Published in final edited form as:

Acta Paediatr. 2017 March ; 106(3): 470–477. doi:10.1111/apa.13724.

***Helicobacter pylori* serology testing is a useful diagnostic screening tool for symptomatic inner city children**

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Abstract

Aim—This study assessed the *Helicobacter pylori* (*H. pylori*) serum antibody test as a diagnostic screening tool in symptomatic inner city children.

Methods—This was a retrospective study of patients aged 1–18 years who were referred to our paediatric gastroenterology department from 2009–2013. We included all patients who had *H. pylori* serum antibodies and, or, faecal antigens who underwent esophagogastroduodenoscopy (EGD) for histology, with or without a gastric tissue rapid urease test.

Results—A total of 395 patients had EGDs carried out to evaluate epigastric pain, heartburn and nausea or vomiting and their overall socioeconomic Z-score was –2.62. The histology was positive for *H. pylori* infection in 52/395 patients (13%), and epigastric pain was documented in 45 of these 52 patients (87%). Compared to histology, the serum *H. pylori* antibody test had a sensitivity of 88.4% and a specificity of 93.4%. The tissue rapid urease test and faecal antigen test had sensitivities of 89.3% and 55.6% and specificities of 89.9% and 98.9%, respectively.

Conclusion—The serum *H. pylori* antibody test had high sensitivity and specificity and it was a good diagnostic screening tool in our study. Epigastric pain was strongly associated with a current *H. pylori* infection in our population.

Keywords

Helicobacter pylori infection; epigastric pain; children; sensitivity; specificity

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a fastidious, gram-negative microaerophilic bacillus, which colonises gastric mucosa and is estimated to have infected more than half of the world's population (1,2). Chronic infection can lead to gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric lymphomas (2–4). The infection is usually acquired during

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Conflict of interest

The authors have no conflicts of interest to declare.

early childhood, particularly in developing countries, and the prevalence of *H. pylori* gastritis in children increases with age (5). Risk factors for the disease include poor socioeconomic conditions, overcrowding, poor hygiene and living with an infected family member (6). Abdominal pain is a common complaint in children and it has been debated whether chronic abdominal pain is caused by the *H. pylori* infection. Previous studies have shown that there is no association between recurrent abdominal pain and the *H. pylori* infection (7–9).

Several non-invasive and invasive tests are available for diagnosing *H. pylori* and it can be challenging to decide which test to choose, especially in children. A wide range of sensitivity and specificity values for each test have been reported in the literature and most of data were from developing countries (10). Non-invasive tests include antibody testing of the serum, urine or saliva, the fecal antigen test and the urea breath test. Serology tests employ enzyme linked immunosorbent assay to detect serum *H. pylori*-specific immunoglobulin G and immunoglobulin A antibodies. The fecal *H. pylori* antigen test is performed using either a monoclonal or polyclonal enzyme immunoassay. The 13C-urea breath test is based on the ability of bacteria to convert urea to carbon dioxide and ammonia. The invasive test requires an esophagogastroduodenoscopy (EGD) under general anesthesia to obtain gastric tissue biopsies for histology analysis, bacteria Gram staining plus culture and tissue rapid urease test among others. An EGD with biopsy was considered as the most reliable tool for diagnosing the *H. pylori* infection in the past (11). Furthermore, guidelines from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) emphasise biopsy-based evaluation for the conclusive diagnosis of *H. pylori* infection in children. The guidelines also state that serum *H. pylori* antibody testing for the diagnosis of current infection is not recommended based on previous studies (12).

The prevalence of *H. pylori* infection is lower in the United States than most parts of the world, but African Americans, Hispanics and Asian Americans living in the country have been shown to have a prevalence of *H. pylori* infection that is similar to those in developing countries (13,14). The Children's Hospital at Montefiore, Bronx, New York, serves children who predominantly come from Hispanic and African-American backgrounds. Many of the patients in our cohort were from low-income families and recent immigrants. The aim of this study was to compare the diagnostic accuracy of two commonly used non-invasive tests in symptomatic pediatric patients, the *H. pylori* serum antibody and faecal antigen tests, and the tissue rapid urease test to the gastric tissue histology obtained from biopsies. The primary hypothesis was that the *H. Pylori* serology testing would prove to be a useful screening tool for the diagnosis of current *H. Pylori* infection in symptomatic paediatric patients from our inner city population.

