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# Real-Time Gastric Juice Analysis in Cirrhotic Patients: Can We Avoid Unrewarding Gastric Biopsies?

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**Keywords**
Cirrhosis · *H. pylori* · Gastric precancerous lesions · Gastric juice analysis · Ammonia · pH

**Abstract**
***Background:*** To search for *H. pylori* infection and gastric precancerous lesions in cirrhotic patients is worthwhile when considering the high incidence of peptic ulcers and gastric cancer in these patients. We tested if gastric juice analysis allows to avoid unrewarding gastric biopsies. ***Methods:*** This prospective study enrolled consecutive patients with liver cirrhosis who underwent upper endoscopy with standard gastric biopsies. Real-time gastric juice analysis was performed with a specific device (EndoFaster®) that test ammonium concentration for *H. pylori* diagnosis, and pH values to suspect extensive atrophy/metaplasia involving gastric body mucosa. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), the overall accuracy, and the likelihood ratio were calculated for both *H. pylori* infection and extensive precancerous lesions on gastric mucosa. ***Results:*** A total of 78 cirrhotic patients (males: 55; mean age: 66 ± 12 years) were enrolled. When considering as positive EndoFaster® results when at least one of two (ammonium and pH levels) tests were positive, the NPVs were as high as 89% and 86%, respectively, to rule out *H. pylori* and extensive precancerous lesions on gastric mucosa, with an overall accuracy of 83% and 74%. ***Conclusions:*** This study supports the evidence that real-time gastric juice analysis allows to avoid clinically unrewarding and potentially unsafe gastric biopsies in a definite portion of cirrhotic patients, but more data are needed.



**Análise do suco gástrico em tempo real em pacientes cirróticos: podemos evitar biópsias gástricas insatisfatórias?**

**Palavras Chave**
Cirrose · *H. pylori* · Lesões pré-malignas gástricas · Análise do suco gástrico · Amónia · pH

**Resumo**
***Introdução/Objetivo:*** A pesquisa de infeção *H. pylori* e lesões pré-malignas gástricas em doentes cirróticos é relevante, considerando a elevada incidência de úlceras pépticas e cancro gástrico nesta população. Avaliámos se a análise do suco gástrico permite evitar biópsias gástricas desnecessárias. ***Métodos:*** Estudo prospetivo

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incluindo doentes cirróticos consecutivos submetidos a endoscopia digestiva alta com biópsias gástricas. Foi realizada análise do suco gástrico em tempo real com dispositivo EndoFaster®, que avalia a concentração de amónia para diagnóstico de *H. pylori* e o pH para avaliação de atrofia/metaplasia extensa da mucosa gástrica. Calculámos a sensibilidade, especificidade, valor preditivo positivo (VPP), valor preditivo negativo (VPN), acuidade global e *likelihood ratio* para a infeção por *H. pylori* e lesões gástricas pré-malignas extensas. ***Resultados:*** Foram incluídos 78 doentes cirróticos (sexo masculino: 55; idade média: 66 ± 12 anos). Considerando resultados positivos do EndoFaster® quando pelo menos um dos dois testes (amónia e pH) apresentava valor positivo, os VPNs atingiram 89% e 86% para exclusão de infeção por *H. pylori* e lesões pré-malignas extensas na mucosa gástrica, respetivamente, com uma acuidade global de 83% e 74%. ***Conclusão:*** Este estudo suporta que a análise do suco gástrico em tempo real permite evitar biópsias gástricas clinicamente desnecessárias e potencialmente inseguras numa determinada percentagem de doentes cirróticos. No entanto, são necessários mais dados.



