



sST2 Levels Show No Association with *Helicobacter pylori* Infection in Asymptomatic Patients: Implications for Biomarker Research

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Abstract

Introduction *Helicobacter pylori* (*H. pylori*) is a prevalent stomach bacterium that can cause a range of clinical outcomes, including gastric cancer. In recent years, soluble suppression of tumorigenicity-2 (sST2) has gained attention as a biomarker associated with various diseases, such as gastric cancer. The purpose of this study was to explore the possible connection between *H. pylori* infection and sST2 levels in patients who do not exhibit symptoms.

Methods A total of 694 patients from the Salzburg Colon Cancer Prevention Initiative (Sakkopi) were included in the study. The prevalence of *H. pylori* infection was determined by histology, and sST2 levels were measured in serum samples. Clinical and laboratory parameters, such as age, sex, BMI, smoking status, hypertension, and metabolic syndrome, were also collected.

Results The median sST2 concentration was similar between patients with (9.62; 7.18–13.44 ng/mL; $p=0.66$) and without (9.67; 7.08–13.06 ng/mL) *H. pylori*. Logistic regression analysis did not show any association (OR 1.00; 95%CI 0.97–1.04; $p=0.93$) between sST2 levels and *H. pylori* infection, which remained so (aOR 0.99; 95%CI 0.95–1.03; $p=0.60$) after adjustment for age, sex, educational status, and metabolic syndrome. In addition, sensitivity analyses stratified by age, sex, BMI, smoking status, educational status, and the concomitant diagnosis of metabolic syndrome could not show any association between sST2 levels and *H. pylori* infection.

Conclusion The results indicate that sST2 may not serve as a valuable biomarker in the diagnosis and treatment of *H. pylori* infection. Our findings are of relevance for further research investigating sST2, as we could not find an influence of asymptomatic *H. pylori* infection on sST2 concentration.

What Is Already Known? Soluble suppression of tumorigenicity-2 (sST2) has gained attention as a biomarker associated with various diseases, such as gastric cancer.

What Is New in This Study? The median sST2 concentration was similar between patients with (9.62; 7.18–13.44 ng/mL; $p=0.66$) and without (9.67; 7.08–13.06 ng/mL) *H. pylori*.

What Are the Future Clinical and Research Implications of the Study Findings? The results indicate that sST2 may not serve as a valuable biomarker in the diagnosis and treatment of *H. pylori* infection.

Keywords Biomarker · *H. pylori* · Cancer · sST2 · Soluble suppression of tumorigenicity-2

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Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that colonizes the human stomach, with an estimated prevalence of 50% worldwide [1–3]. Although *H. pylori* infection is usually asymptomatic, it can cause a range of clinical manifestations, including gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma [1, 2]. The impact of *H. pylori* on individual and public health is significant, as it is estimated to be responsible for 90% of duodenal ulcers, 80%

of gastric ulcers, and 60% of gastric cancers [4]. Further, *H. pylori* infection is associated with extraintestinal systemic diseases such as immune thrombocytopenia [5] and iron deficiency anemia of unknown origin [6]. Therefore, *H. pylori* infection should be treated once diagnosed [4].

Soluble suppression of tumorigenicity-2 (sST2) is a biomarker that has been extensively studied in recent years [7–9]. It is a member of the interleukin-1 receptor family [10] and is secreted in response to various forms of cellular stress, including inflammation, tissue injury, and mechanical strain [11]. sST2 was proposed as a marker for heart failure [12, 13], but emerging evidence suggests that it may also play a role in autoimmune diseases [14], infectious diseases [9], and cancer [15]. Of note, sST2 has been shown to be elevated in patients with gastric cancer [16]. Further, IL-33 and ST2 have been shown to be involved in exacerbated *H. pylori* infection in vitro [17].

Our study is predicated on the hypothesis that sST2 levels may be altered in asymptomatic patients with *H. pylori* infection, which holds significant implications for the diagnosis and management of *H. pylori* infection. While *H. pylori* infection can be diagnosed through invasive procedures like endoscopy and biopsy, less invasive methods such as stool antigen testing, breath tests, or serology are also available, albeit with potentially lower accuracy [2]. As a non-invasive biomarker, sST2 could offer a promising addition in combination to current diagnostic methods. Moreover, if *H. pylori* infection does influence sST2 levels, this may have implications for other disease contexts, such as autoimmune diseases and heart failure, where sST2 has been implicated. To the best of our knowledge, this is the first study to investigate the potential association between *H. pylori* infection and sST2 levels in asymptomatic patients. We aim to compare sST2 levels in patients with and without *H. pylori* infection, while assessing the relationship between sST2 and other clinical and laboratory parameters. It is worth noting that both sST2 and *H. pylori* infection have been linked to metabolic risk factors like obesity, insulin resistance, and metabolic syndrome, which may also play a role in our findings [18]. Another objective was to investigate whether there is a correlation between *H. pylori* infection and changes in sST2 levels, while also examining whether this correlation remains significant regardless of the presence of common metabolic risk factors.

