged, as unpublished or negative studies may not have been included, introducing a source of bias. Furthermore, despite our efforts to address heterogeneity, variations in study design, populations, and methodologies among the included studies could have influenced our results. The variability in study quality and the risk of unmeasured confounders also pose challenges. Therefore, while our findings indicate a potential association between *H. pylori* infection and hepatobiliary cancer, further research, particularly longitudinal cohort studies and mechanistic investigations, is warranted to validate and elucidate this relationship. Such endeavors will not only enhance our understanding but also contribute to the development of preventive and therapeutic strategies for hepatobiliary cancer.

In conclusion, our systematic review and meta-analysis provide compelling evidence of a significant association between *H. pylori* infection and hepatobiliary cancer. This comprehensive analysis, involving eight high-quality studies, revealed a substantial increase in the risk of hepatobiliary cancer among individuals with *H. pylori* infection. Importantly, our findings highlight the critical influence of diagnostic methods and specimen types on the strength of this association, with PCR-based studies and bile samples displaying particularly noteworthy results. These results have significant implications for both clinical practice and public health, emphasizing the importance of early detection and eradication of *H. pylori* infection as a potential preventive measure against hepatobiliary cancer. Nonetheless, further research is warranted to elucidate the underlying mechanisms and establish causality definitively, paving the way for more targeted interventions in the future.

Author Contribution Statement

JLGR Peñaflorida, JRU Requesto, KYB Romero, AER Africa, MIC de la Torre, JNN Pateña, JAH Manzano, and RE Tiongco performed the literature search, collection and organization. All authors took part in the study assessment and selection, data extraction, and in performing the actual meta-analysis protocol. JLGR Peñaflorida, JRU Requesto, KYB Romero, AER Africa, MIC de la Torre, and JNN Pateña drafted the initial manuscript. JAH Manzano, RE Tiongco, and PMS Albano finalized the manuscript. All authors agreed to the final version of the manuscript.

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Data Availability

All data are available in the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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