## Introduction

Patients with liver cirrhosis have several alterations on the gastroduodenal mucosa that may impair the repair processes following an injury [1, 2]. Indeed, these patients are at higher risk of developing peptic ulcer, despite *H. pylori* prevalence – namely the main factor for peptic ulcer development – is similar to that of controls [2, 3]. Some evidences also suggest that the incidence of gastric cancer is increased in cirrhotic patients [4]. In detail, the risk of developing gastric cancer was fund to be increased by 1.7- and 5-fold in patients <60 years and >75 years old, respectively, and by 2.6-fold cumulatively as compared to the general population [4]. In the large majority of cases, gastric cancer is preceded by precancerous lesions, including extensive atrophy or metaplasia involving both antrum and gastric body mucosa [5], and the intestinal metaplasia is frequently detected on gastric mucosa of cirrhotic patients [6]. Therefore, to search for *H. pylori* infection and precancerous lesions by taking standard biopsies on gastric mucosa during upper endoscopy is worthwhile in these patients. However, clotting impairment due to both platelets and coagulation factors reduction due to liver cirrhosis may potentially increase the risk of bleeding following gastric biopsies [7, 8]. For instance, bleeding complications during percutaneous liver biopsy, central venous cannulation, paracentesis and thoracocentesis procedures, as well as surgical interventions, were reported to occur more frequently in cirrhotic patients than controls [7]. However, taking into account data of 9 studies with 587 cirrhotic patients who underwent gastric biopsies, no major bleeding was observed when platelets count was >45,000/mm$^3$ and prothrombin activity >45% [8]. Therefore, a biopsy-free test able to suspect or rule out *H. pylori* infection and extensive precancerous lesions in the stomach could be advantageous. By performing a real-time analysis of gastric juice, the current version of EndoFaster® – a device firstly developed on 2005 [9] – is able to accurately discard the presence of *H. pylori* infection and extensive precancerous lesions through measure of ammonium concentration and pH levels, respectively [10]. In detail, a systematic review of several studies showed that when the results of EndoFaster® testing are negative, the negative predictive value (NPV) for excluding *H. pylori* infection and extensive precancerous lesions on gastric mucosa is approaching 100% [10]. In detail, by considering data of 11 studies, the NPV to rule out either *H. pylori* infection or extensive precancerous in the stomach was >96% in all, but two studies showing values of 84.3%–85.4% [10]. However, to our knowledge, no data on the use of EndoFaster® in cirrhotic patients are available. Indeed, the modifications of ammonia content in the gastric juice of cirrhotic patients [11], from one side, and the alterations of gastric acid output [12], in the other, may potentially affect the accuracy of gastric juice analysis with such a device. We therefore designed this study to evaluate the accuracy of gastric juice analysis to rule out *H. pylori* infection and extensive precancerous lesions in patients with liver cirrhosis, aiming to avoid clinically useless and potentially unsafe gastric biopsies in these patients.

## Materials and Methods

### *Study Design and Patients*

In this prospective study, consecutive cirrhotic patients who underwent upper endoscopy for any indication in our endoscopy unit were considered for the enrolment. Inclusion criteria were the presence of a documented liver cirrhosis on the basis of clinical findings, abdominal sonogram, laboratory parameters, or liver biopsy and age >18 years. Patients with marked clotting impairment (platelet counts <50,000/mm$^3$ and/or international normalized ratio (INR) > 1.5) were excluded [8]. Informed consent was obtained for all procedures. In detail, following explanation on the clinical research, patients

were informed and signed the consent for both procedures (endoscopy with biopsies and real-time gastric juice analysis) and anonymous use of their data for scientific purposes. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Since no experimental drugs were administered, no additional costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received, a formal approval by Investigational Review Boards could be waived.

*Endoscopic Procedures*

All patients underwent endoscopy and standard biopsy sampling (2 antrum, 1 angulus, and 2 gastric body) of gastric mucosa were performed with standard 5-mm biopsy forceps. After removing the biopsy specimens, we waited for haemostasis to take place. Biopsies were used for histological assessment and to search for *H. pylor*i. The infection was considered present when histological assessment revealed the presence of bacteria together with a feature of chronic active gastritis. Extensive atrophy or intestinal metaplasia were considered present when these histological findings involved both antral and gastric body mucosa, as reported in the RE.GA.IN system and graded according to the OLGA-OLGIM systems [13, 14].

Gastric Juice Analysis

Gastric juice analysis was performed by using EndoFaster® (Manufacturer: NISO Biomed S.r.l, Turin; Italy; Italian distributor: Waldner Tecnologie Medicali, Trento; Italy). The device was provided for 2 months to the endoscopic unit without any adjunctive cost for both hospitals and patients. In detail, the device was interposed between the endoscope and the suction system, so that no adjunctive invasive procedure was required and without any discomfort for the patient [10]. During endoscopy, lumen washing was avoided until the stomach was reached and until 3 mL of gastric juice were aspirated. *H. pylori* diagnosis was based on the determination of ammonium concentration, as a consequence of the urease activity of the bacterium within 60–90 s that is during endoscopy. The device performs in the meantime also $H^+$ concentration. The infection was considered to be present when the ammonium concentration in gastric juice was >62 ppm, whilst extensive atrophy/metaplasia involving gastric body mucosa was suspected when pH values of were >4.5, as reported elsewhere [15, 16].