In summary, this paper investigates the potential association between *H. pylori* infection and sST2 levels in asymptomatic patients. *H. pylori* infection is a significant public health issue, and sST2 is a biomarker that has been proposed to play a role in various disease settings. Our study aims to shed light on the potential relationship between these two factors and may have implications for the diagnosis and management of *H. pylori* infection as well as other disease settings.

Methods

Subjects

Our study recruited participants from the Salzburg Colon Cancer Prevention Initiative (Sakkopi), a cohort of asymptomatic patients screened for colorectal cancer at a single center in Austria who were offered a screening esophagogastroduodenoscopy (EGD). We assessed all patients ($n = 1047$) enrolled between 2018 and 2020. In 718 patients we had serum samples available for sST2 measurement. We further excluded 24 patients who refused EGD. Ultimately, our analysis consisted of 694 patients who had both serum samples available for sST2 measurement as well as undergone EGD with biopsy. All enrolled subjects had clinical and laboratory parameters collected as part of the study [19, 20]. In addition, patients were asked to complete a medical history questionnaire. We assessed and calculated various parameters, including body mass index (BMI), smoking status, arterial hypertension, and metabolic syndrome, based on current guidelines [21]. We assessed the presence of *H. pylori* through histology, using biopsies collected during EGD. We performed the study and all procedures according to the principles of the Declaration of Helsinki. The local ethics committee for the province Salzburg approved the study protocol (Approval No. 415-E/1262). Written informed consent was obtained from every participant.

Measurement of sST2

Serum levels of sST2 were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Duoset DY206; R&D Systems, USA). The assay was performed according to the manufacturer's protocol. Serum samples and standard protein were added to the wells on a 96-well plate (Maxisorp plate, Nunc-Immuno, Sigma Aldrich, Austria) and incubated for 2 h. After this incubation period, 96-well plates were washed for three times with washing buffer containing Tween-20. Then, a biotin-labelled secondary antibody was added to the wells and plates were incubated for further 2 h. Later, plates were washed again and Streptavidin-horseradish-peroxidase was added. A colour reaction was achieved using tetramethylbenzidine (TMB; Sigma Aldrich, USA). The reaction was stopped using diluted sulfuric acid. Optical density values were measured at 450 nm on an ELISA plate-reader (Bio-Rad Laboratories, Austria). Serum levels of sST2 were then calculated for each sample using a Excel spreadsheet.

Statistical Analysis

Continuous variables were presented as median with interquartile range (IQR) and compared using Mann–Whitney *U* Test. Categorical variables were expressed as numbers

with percentages and analyzed using the chi-square test. We visualized the distribution of sST2 (Fig. 1) in patients