METHODS

Study population

A retrospective chart review was conducted for symptomatic paediatric patients aged 1–18 years who underwent a first-time EGD between January 2009 and December 2013. Only

patients who had *H. pylori* serum antibodies and, or, a faecal antigen test, and who had a subsequent EGD with biopsy were included. The exclusion criteria for this study were patients who had non-invasive tests, including the *H. pylori* serum antibody and faecal antigen tests carried out more than five years prior to the EGD and patients one year of age. Patients with a prior known history of *H. pylori* infection and those who received antibiotics for other indications in the period between non-invasive tests and the EGD were also excluded. The study was approved by the Institutional Review Board of the Einstein-Montefiore Institute for Clinical and Translational Research.

Data collection

Data on the patient demographic characteristics, presenting symptoms, indications for EGD, anthropometric measurements, laboratory and histology results and International Classification of Diseases – Ninth Revision (ICD-9) codes were extracted from patient's electronic medical records and from the clinical information system using Clinical Looking Glass quality improvement healthcare surveillance software (Emerging Health Information Technology, New York, USA). The epigastric pain and non-epigastric pain, including the locations of pain anywhere other than epigastric area, such as generalised or periumbilical abdominal pain, were recorded based on ICD-9 codes. *H. pylori* serum antibody, faecal antigen and tissue rapid urease test results were compared to the gastric tissue histology, which was used as a reference standard for the diagnoses of *H. pylori* infection.

The *H. pylori* serology test was performed using a commercial second generation enzyme linked immunosorbent assay II (Wampole Laboratories, New Jersey, USA). The concentration of serum *H. pylori* antibody immunoglobulin G can be measured and quantified by using the optical density. Results were considered negative if the optical density ratio was 0–0.90, equivocal if it was 0.91–1.09 and positive if it was ≥ 1.10 . For our study, an optical density ratio of < 1.10 was categorised as a negative result and ≥ 1.10 as a positive result.

An enzyme immunoassay was used to detect *H. pylori* antigen in frozen stool specimens, by employing a mixture of monoclonal anti-*H. pylori* antibodies as the capture antibody and a mixture of peroxidase-conjugated monoclonal anti-*H. pylori* antibodies as the detection antibody. Based on the intensity of the colour that developed, the results were reported as *H. pylori* antigen detected or not detected. The specimens were analysed at the Quest Diagnostics Laboratories, New York, USA.

All EGDs were performed by paediatric gastroenterologists and patients underwent general anaesthesia provided by paediatric anaesthesiologists. The histology was examined by expert paediatric pathologists. Gastric biopsy tissues were fixed in 10% formalin and embedded in paraffin. The tissue was then stained with hematoxylin-eosin and Warthin-Starry stains. The bacteria stained dark-brown to black over a yellow background under Warthin-Starry stains (15). The presence of positive Warthin-Starry staining was considered as *H. pylori* positive histology.

The gastric tissue rapid urease test was also performed to detect *H. pylori* urease activity using a commercially available HpFast (GI Supply, Pennsylvania, USA) from June 2011 to

2013. The tissue was incubated in the agar medium containing urea. The presence of a colour change from the hydrolysis of the urea by the bacterial urease in the pH-sensitive chemicals of the medium was marked as positive results by two trained endoscopy technicians.

Statistical analysis

Descriptive statistics were used to summarise the patient demographic and clinical characteristics. Race and ethnicity were self-reported. Clinical Looking Glass provided a pre-calculated quantitative estimate for each patient's social economic status based on their home address and neighbourhood information, which included the median household income, housing unit values, education level and occupation statistics for individuals in that area. The patient's age was categorised into three groups based on the Center for Disease Control and Prevention's classification: toddlers to preschoolers if they were aged 1–5 years, middle childhood if they were 6–11 years and older children if they were 12 years or more. Based on the test assumptions of normality and equal variance, continuous variables were presented as means and standard deviations or medians with inter-quartile ranges. The Student's t-test, analysis of variance (ANOVA) or their respective non-parametric tests were used when appropriate to determine statistically significant differences. An odds ratio was calculated with Pearson's chi-square test. Using gastric biopsy histology as the reference standard, the sensitivity, specificity and likelihood ratios of *H. pylori* serum antibody, faecal antigen and gastric biopsy tissue rapid urease test were calculated with 95% confidence intervals (95% CI). The receiver operating characteristic analysis was also conducted to illustrate the performance of the *H. pylori* serum antibody and faecal antigen tests. For all analyses, p values of less than 0.05 were considered statistically significant. The data analysis was performed using Stata version 13.1 (StataCorp LP, Texas, USA).