**Table 1.** Demographic and clinical characteristics

| Variable | Finding |
|---|---|
| Male/female | 55/23 |
| Age, mean±SD, years | 66±12 |
| Cirrhosis aetiology | |
| Hepatitis C virus | 23 |
| Hepatitis B virus | 7 |
| Hepatitis C virus + Hepatitis B virus | 2 |
| Alcohol | 12 |
| Primary Biliary Cholangitis | 4 |
| Non-alcoholic steatohepatitis | 20 |
| Autoimmune | 1 |
| Wilson's disease | 1 |
| Cryptogenic | 8 |
| Cirrhosis Child-Pugh class | |
| A | 49 |
| B | 22 |
| C | 7 |
| Upper endoscopy indication | |
| Portal hypertension evaluation | 31 |
| Varices follow-up | 36 |
| Melena | 3 |
| Anaemia | 6 |
| Dyspepsia | 2 |
| Ongoing proton pump inhibitor therapy | 38 |
| Varices | |
| Absent | 9 |
| Oesophageal | 66 |
| Oesophageal plus gastric | 3 |
| Congestive gastropathy | |
| Absent | 22 |
| Mild | 26 |
| Marked | 30 |
| OLGA/OLGIM score | |
| 0 | 41 |
| I | 26 |
| II | 6 |
| III | 4 |
| IV | 1 |

*Statistical Analysis*

Frequencies, percentages and means values with standard deviations were calculated for all observations. Sensitivity, specificity, positive predictive value (PPV), NPV, the overall accuracy, and the likelihood ratios were calculated by considering the histology as gold standard for both *H. pylori* infection and extensive precancerous lesion on gastric mucosa. To assess the cumulative impact of gastric juice analysis for clinical practice, the accuracy values were also calculated by combining data of both results of testing, by

**Table 2.** Accuracy of EndoFaster® for either *H. pylori* infection or extensive precancerous lesions on gastric mucosa

| | *H. pylori* | Precancerous lesions |
|---|---|---|
| Sensitivity | 65 (46–85) | 68 (50–86) |
| Specificity | 75 (63–86) | 60 (47–74) |
| Positive predictive value (PPV) | 52 (34–70) | 45 (29–61) |
| Negative predictive value (NPV) | 84 (73–94) | 80 (68–92) |
| Accuracy | 72 (62–82) | 63 (52–74) |
| Likelihood ratio positive | 3 | 2 |
| Likelihood ratio negative | 0.5 | 0.5 |

Percentages and their 95% confidence intervals.

considering eventually missed diagnosis when both tests were negative, but histology revealed at least one of the investigated conditions (*H. pylori* and/or precancerous lesions).

## Results

Demographic and the main clinical characteristic of the 78 cirrhotic patients enrolled in this study are provided in Table 1. Beyond varices and congestive gastropathy, at upper endoscopy 4 (5.1%) patients had erosive oesophagitis, 1 (1.3%) Barrett's oesophagus, 16 (20.5%) erosive gastritis, 4 (5.1%) gastric ulcer, 8 (8.2%) erosive duodenitis, and 1 (1.3%) duodenal ulcer. No case of bleeding following gastric biopsies occurred. At histology, *H. pylori* infection was diagnosed in 23 (29.5%) patients, whilst extensive atrophy/metaplasia – that is involving antral and gastric body mucosa, irrespective of grade – was present in 23 (29.5%) patients, and a grade III-IV OLGA/OLGIM was overall detected in 5 (6.4%) cases. The values of sensitivity, specificity, PPV, NPV, the overall accuracy, the likelihood ratios positive (LH+) and negative (LH−) for *H. pylori* infection were 65%, 75%, 52%, 84%, 72%, 3, and 0.5, and that for extensive precancerous lesions were 68%, 60%, 45%, 80%, 63%, 2, and 0.5 (Table 2). In detail, NPVs of 84% and 80% were found, respectively, in ruling out *H. pylori* infection and extensive atrophy/metaplasia on gastric mucosa. However, by considering as positive EndoFaster® results when at least one of two tests (ammonium and pH levels) were positive, the NPVs increased to 89% and 86%, respectively. These values indicate that a missed *H. pylori* infection occurred in only 8 cases every 100 patients with negative EndoFaster result for ammonium concentration, and a missed extensive precancerous condition in only 9 cases every 100 patients with normal pH values.

