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Prospective Study on Association of Helicobacter Pylori Infection in Colorectal Cancer

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Abstract
Background: *Colorectal cancers were studied extensively for their association with environmental and dietary factors, and gut microflora.* Helicobacter pylori *is known to be associated with a large spectrum of gastric and extra-gastric conditions.* H. pylori *has been recognized as a class I human carcinogen by the International agency for cancer research . There are recent reports on the role of* H. pylori *in the promotion of tumour growth in extra-gastric organs, of which its role in colorectal neoplasm is gaining interest.*
Aims and objectives: *This study aims to evaluate the association of* H. pylori *infection and colorectal cancers. To determine the prevalence of* Helicobacter pylori *infection in patients with colorectal cancers and compare with controls.To examine the possible correlation of overall* H. pylori *infection and the CagA strains with the site, histopathological differentiation, stage and metastasis of colorectal cancer*
Materials and methods: *A prospective case-control study conducted in 90 patients admitted in department of general surgery ,Government Rajaji Hospital,Madurai from August 2019 to August 2020.*
Observations and Results: *The overall prevalence of* H. pylori *was 60% with 66% (31/47) of study patients and 53.5%(23/43) of control patients being positive.On site-specific analysis, 71.4% (5/7) of study and 65% (26/40) of control were positive.On stage-specific analysis, 65.2% (15/23) of high stage cancers and 66.7% (16/24) of low stage cancers were infected with* H. pylori.*The CagA seroprevalence in the study group was 38.3% (18/47) and in the control group was 21% (9/43). On comparing stage- specific association with CagA strains of* H. pylori *infection, 39% (9/23) of high stage tumours and 37.5% (9/24) of low stage tumours were CagA seropositive, significant p-value of 0.009 was noted with histopathological differentiation.*
Conclusion: *The present study showed that there was no association between* H. pylori *infection and colorectal cancers and also there was no association of site, histopathological differentiation, stage and presence of metastasis in the tumour with this infection*
Key Words: *CAG A, Colorectal cancer ,ELISA, H.Pylori, Rapid Urease Test.*

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I. Introduction:

Colorectal cancers hold a major burden of cancer and cancer-related deaths in the world. Colorectal cancers were studied extensively for their association with environmental and dietary factors, and gut microflora. As these include modifiable risk factors there is a potential for their role in primary prevention of colorectal cancers. Helicobacter pylori (H. pylori) being highly prevalent in general population, any evidence of its role in colorectal carcinomas will warrant early screening and eradication of this risk factor.H. pylori is known to be associated with a large spectrum of gastric and extra-gastric conditions. H. pylori has been recognized as a class I human carcinogen by the International agency for cancer research (2). There are recent reports on the role of H. pylori in the promotion of tumour growth in extra-gastric organs(1), of which its role in colorectal neoplasm is gaining interest.The pathogenic role of H. pylori in the development of colorectal malignancies is not clear (2). A possible mechanism described attributes it to the expression of the cytotoxin-associated gene (CagA) by the H. pylori strains (3). CagA strains result in the development of chronic atrophic gastritis which further leads to hypergastrinemia. Hypergastrinemia through a reverse feedback mechanism is known to facilitate the development of colorectal cancer (3-5). Moreover, hypochlorhydria induced by the chronic atrophic gastritis also results in the overgrowth of microflora like B. fragilis and E. faecalis which are implicated in the colorectal cancer progression^). Alternatively, the inflammatory response mediated damage to the colorectal epithelium induced by H. pylori may also promote the development of colorectal neoplasia(l).The correlation between H. pylori and colorectal malignancies, however, remains controversial. A higher seroprevalence of H. pylori has been reported in people with colorectal malignancy in various studies (7-11). A study by Strofilas et al demonstrated an association between H. pylori and colorectal neoplasia as statistically not significant, however, the same study reported a statistically significant association between

hypergastrinemia) and lymph node metastasis(12).There is a death of studies correlating the role of H. pylori in the development of colorectal neoplasia from Asia. The direct etiological association of H. pylori in colorectal malignancy, hence, can neither be supported nor rejected and requires more clinical studies to confirm its association^ 3). Hence this study is being carried out to evaluate the association of H. pylori and colorectal malignancy in our population.

II. Aims And Objectives:

To evaluate the association of H. pylori infection and colorectal cancers.

Primary objectives

To determine the prevalence of Helicobacter pylori infection in patients with colorectal cancers and compare with controls.