RESULTS

The overview of our study population selection is presented in Figure 1. A total of 474 patients had *H. pylori* serum antibody and, or, faecal antigen testing followed by an EGD with biopsy. Data were analysed for 395 patients and the remaining 79 patients were excluded. All patients who met the inclusion criteria had the serum antibody test, faecal antigen test, or both the antibody and antigen tests prior to their EGDs. Of the 395 patients who had an EGD, 171 patients also had the gastric tissue rapid urease test carried out at the time of procedure. The median time between the *H. pylori* serum antibody test and the EGD was 2.8 months (inter-quartile range 1.3–8.2), and the median time between the faecal antigen test and the EGD was 1.7 months (inter-quartile range 0.8–3.8).

The demographic characteristics of our study population are summarised in Table 1. Of the 395 patients who underwent an EGD, 52 patients had a positive *H. pylori* result based on the gastric tissue histology (13%) and the remaining 343 patients were negative (87%). The overall median age of patients was 14 years (inter-quartile range 9–16) and there was no age difference between histology positive and negative groups. The two older age groups, aged 6–11 years and 12–18 years, accounted for 91% of the total study patients. The proportion of patients who were *H. pylori* positive on histology in each age group was 1–5 years (4%), 6–

11 years (23%) and 12–18 years (73%). The overall median socioeconomic Z-scores of the patients was -2.62 , but the Z-score was lower (-3.03) in patients with *H. pylori* positive histology than those with negative histology (-2.52). The majority of the cohort (61%) were Hispanic and 38% of the patients were not Hispanic. The measurement of serum iron, haemoglobin and body mass index of the patients is summarised in Table 2. There was no statistically significant difference in median iron levels, mean haemoglobin and mean body mass index between the *H. pylori* histology positive and negative groups in this study.

Common indications for EGD are listed in Table 3. The majority of the patients (344/395, 87%) who underwent an EGD had more than one clinical indication for the procedure and persistent epigastric abdominal pain was the most common presenting complaint (201/395, 51%). Of the 52 patients who had positive histology for *H. pylori* infection, 45 patients (87%) had a documented complaint of epigastric pain, with an odds ratio of 7.71 (95% CI 3.31–20.74, $p < 0.001$) and 30 patients (58%) experienced heart burn with an odds ratio of 1.88 (95% CI 1.01–3.58, $p = 0.03$). From a total 129 patients who had non-epigastric abdominal pain, consisting of periumbilical, generalised or lower quadrant pain, only three (6%) patients had positive histology for *H. pylori*, with an odds ratio of 0.11 (95% CI 0.02–0.34, $p < 0.001$). Other indications included nausea or vomiting, a history of failed proton pump inhibitors or histamine type 2 blockers, unexplained weight loss, poor appetite and dysphagia. Patients with these indications were not statistically different in *H. pylori* histology positive and negative groups.

The performance characteristics of the *H. pylori* antibody test, the faecal antigen test and the gastric tissue rapid urease test are presented in Table 4. The results of the *H. pylori* antibody test were available for 254 patients, including 196 patients who just had antibody tests results and 58 patients who had both antibody and antigen results. Of those, 38 patients had both positive *H. pylori* serum antibody and histology results and 197 patients were negative for both tests. Five patients had negative serum antibody tests, but their *H. pylori* histology tests were positive and 14 patients had a positive serum antibody tests but a negative *H. pylori* histology. *H. pylori* antibody testing had a sensitivity of 87.8% and a specificity of 94.8% in our study population. The test had positive likelihood ratios of 13.3 and negative likelihood ratios of 0.12, with an accuracy of 92.5%. The receiver operating characteristic analysis demonstrated an area under the curve of 0.91. Overall, the median serum antibody optical density ratio in the *H. pylori* positive patients was 1.82 (inter-quartile ranges 1.26–2.47) and this was significantly higher than the *H. pylori* negative patients (0.43, inter-quartile ranges 0.27–0.60; $p < 0.001$) (Figure 2). This difference was statistically significant in the age groups 6–11 years and 12–18 years with $p = 0.004$ and $p = 0.01$ respectively. The difference was not statistically significant in the youngest age group of 1–5 years and two patients in this group were found to have a positive histology for *H. pylori* despite their negative antibodies.