## Discussion

The prevalence of gastric and duodenal ulcers has been reported to be 10-fold higher in cirrhotic patients than in controls [17], accounting for a 7.4–16% rate of upper gastrointestinal bleeding, with a 5-fold increased mortality rate in these patients [2]. Data of a meta-analysis showed that *H. pylori* infection significantly increases peptic ulcer risk in these patients, with an estimated odds ratio of 2.70 (95% CI = 1.91–3.82) as compared to controls [18]. Moreover, some studies suggested a potential role of *H. pylori* in causing hepatic encephalopathy by ammonia production in the stomach, although data are largely controversial [19]. On the other hand, the incidence of upper gastrointestinal (oesophageal, gastric, pancreatic) cancers in patients with cirrhosis was reported to be higher as compared to controls [20]. In detail, the incidence of gastric cancer was 2.6-fold increased in these patients as compared to that expected in the general population [4]. Moreover, gastric epithelial cell proliferation is increased in patients with cirrhosis, particularly when congestive gastropathy and *H. pylori* infection were present [21], and intestinal metaplasia is frequently detected in these patients [6, 22]. In detail, the present study showed a prevalence of extensive precancerous lesions on gastric mucosa as high as 30%, with a stage III-IV OLGA/OLGIM present in 6.4% of cases. The latter value is in agreement data of previous Italian studies showing a frequency ranging from 2.3 to 7.8% in routine endoscopic examinations [16]. These

patients deserve scheduled follow-up to detect early neoplastic lesions amenable of endoscopic removal [23]. Some evidences suggest that the endoscopic submucosal dissection is safely performed also in cirrhotic patients, allowing to avoid a more harmful surgical approach [24]. All these observations clearly suggest how it is clinically worthy to exclude the presence of both *H. pylori* infection and precancerous lesions at endoscopy in cirrhotic patients.

This is first study that evaluated the accuracy of real-time gastric juice analysis by EndoFaster® for ruling out both *H. pylori* infection and extensive precancerous lesions on gastric mucosa in patients with cirrhosis. Our data found that when the cumulative results of the test were considered, a NPV of 89% and 86% in excluding *H. pylori* infection and extensive atrophy/metaplasia on gastric mucosa, respectively, were found, indicating an acceptably high precision for these purposes. Indeed, the NPV for *H. pylori* diagnosis we observed was consistent with the 92.3% reported for the $^{13}$C-urea breath testing in these patients [25]. Therefore, gastric juice analysis during endoscopy allows to safely avoid useless biopsies on normal appearing gastric mucosa, a procedure particularly advantageous in cirrhotic patients, when considering their clotting impairment [7, 8]. However, a negative EndoFaster® result decreases the post-test probability of finding both *H. pylori* infection and extensive precancerous, but in those situations where the bleeding risk is not prohibitive, biopsies should still be performed. On the other hand, a positive EndoFaster® increases the post-test probability and should lead to performing biopsies, when considering that both PPV and positive likelihood ratio values are not enough elevated.

Although satisfactory, the data of this study would suggest that the EndoFaster® performs less well than what observed in patients without liver cirrhosis. Indeed, data of previous studies found NPV values as high as 96% and 97% for *H. pylori* and precancerous lesions, respectively, in more than 2,000 investigated patients [10]. The reasons of a lower performance of gastric juice analysis in cirrhotic patients remain unclear. The relatively low sample size ($N$ = 78) of cirrhotic patients studied in the present study may have played a role in estimating the EndoFaster® performance. However, the a posteriori calculation of the study's power with an alfa error of 0.05 was 91.3%, by considering a NPV of 86% we computed and the 96% found in non-cirrhotic patients [10]. On the other hand, the levels of ammonium concentrations in gastric juice – that could potentially impair ammonium testing with EndoFaster® – of patients with liver cirrhosis with or without *H. pylori* infection were reported to be very similar to that of matched controls [11]. On the other hand, gastric acid output – that could potentially impair pH evaluation with EndoFaster® irrespective of extensive gastric mucosa atrophy – has been inconsistently reported to be lower, similar or increased compared to controls [26]. Therefore, the findings of present study should be confirmed in further studies.

## Conclusions

This study adds evidence that real-time gastric juice analysis might avoid clinically unrewarding and potentially unsafe gastric biopsies in a definite portion of cirrhotic patients, also reducing the environmental impact [27], but more data are needed.

## Statement of Ethics

Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required, and no funds were received, the Investigational Review Boards of University of Palermo waived formal approval for this cross-sectional study performed in clinical practice. Patients signed informed consent for both procedure and anonymous use of their data for scientific purposes.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

Sergio Peralta and Angelo Zullo conceived the study. Sergio Peralta, Vincenza Calvaruso, Francesca Di Giorgio, Vincenzo Di Martino, and Ada Maria Florena provided data acquisition; Angelo Zullo analysed data and wrote the manuscript providing critical revision. All authors read and approved the final version of the manuscript.

## Data Availability Statement

All data are available following reasonable enquiries directed to the first author, Sergio Peralta.

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