Secondary objectives

To examine the possible correlation of overall H. pylori infection and the CagA strains with the site, histopathological differentiation, stage and metastasis of colorectal cancer.

III. Materials And Methods:

The participants were categorized into two groups namely study and control groups. The study group included all consecutive patients of age >18 years with histologically proven colorectal malignancy in the Department of Surgery, GRH, Madurai. The control group included age and gender-matched patients undergoing groin hernia repair (males) and treatment for extra abdominal benign conditions (females) in the Department of Surgery, GRH, Madurai.

The following patients were excluded from the study:

1. Patients receiving gastric anti-secretory medications and NSAIDs on a long-term basis.
2. History of previous gastro-duodenal surgery.
3. History of Zollinger Ellison syndrome.

The effect of Non-steroidal anti-inflammatory drugs on H. pylori and vice versa was proposed and studied by many. But both, independent risk factors for gastric diseases, being synergistic or antagonistic is not identified in any study. Though many mechanisms were proposed none of them was proved. As the interaction between both risk factors was not well understood, patients receiving these drugs on a long-term basis were excluded (72, 73).In patients who underwent any gastroduodenal surgeries, bile reflux will affect the growth of H. pylori and also some studies showed there is the spontaneous eradication of H. pylori after surgery (56).Patients with Zollinger Ellison syndrome were excluded as they have hypergastrinemia which acts as a confounding factor for colorectal malignancies (67-69).

DATA COLLECTION

Data was collected from both the study group and control group using a pre-approved data collection Proforma. It included independent variables such as:

1. Age
2. Gender
3. History of smoking
4. Prevalence of H. pylori infection

The outcome variables recorded were:

1. Histopathological type
2. Stage of colorectal malignancy
3. Presence/absence of lymph node metastasis.
4. Metastasis
5. Differentiation of the tumour

IV. Observations And Results:

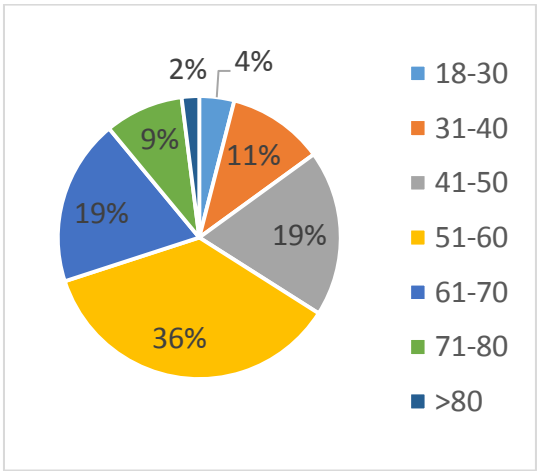

Figure I: Age distribution (in years) in the study group (n=47)

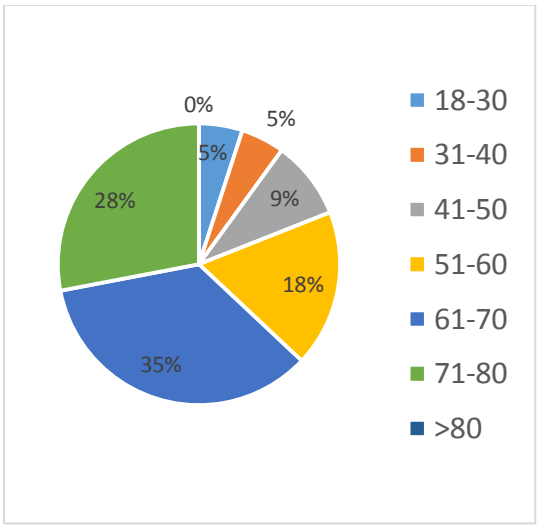

Figure II: Age distribution (in years) in the Control group (n=43)