Faecal antigen testing was carried out on 198 patients, including 140 patients who just had the antigen test and 58 patients who had both the antigen and antibody tests. Of those, eight patients had positive faecal antigen and histology results and 178 were negative for both tests. In addition, eight patients had negative faecal antigen tests, but their histology was positive for *H. pylori* and two patients had positive faecal antigen but negative *H. pylori*

histology. This result demonstrated a sensitivity of 52.9% and a specificity of 98.9%, with a positive likelihood ratio of 50 and a negative likelihood ratio of 0.45 and an area under the curve of 0.77. The faecal antigen test had a calculated test accuracy of 95%. In our study, 54 (27%) of the 198 patients who had the faecal antigen test reported that they had been on either proton pump inhibitors or histamine type 2 blockers at the time of test. Of the 395 patients who had an EGD, 171 patients also had a concurrent tissue rapid urease test. The rapid urease test and histology were both positive in 25 patients and were both negative in 129 patients. Three patients had negative rapid urease test but their *H. pylori* histology was positive and 14 patients had positive rapid urease test but negative *H. pylori* histology. The concordance was found in 154 patients (90%), with a sensitivity of 89%, specificity of 90% and accuracy of 90%.

DISCUSSION

A variety of both non-invasive and invasive tests are available for the diagnosis of *H. pylori* infection in the clinical setting. The NASPGHAN and ESPGHAN guidelines state that an EGD with biopsy is the only reliable method for a definitive diagnosis of *H. pylori* infection and the use of serology testing for diagnosis is not recommended (12). Many studies have assessed the performance of the *H. pylori* serology test in children from lower-middle socioeconomic parts of the world, but there is limited data on the serology test in ethnically different populations in North America.

Serum antibody based tests are relatively cheap, rapidly performed and cause minimal patient discomfort. However, the performance of serum antibody tests have been inconsistent, as reported by multiple studies (10,16,17). It has been shown to have wide variations in sensitivity and specificity in children and the test is mostly used for epidemiology studies. Another cited limitation of the serology test has been its inability to differentiate between past and present *H. pylori* infections (18). The *H. pylori* antibody test in our study population had a high sensitivity (88.4%, 95% CI 75–96%) and specificity (93.4%, 95% CI 89–96%). Our data demonstrated that there was good correlation between the *H. pylori* serum antibody and histology results. The *H. pylori* antibody test had a screening ability to diagnose the *H. pylori* infection in symptomatic pediatric patients. Of the 211 patients with negative histologies, only 10 patients had positive antibodies (4.7%). This discrepancy may have been due to a false positive antibody, false negative histology or the antibody remaining positive after the clearance of the *H. pylori* infection. The serology test was also noted to be more sensitive and specific in the older age groups of 6–11 years and 12–18 years. Two patients in the younger age group of 1–5 years had positive histologies, but they both had negative antibodies. This may be due to the fact that the duration of the infection may have been too short to mount a sufficient immune response in the younger age group. In contrast, older children may have a more robust antibody production as they may have prolonged bacteria exposure (19). It is postulated that the guidelines are useful in general North American areas, but we also need to consider some areas with healthcare disparities.

A meta-analysis study of *H. pylori* diagnostic tests in children found that fecal *H. pylori* antigen detection using a monoclonal antibody had a sensitivity that ranged from 96.6 to

98% and specificity that ranged from 94.7 to 100% (10,17). An earlier study showed that the faecal antigen test had a low sensitivity and specificity in children younger than two years of age, even with a high prevalence of *H. pylori* (20). In our study, the faecal antigen test had a high specificity (99%), but it had a lower sensitivity (55.6%). It is unclear why our faecal antigen test sensitivity was lower. We hypothesise that there may have been some inconsistencies in the stool sample collection and processing that may have led to a higher false negative rate. In addition, adult studies have demonstrated that the use of proton pump inhibitors can reduce the faecal *H. pylori* bacterial load (21). In our study, 27% of the patients who had the faecal antigen test were previously or currently on proton pump inhibitors or histamine type 2 blockers. This could have led to an increase in false negative results and a subsequent decrease in the test sensitivity.