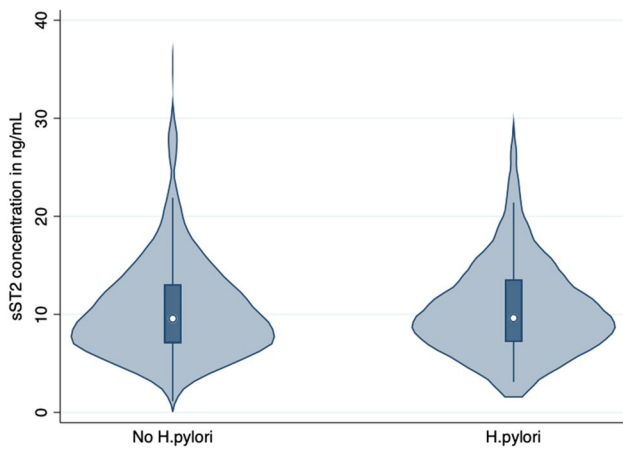
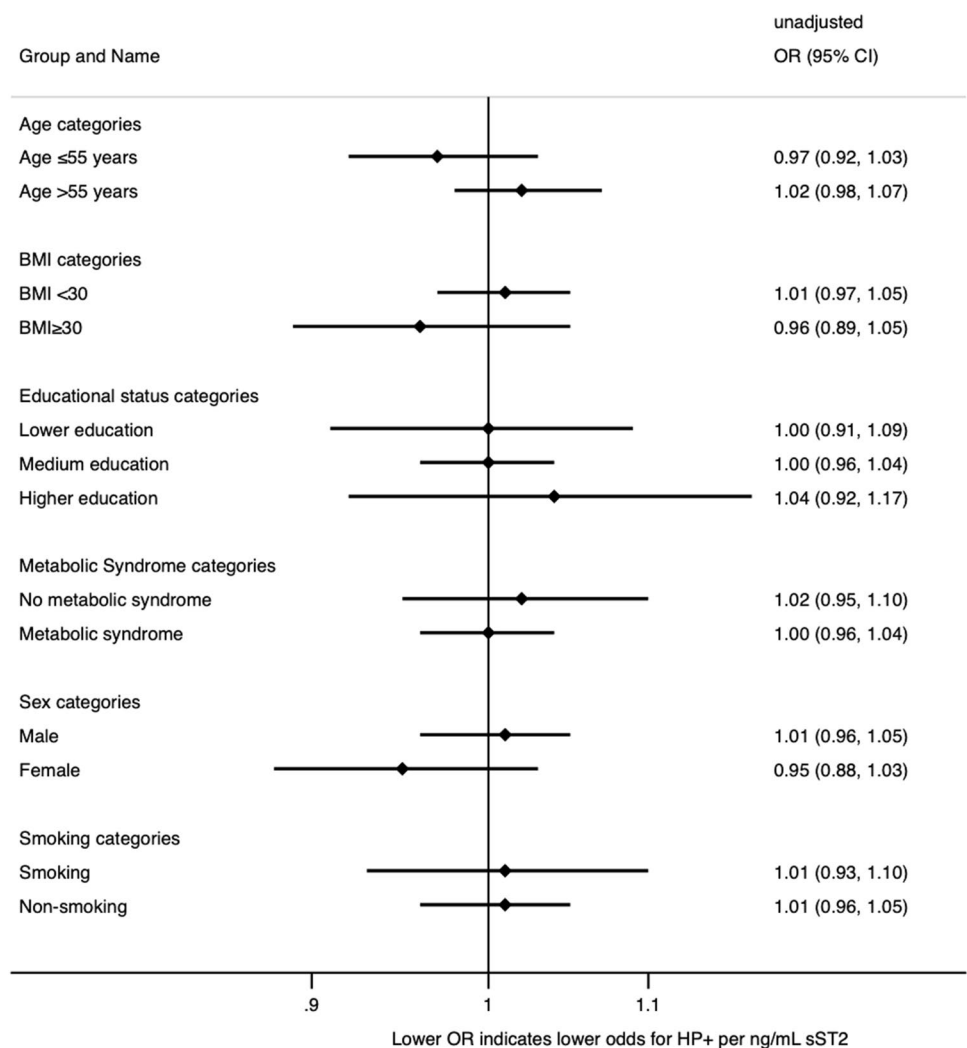


Fig. 1 We visualized the distribution of sST2 in ng/mL (this figure) using vioplot command [22] in patients with and without *H. pylori*

with and without *H. pylori* infection using the vioplot command [22]. All statistical tests were two-tailed, and a *p* value less than 0.05 was considered statistically significant. The primary endpoint in our study was the histological diagnosis of *H. pylori*, and the primary exposure was the concentration of sST2. We fitted logistic regression models to examine the relationship between sST2 concentration and *H. pylori* status. In Model-1, sST2 concentration was the independent variable, and the occurrence of *H. pylori* was the dependent variable. In Model-2, sST2 concentration, age, sex, educational status and concomitant metabolic syndrome diagnosis were fixed effect-dependent variables. Sensitivity analyses (Fig. 2) were also performed to explore the relationship between *H. pylori* status and sST2 concentration, with patients stratified by sex (male versus female), age (patients aged ≤ 55 years and patients aged > 55 years), BMI (BMI < 30 kg/m² versus BMI ≥ 30 kg/m²), concomitant metabolic syndrome diagnosis, and current smoking status. We obtained adjusted odds ratios (ORs) and corresponding

Fig. 2 To investigate the association between sST2 concentration and *H. pylori* infection, we performed sensitivity analyses using logistic regression models. The occurrence of *H. pylori* was set as the dependent variable, and sST2 concentration was the independent variable. The patients were stratified by sex, age, BMI, concomitant metabolic syndrome diagnosis, smoking, and educational status. However, we did not observe any significant relationship between sST2 concentration and *H. pylori* infection in any of the subgroups analyzed



95% confidence intervals (CIs). All statistical analyses were conducted using Stata/IC 17.