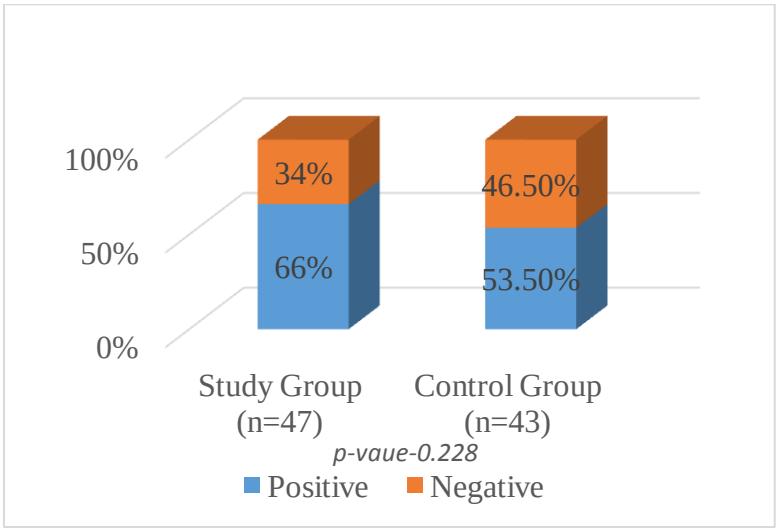

Figure III: Prevaence of H.pylori infection in study and control groups.

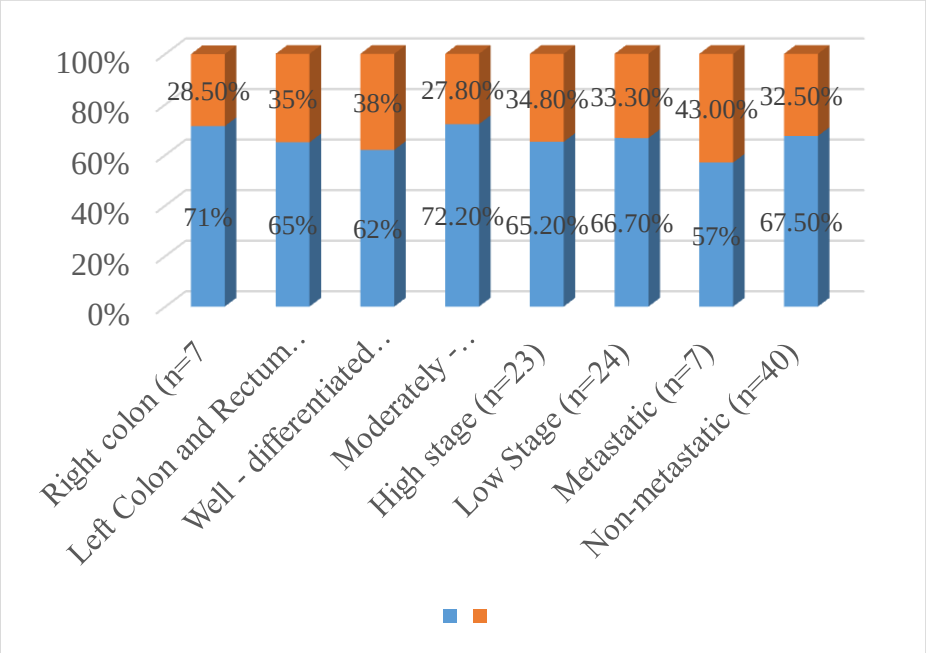

Figure IV: Comparison of H.pylori infection in relation to the site, histopathological differentiation, stage and metastasis of colorectal cancers in the study group (n=47)

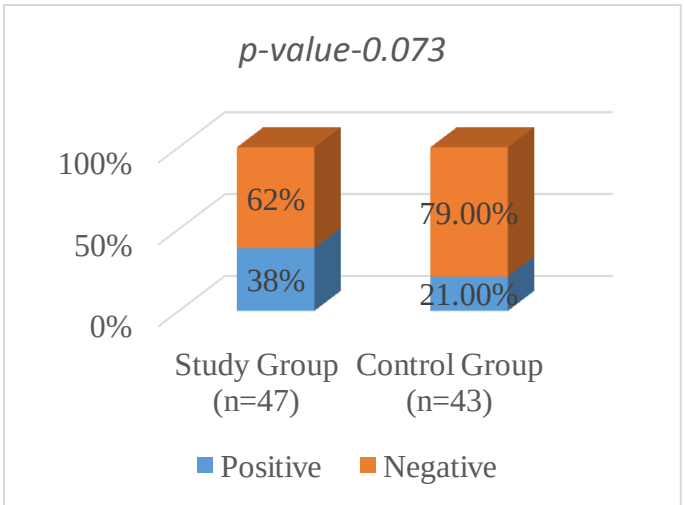

Figure V: Prevalence of CagA seroprevalence of H-pylori in study and control groups.