Multiple studies have shown that there is no correlation between abdominal pain and the *H. pylori* infection (7–9). However, the location of abdominal pain was not well specified in those studies. A prospective study showed the rate of positive *H. pylori* serology was significantly higher in children referred to gastroenterology departments with symptoms of abdominal pain (22). The current NASPGHAN and ESPGHAN guidelines recommend against testing for the *H. pylori* infection in patients with abdominal complaints, such as pain, nausea or dyspepsia, as they may be non-specific or functional in aetiology (12). The majority of our patients (86.5%) with histology a proven *H. pylori* infection had persistent epigastric pain. The odds for having the *H. pylori* infection on histology were about eight times higher in those who presented with persistent epigastric pain than those without epigastric pain. In contrast, patients with non-epigastric abdominal pain had 89% lower odds of having *H. pylori* detected on histology. To the best of our knowledge, this is the first study to clarify a relationship between abdominal pain and *H. pylori* infection. Persistent epigastric abdominal pain, but not non-epigastric pain, was strongly associated with *H. pylori* infection. These findings suggest that clinicians should have a high index of suspicion for *H. pylori* infections in patients presenting with persistent epigastric pain, especially in areas with a higher prevalence of *H. pylori* infection. Clinicians should also explore other aetiologies for patients with non-epigastric pain, since the *H. pylori* infection is unlikely in patients with this type of abdominal pain.

Iron deficiency anaemia is known to be associated with the *H. pylori* infection in paediatric populations (23,24). However, in our study the median serum iron, mean haemoglobin and mean body mass index values of patients were similar in both *H. pylori* infected and non-infected groups. These findings may be secondary to the fact that our study subjects may have lacked prolonged chronicity.

Our patients' demographic features were unique as a high percentage of the patients were Hispanics. A low socioeconomic status has been shown to influence the prevalence of paediatric *H. pylori* infection (25–27). The overall median socioeconomic Z-score in our study population was –2.62, which was lower than national standards. The Z-score was even lower in children with the *H. pylori* infection (–3.03) than to children who were not infected (–2.52).

Our study had various limitations, due to its retrospective design. More than one expert pathologist was involved in the histology assessments and they were not blinded to the patients' clinical and test information. This may have introduced some observer or misclassification bias.

CONCLUSION

Our study suggest that serum *H. pylori* antibody testing may still have a role to play as a screening tool in diagnosing symptomatic patients in certain areas of the United States. The overall socioeconomic Z-score of the patients in this study was -2.62, which was lower than national standards. The current guidelines apply to the general paediatric population, but may not apply as well to this patient population. Clinicians should consider serum *H. pylori* antibody testing, especially when routine blood work is indicated in such a patient or they live in an area with a low socioeconomic Z-score and a high prevalence and, or, limited diagnostic tools, for the *H. pylori* infection. Our data revealed a strong relationship between persistent epigastric pain and the *H. pylori* infection. Patients presenting with this symptom should undergo an evaluation to rule out *H. pylori* infection.

Acknowledgments

FUNDING

This study was funded by a National Institutes of Health/National Center for Advanced Translational Science Einstein-Montefiore Clinical and Translational Science Awards Grant (Award number UL1TR001073) to Priya Raj.

Abbreviations

EGD	Esophagogastroduodenoscopy
<i>H. pylori</i>	Helicobacter pylori

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Key notes

- We assessed the *Helicobacter pylori* (*H. pylori*) serum antibody test as a diagnostic screening tool in 395 symptomatic inner city children aged 1–18 years.
- The histology was positive for *H. pylori* infection in 52/395 patients (13%) and epigastric pain was documented in 45 of these 52 patients (87%).
- The serum *H. pylori* antibody test had high sensitivity and specificity and it was a good diagnostic screening tool in our study.

Figure 1.
Overview of subject selection process

Figure 2.