Results

We compared various clinical and laboratory parameters between patients with ($n = 131$) and without ($n = 563$) *H. pylori* infection. There was no significant difference in age, with both groups having a median age of 57 years ($p = 0.75$). Similarly, there was no difference in the proportion of patients aged 55 years or younger versus those over 55 years of age ($p = 0.95$). The proportion of female patients was similar in both groups, with 48% of patients without *H. pylori* infection and 39% of patients with *H. pylori* infection being female ($p = 0.73$). The median BMI was slightly higher in patients with *H. pylori* infection compared to those without infection (27 kg/m² vs. 26 kg/m², $p = 0.02$). However, there was no significant difference in the proportion of patients with a BMI less than

30 kg/m² versus those with a BMI of 30 kg/m² or greater ($p = 0.11$). The frequency of hypertension, diabetes, and metabolic syndrome did not show any significant difference between the two groups (Table 1). Additionally, smoking status was comparable in both groups. We also found no significant variations between the two groups in the laboratory parameters analyzed, including HbA1c, cholesterol, LDL, HDL, creatinine, hemoglobin, white blood cell count, CRP, and platelet count. There was no significant difference in the median sST2 concentration between patients without (9.67; 7.08–13.06 ng/mL) and those with (9.62; 7.18–13.44 ng/mL; $p = 0.66$) *H. pylori* infection (Fig. 1). In the logistic regression, sST2 was not associated with the diagnosis of *H. pylori* (OR 1.00; 95%CI 0.97–1.04; $p = 0.93$) and remained so after multi-variable adjustment for age, sex, educational status and the diagnosis of metabolic syndrome (aOR 0.99; 95%CI 0.95–1.03; $p = 0.60$). In the sensitivity analyses stratified by age, sex, BMI, smoking and educational status as well as the concomitant diagnosis of metabolic syndrome, we

Table 1 Baseline characteristics of patients with ($n = 131$) and without ($n = 563$) *H. pylori* infection

	No <i>H. pylori</i> <i>N</i> = 563	<i>H. pylori</i> <i>N</i> = 131	<i>p</i> value
Age (years)	57 (52–63)	57 (53–64)	0.75
Age categories			0.95
Age ≤ 55	40% (226)	40% (53)	
Age > 55	60% (337)	60% (78)	
Female sex	48% (268)	39% (51)	0.73
BMI (kg/m ²)	26 (24–29)	27 (25–30)	0.02
BMI categories			0.11
BMI < 30 kg/m ²	80% (452)	74% (97)	
BMI ≥ 30 kg/m ²	20% (111)	26% (34)	
Hypertension (yes/no)	61% (342)	62% (81)	0.82
Metabolic syndrome (yes/no)	83% (469)	80% (105)	0.39
Diabetes (yes/no)	31% (174)	32% (42)	0.80
Hba1c (%)	5.4 (5.2–5.6)	5.4 (5.2–5.7)	0.44
Cholesterol (mg/dL)	224 (194–253)	220 (195–244)	0.31
LDL (mg/dL)	147 (118–173)	143 (121–165)	0.49
HDL (mg/dL)	57 (48–68)	56 (47–66)	0.59
Creatinine (mg/dL)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.24
Hemoglobine (mg/dL)	14.6 (13.8–15.4)	14.9 (13.9–15.6)	0.12
White blood count (G/L)	5.6 (4.7–6.7)	6.0 (5.0–7.2)	0.35
CRP (mg/dL)	0.1 (0.1–0.3)	0.2 (0.1–0.3)	0.68
Platelets (G/L)	240 (208–276)	238 (208–274)	0.89
Smoking status			0.14
Non-smoker	83% (433)	78% (94)	
Current smoker	17% (86)	22% (27)	
ST2 (pg/mL)	9.57 (7.08–13.06)	9.62 (7.18–13.55)	0.66

Continuous data are given as median ± inter-quartile range (IQR) and compared using Mann's Whitney *U* Test. Categorical data are given as numbers (percentage) and compared using the chi-square test. All tests were two-sided, and a *p* value of <0.05 was considered statistically significant

found no association between sST2 and *H. pylori* infection in any of the subgroups.