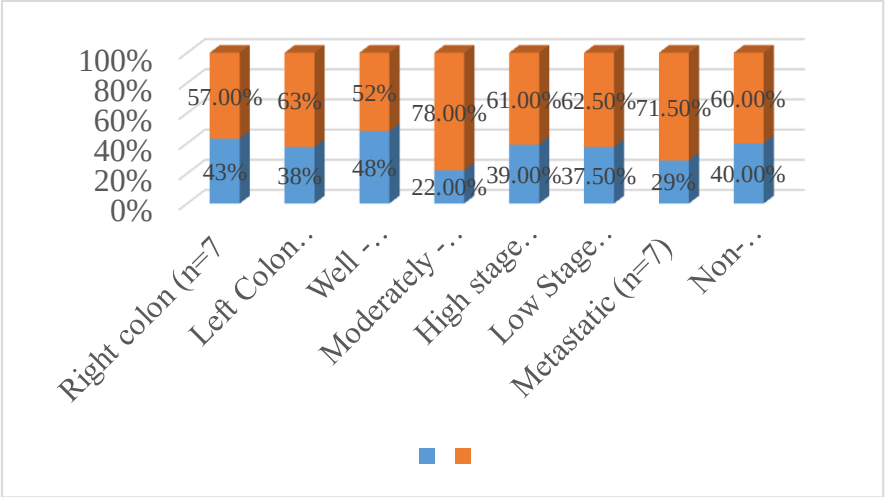

Figure VI: Comparison of CagA seroprevalence for h.pyori in relation to the site, histopathological differentiation, stage and metastasis of colorectal caners in the study group (n=47).

Figure VIII: Positive test for *H. pylori* stool antigen by Immunochromatography Assay (On-Site *H. pylori* rapid test); positive (arrow)

Figure IX: Negative test for *H. pylori* stool antigen by Immunochromatography assay (On-Site *H. pylori* rapid test).

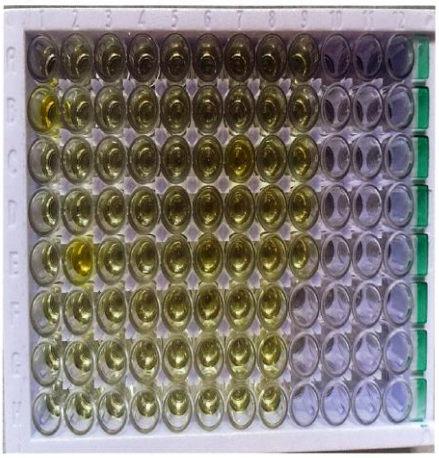

Figure X: *H. pylori* CagA ELISA kit in process (Bioassay Technology Laboratory). ELISA-Enzyme-Linked Immunosorbent Assay

V. Discussion

H. pylori is a ubiquitous organism with a high prevalence in general population despite the geographical variations. Many recent studies were done to identify the epidemiological association of this organism with different gastric and extra-gastric diseases(74). Though some have adequate evidence to define its causative role in gastric cancer, MALToma, etc., others are still under evaluation. The clinical outcome from H. pylori infection depends on various host response factors, different strains of bacteria and environmental factors. With the recent evidence showing possible correlation with colorectal cancers, there is growing interest in studying their correlation worldwide. Colorectal cancers are one of the top five leading causes of cancer-associated mortality globally. The multifactorial aetiology for these cancers is well known and evaluated. However, further research to identify other possible risk factors which could elaborate our knowledge on the aetiology and aid in the management of colorectal cancers is needed. Many case- control, cross-sectional studies and meta-analysis were done widely in pursuit of knowing the relationship between H. pylori infection and colorectal cancers(41). Yet their association is far from any conclusion with conflicting evidence and many of the studies are not without limitations.

The present study was carried out to study the association between H. pylori infection and colorectal cancers, with special reference to CagA strains and also its association with respect to the site, histopathological differentiation, stage and metastasis of malignancy. In the present study, age distribution, gender distribution and smoking status were similar in both groups. A higher trend of the prevalence of H. pylori positivity was identified in the study (colorectal cancer) group when compared to controls (66% vs 53.5%), however, the analysis showed no significant difference. Similarly, CagA seroprevalence for H. pylori was high in the study group (38.3% vs 21%) when compared to the control group, however, the difference was not significant. In the present study, no association was found between colorectal cancer and H. pylori infection. Also, no correlation of colorectal cancer was found with CagA strains of H. pylori. Further analysis of the study group with respect to the site, differentiation, stage and metastasis between H. pylori infection and specifically with CagA strains did not reveal positive correlation. In patients with positive H. pylori infection in the study group, a significant correlation of CagA strains of H. pylori was found with histopathological differentiation. Here a higher prevalence of these strains was observed in well-differentiated adenocarcinomas (p-value-0.009).