Optical density ratio of serological test in different age groups based on *H. pylori* infection status. (Boxplot showing median and Inter quartile range), y=years

TABLE 1Demographic characteristics of patients with *H pylori* status

Characteristic	Overall n (%) n=395	Histology +ve (%) n=52	Histology -ve (%) n=343
Female	232 (59)	35 (67)	197 (57)
Male	163 (41)	17 (33)	146 (43)
Age (y) median (IQR)	14 (9,16)	15 (11,17)	14 (9,16)
Age Groups			
• 1 – 5 years	35 (9)	2 (4)	33 (10)
• 6 – 11 years	109 (28)	12 (23)	97 (28)
• 12 – 18 years	251 (63)	38 (73)	213 (62)
Socio-economic Z-Score* median (IQR)	-2.62 (-5.93, -1.1)	-3.03 (-5.52, -1.11)	-2.52 (-5.97, -1.1)
Race ethnicity n			
• Hispanic	240 (61)	34 (65)	206 (60)
• Non-Hispanic	150 (38)	16 (31)	134 (39)
• Other/Unknown	5 (1)	2 (4)	3 (1)

* Z-score compared to national average; based on home address, median household income, housing unit values, education level, occupation statistics; SD=Standard Deviation; IQR=Inter Quartile Range

TABLE 2Serum iron, hemoglobin and BMI of patients with *H pylori* status

Characteristic	Overall n n=395	Histology +ve n=52	Histology -ve n=343	p- value
Iron median (IQR) (ng/ml)	69 (45, 90) (n=128)	76 (51, 99) (n=12)	69 (45, 88) (n=116)	0.54
Hemoglobin (mean $\pm$ SD) (g/dL)	12.8 $\pm$ 1.5 (n=388)	12.6 $\pm$ 1.3 (n=51)	12.8 $\pm$ 1.5 (n=337)	0.10
BMI (mean $\pm$ SD)	22.9 $\pm$ 9.8	23.8 $\pm$ 9.3	22.8 $\pm$ 9.9	0.35

SD=Standard Deviation; IQR=Inter Quartile Range, BMI=Body Mass Index; g/dL=grams/deciliter; ng/ml=nanograms' milliliter

TABLE 3

Indications for Upper Endoscopy Evaluation

Indications	Overall n(%) n=395	HP +ve n=52 n(%)	HP -ve n=343 n(%)	OR (95% CI)	p-value
Epigastric Abdominal Pain	201 (51)	45 (87)	156 (46)	7.71 (3.31, 20.74)	<0.001
Non-Epigastric Abdominal Pain	129 (33)	3 (6)	126 (37)	0.11 (0.02, 0.34)	<0.001
Heart Burn	174 (44)	30 (58)	144 (42)	1.88 (1.01, 3.58)	0.03
Nausea or Vomiting	172 (44)	24 (46)	148 (43)	1.13 (0.60, 2.11)	0.68
Failure of PPI or H2 Blocker Therapy	99 (25)	16 (31)	83 (24)	1.39 (0.68, 2.73)	0.31
Loss of Weight	67 (17)	7 (14)	60 (18)	0.73 (0.27, 1.75)	0.47
Loss of Appetite	46 (12)	7 (14)	39 (11)	1.21 (0.43, 1.97)	0.66
Dysphagia	13 (3)	0 (0)	13 (4)	n.a	n.a

HP +ve = *H. pylori* positive; HP -ve = *H. pylori* negative; Infection status as determined by reference histology analysis; OR (95% CI) = Odds Ratio (95% Confidence Interval); PPI = Proton pump inhibitor, H2 Blocker = Histamine 2 receptor blocker; n.a = not applicable

TABLE 4

Performance characteristics of each diagnostic test

Characteristic	Serum IgG Antibody Test	Fecal Antigen Test	Rapid Urease Test
Sensitivity % (95% CI)	88.4 (74.9, 96.1)	55.6 (30.8, 78.4)	89.3 (71.8, 97.6)
Specificity % (95% CI)	93.4 (89.1,96.3)	98.9 (96, 99.8)	89.9 (83.7, 94.4)
Positive Likelihood Ratio (95% CI)	13.3 (7.9, 22.4)	50.0 (11.9,210.8)	8.86 (5.31, 14.8)
Negative Likelihood Ratio (95% CI)	0.12 (0.05,0.28)	0.45 (0.27, 0.75)	0.12 (5.31, 14.8)
Area Under the Curve	0.91	0.77	0.89

95% CI = 95% Confidence Interval, IgG =Immunoglobulin G