Discussion

The previous literature on sST2 and *H. pylori* infection is scarce. Bergis et al. investigated the role of Interleukin-33 (IL-33), its membrane bound cellular receptor ST2L, and its soluble receptor sST2 in gastric cancer [16]. Thirty gastric cancer patients, 51 gastritis patients, and 40 healthy volunteers were enrolled, and the levels of IL-33 and sST2 were determined by ELISA. The results showed that sST2 levels in gastric cancer were significantly higher than in gastritis or healthy controls, and higher levels of sST2 were seen in patients with lower degree of tumor differentiation. Soluble ST2 was significantly associated with a more advanced tumor stage, metastatic disease, and significantly correlated with the duration of the disease [16]. Another study investigated the interaction between *H. pylori* and the proinflammatory cytokine IL-33 and its receptor ST-2 [17]. The results showed that *H. pylori* infection elevated expression levels of IL-33 and ST-2 and caused ST-2 mobilization into membrane lipid rafts. Depletion of membrane cholesterol reduced *H. pylori*-induced IL-33 and IL-8 production. In vivo studies revealed that *H. pylori* infection led to upregulation of IL-33/ST-2 and severe leukocyte infiltration in gastric tissues, indicating that ST-2 recruitment into the lipid rafts serves as a platform for IL-33-dependent *H. pylori* infection, which aggravates inflammation in the stomach. Two other studies showed that IL-33, for which sST2 is the soluble decoy receptor, is involved in inflammation mediated by *H. pylori* infection [23, 24]. Based on these preliminary studies, we speculated about a role of sST2 in asymptomatic *H. pylori* infection. However, our study did not find any significant association between sST2 levels and *H. pylori* infection in asymptomatic patients. This suggests that sST2 may not serve as a valuable biomarker for the diagnosis and management of *H. pylori* infection. All of our patients were asymptomatic and underwent gastroscopy because it was offered to them as part of an opportunistic colon cancer screening program using colonoscopy. However, some of our patients may have had more severe gastritis than others, or even subtle symptoms. Unfortunately, we do not have this data. sST2 is a biomarker that has been extensively studied in recent years [7–9]. An association between sST2 and mortality has already been demonstrated in several populations [25, 26]. sST2 was proposed as a marker for heart failure [27], but emerging evidence suggests that it may also play a role in autoimmune diseases [28], infectious diseases [9], and cancer [14]. In autoimmune diseases, sST2 has been shown to be associated with disease activity in conditions such as systemic lupus erythematosus [29] and rheumatoid arthritis

[30]. In infectious diseases, sST2 levels have been reported to be elevated in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [31] and sepsis [9, 32]. In cancer, sST2 levels have been linked to tumor progression and metastasis [15, 16]. sST2 has also been investigated in cardiovascular diseases, such as acute myocardial infarction [33], heart failure [12], and atherosclerosis [34]. Furthermore, sST2 has been studied in the context of chronic obstructive pulmonary disease [35], chronic kidney disease [11], and type 2 diabetes mellitus [36].

Therefore, it is actually surprising that there has been no data on the association between sST2 and *H. pylori* infection so far. Based on our data, we can exclude such an association for asymptomatic patients. Nevertheless, we consider it important to document and publish our unequivocal negative results. First, to avoid reporting bias. Reporting bias refers to the systematic error that can arise in research studies when there is selective reporting or publication of certain results or outcomes over others [37]. It can occur when the researchers choose to report only the results that support their hypothesis or research question, or if journals are more likely to accept and publish positive results rather than negative or inconclusive ones [38, 39]. This bias can lead to an incomplete or misleading understanding of the research question being studied, as important information may be left out or overemphasized. It can also lead to a skewed perception of the efficacy or safety of a particular intervention or treatment. Reporting bias can be minimized by ensuring that all study outcomes are reported, regardless of whether they are statistically significant or not. Second, to state that sST2 is definitely not a suitable biomarker for the detection of *H. pylori*. And third, to show scientists who are investigating other diseases (diabetes, cancer, cardiovascular diseases) and sST2 that any concomitant asymptomatic *H. pylori* infection does not bias their results.

Conclusion

In conclusion, this study found no significant association between *H. pylori* infection and sST2 levels in asymptomatic patients. The median sST2 concentration was similar in both infected and non-infected patients. Logistic regression analysis and sensitivity analyses also did not show any association between sST2 levels and *H. pylori* infection. These results suggest that sST2 may not serve as a useful biomarker for the diagnosis and management of *H. pylori* infection. These findings have relevance for researchers investigating sST2 in various diseases and indicate that asymptomatic *H. pylori* infection does not bias the results of sST2 studies.

Author's contribution SW, BW, ML and CD conceived the presented idea. All authors contributed to the final version of the manuscript and approved the final version.

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Data availability Data are available upon reasonable request.

Declarations

Competing interests CD is part of the scientific advisory board of SPAR Austria.

Ethical approval We performed the study and all procedures according to the principles of the Declaration of Helsinki. The local ethics committee for the province Salzburg approved the study protocol (Approval No. 415-E/1262). Written informed consent was obtained from every participant.

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