Even though abundant studies were available over different cohorts, they have their own limitations in providing strong and reliable evidence for the correlation. Some of those limitations include small sample size, selection bias from hospital-based sampling and inability to correct for confounding factors. Studies done retrospectively are less reliable when compared to prospective studies. In retrospective studies, the duration of risk exposure and the lag period from risk exposure to onset of disease cannot be studied. Some studies have shown a positive correlation between the two (7-9,11,75-77) whereas others showed no association (10,71,78-84). Two studies which were based on urea breath test did not show any correlation (82,85). A Japanese study where three non-serological tests as rapid urease test, histology and urea breath test showed a positive correlation(75). Most of the studies were case-control studies and only two prospective studies were done but they were limited by their small sample size(71,84). There is a dearth of studies in Asian population particularly in India where there is a need for reliable large population-based analysis of H. pylori infection and its associations with different diseases.

The present study showed an overall H. pylori prevalence of 60%, which is comparable to the prevalence in general population (15). A prevalence of 66% in study group and 53.5% in control group was noted in the present study which is relatively higher in comparison to a large population-based case-control study conducted in Germany by Zhang et al, which showed a seroprevalence of H. pylori as 46.1% and 40.1% in cases (n=1712) and controls (n=1669). The previous report demonstrated a positive association of H. pylori with colorectal cancers (odds ratio of 1.30; p-value of 0.001) (86). A meta-analysis conducted by Zumkeller et al from 1991-2002 had a prevalence of 67%(666/997) in cases and 60%(881/1476) in controls with an odds ratio of 1.4(2). Strofilas et al conducted a prospective case- control study in Greece which showed a prevalence of 71% (66/93) in colorectal cancers and 65% in control group with no statistical significance(12). A similar association was found in the present study as well, although not significant. A meta-analysis done by Wu et al revealed a pooled OR of 1.39 and 1.42 in Western and Eastern studies(13). Limburg et al studied H. pylori with colorectal cancer risk which showed an H. pylori seroprevalence of 72% in cases and 78% in controls with an odds ratio of 0.83(71).

The present study demonstrated a CagA seroprevalence for H. pylori of 38.3% in the study and 21% in the control groups. Among the H. pylori- infected colorectal cancer patients CagA prevalence was 58%. In the control group, CagA seroprevalence was 39% among overall H. pylori-infected patients. These results show a higher prevalence in the study group and less prevalence in the control group in comparison to a study, which showed a CagA seroprevalence of 34% and 29.9% in cases and controls respectively(86), however, there was no significant difference in CagA seroprevalence in both groups. Also, CagA prevalence increased with age in both groups in this study. A study conducted by Strofilas et al demonstrated a CagA positivity of 56% in cases and

38.4% in control group with no statistical significance (12). Wu et al meta-analysis on H. pylori and colorectal cancers showed a pooled OR of 1.37 for CagA positivity(13). The prevalence of CagA antibodies noted in a study conducted by Limburg et al was 59% in control group and 62% in cases with an odds ratio of 1.21, but with no statistical significance).

On site-specific analysis, the present study revealed that 5(71.4%) out of 7 patients with right-sided colon cancers and 26(65%) out of 40 patients with left colon and rectal cancers were positive for H. pylori. Although a higher trend was noted, the number of patients with right colon cancers was low to draw conclusions. When compared the published reports by Zhang et al which showed a prevalence of 43.9%(243/553) in right colon cancers and 47% (553/1176) in left colon and rectum cancers, the prevalence in the present study was high. The adjusted odds ratio for H. pylori in left colorectal cancers was 1.32(86). Only two studies have evaluated the site-specific association of H. pylori with colorectal cancers(71,80). As there is increasing evidence for a difference in aetiologies and behaviour of malignancy according to the site, this type of analysis is required(42,86).

In the present study, considering CagA positive strains correlation with the site of cancer, a 43% prevalence in right colon cancers and 37.5% prevalence in left colon and rectal cancers was observed. The prevalence of CagA in right colon was 60.1% (146/243) when compared to 64.2% (355/553) in left colorectal cancers, in a study where adjusted odds ratio was 1.22 (95% CI-1.05 - 1.57) in left colorectal cancers and OR was 1.00 (95% CI-0.77 - 1.29) in right colon cancers(86). The present study showed a lower prevalence in comparison with the above study in both groups.

With respect to differentiation of histopathology H. pylori prevalence of 62% in well differentiated and 72.2% in moderately differentiated carcinomas was noted. A study conducted by Kapetanakis et al revealed a high prevalence of H. pylori infection in colorectal cancers with mild dysplasia (mild dysplasia-89% and moderate/severe dysplasia-83%) (87).

In the present study, 65.2% of high stage cancers and 66.7% of low stage cancers had H. pylori infection. A higher prevalence was observed when compared to the prevalence of 47.7% (443/929) in low stage and 44.4% (346/780) in high stage cancers, which were noted in a study with an adjusted odds ratio of 1.34 in low stage and 1.16 in high stage cancers (86). But there was no significant difference noted in the present study. Analysis for the stage was emphasized as there was evidence for association with colorectal adenomas (7,9,75). Some studies observed that gastrin causes mucosal proliferation in the colon by activating certain receptors which were found to have a role in advanced malignancy and adenoma-carcinoma sequence (8,66,88).

The present study showed the prevalence of CagA in the low and high stage as 39% and 37.5%, with no significant variation. The observed results were less when compared to a case-control study, which showed a CagA seroprevalence of 65% (288/443) in low stage and 60.1% (208/346) in high stage cancers with an adjusted odds ratio of 1.48 and 1.16 respectively(86).

The results from the present study provide data regarding the prevalence of H. pylori infection in colorectal cancers, which can be used as a basis for further studies. As the prevalence varies in different cohorts, the present study which was carried out in a single centre, it can provide data for this region which can be compared with other regions.

Colorectal cancers have a multifactorial aetiology which needs to be studied elaborately to define the causative role of each factor. H. pylori infection is easy to diagnose and it can be eradicated with a combination of antibiotics in a short duration effectively. As H. pylori is highly prevalent in general population especially in developing country like ours, any evidence of its association with colorectal cancers would direct for its eradication in these patients, particularly in the high-risk population. H. pylori eradication is a cost- effective and acceptable method of primary prevention. This method was found to decrease the incidence of gastric malignancies(89,90). Some researchers have proposed that if any correlation is recognised, in patients with gastric cancers infected with H. pylori, surveillance by colonoscopy for colorectal cancers may be considered. However, attempts to eradicate this organism should be limited to high-risk patients considering the high prevalence in general population because achieving complete eradication is financially demanding and difficult. Also, the long-term outcomes after eradication are not known.

In the present study, we studied overall H. pylori prevalence and also more virulent CagA strains in our centre. Two tests were used to increase the sensitivity of identifying H. pylori infection. H. pylori prevalence and CagA seroprevalence for H. pylori were compared with respect to stage, differentiation, site and metastasis in the study group. Very few studies in the past few decades included the above analysis and the present study gives a comprehensive analysis of the above. The tests used in our study are non- invasive, simple, acceptable, which can be adopted over large populations. Special emphasis was given to CagA strains as they were known to cause a greater inflammatory response, higher elevation in serum gastrin levels and are associated with increased risk of gastric carcinomas. Their role in colorectal cancers is inconclusive (2,8,10,71,80). Shmuely et al identified a 10- fold rise in risk with CagA strains.

The present study has its own limitations. The study was done in a single centre among hospital patients, which sometimes due to the limited number of patients can become a disadvantage. Although age and

smoking were analysed, metabolic syndrome and other factors were not included in the study which act as confounding factors. This study being a case-control study has an inherent drawback of inability to identify a causative role in disease pathology.

The evidence on the relationship between H. pylori infection and colorectal cancers is not as strong as that identified in relation to gastric conditions. The results are inconsistent and far from any conclusion. In this study even though a trending high prevalence was noted, no significant correlation was found. Further evaluation requires large-scale studies over a large geographical area over an adequate time period with rigorous methodology considering all confounding factors for colorectal cancers. Considering the plausible role of H. pylori in colorectal cancers preventive measures should be taken and all attempts should be made to elucidate the correlative pathology in colorectal cancers. In view of the high general prevalence of H. pylori, further prospective interventional studies with targeted treatment for high-risk patients with H. pylori infection are warranted. Further research may include risk factors as gastrin, atrophic gastritis, level of CagA antibodies and other antibodies to major virulence factors which help in identification of the mechanism of carcinogenesis and also risk stratification of patients for the decision on the time of intervention

VI. Conclusion

Though our study did not show any correlation of H. pylori infection with colorectal cancers, it would add a small amount of evidence to the large pool of further research required to objectify the correlation between the two. A continuing effort to find the same with better-designed studies is warranted

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