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Role of exhaled hydrogen sulfide in the diagnosis of colorectal cancer

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ABSTRACT

Background Colorectal cancer (CRC) is often accompanied by increased excretion of hydrogen sulfide (H_2S). This study aimed to explore the value of exhaled H_2S in the diagnosis of CRC.

Methods A total of 80 people with normal colonoscopy results and 57 patients with CRC were enrolled into the present observational cohort study. Exhaled oral and nasal H_2S were detected by Nanocoulomb breath analyser. Results were compared between the two groups. Receiver operating characteristic (ROC) curves were analysed and area under the curves (AUCs) were calculated to assess the diagnostic value of exhaled H_2S. Meanwhile, the clinicopathological features, including gender, lesion location and tumour staging of patients with CRC, were also collected and analysed.

Results The amount of exhaled H_2S from patients with CRC was significantly higher than that of those with normal colonoscopy results. The ROC curve showed an AUC value of 0.73 and 0.71 based on oral and nasal H_2S detection, respectively. The exhaled H_2S in patients with CRC was correlated with gender, lesion location and tumour progression, including depth of invasion, lymphatic metastasis and TNM (Tumor, Lymph Nodes, Metastasis) staging.

Conclusion Exhaled H_2S analysis is a convenient and non-invasive detection method for diagnosing CRC, suggesting a potential role in population screening for CRC.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Non-invasive detection technology is an urgent need for the diagnosis of colorectal cancer (CRC).
⇒ Exhalation detection is an accurate and reliable technique.
⇒ Hydrogen sulfide (H_2S) exhalation is associated with abnormal metabolism.

WHAT THIS STUDY ADDS

⇒ This study found that the amount of H_2S exhalation in patients with CRC was significantly higher than that in people with normal colonoscopy results.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Exhalation H_2S analysis has the potential to become a novel, convenient and non-invasive detection method for screening CRC in a large population.

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant tumour and the second leading cause of cancer deaths worldwide.[1] Early diagnosis and treatment remain the key to prolonging survival and reducing mortality rates in patients with CRC. Colonoscopy with pathology confirmation is considered the 'gold standard' for diagnosis of CRC. However, using colonoscopy as a primary screening method is invasive, expensive and offers limited population benefit. Preceding it with a non-invasive test, like breath testing, could effectively target high-risk patients.

With recent development and advancements of non-invasive medical diagnosis, respiratory gas diagnosis has rapidly been gaining recognition for its convenience and accuracy. Breathing gas consists of a mixture of gases, which contains not only air components, but also various metabolites. These metabolites are mainly substances in the blood that are emitted from the body through the respiratory system.[2] Therefore, respiratory gas diagnosis is used in various metabolic diseases, such as gastrointestinal diseases and diabetes mellitus.[3 4]

Hydrogen sulfide (H_2S) is the third gas signal molecule discovered after nitric oxide and carbon monoxide. H_2S is generated in humans via two major routes: ubiquitous endogenous enzymes and the gut microbiota, particularly sulfate-reducing bacteria (SRB). The endogenous H_2S in the human body is mainly synthesised by the core enzyme system composed of cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST). H_2S in the cytoplasm is produced from L-cysteine catalysed by CBS or CSE. In the mitochondria, 3-MST catalysed mercaptopyruvate to produce H_2S.[5] It was reported that SRB in the intestine was closely related to the occurrence and development of irritable bowel syndrome, metabolic syndrome,

inflammatory bowel disease (IBD), CRC and other diseases.[6 7] H_2S produced by the intestine is a risk factor for CRC.[8] Szabo *et al* compared human colon cancer tissues with matched normal mucosal tissues and found that H_2S synthase CBS was selectively upregulated in cancer tissues.[9] Correspondingly, the level of H_2S in the faeces of patients with CRC is significantly higher than that of patients without tumour.[10 11]

In addition to being excreted with faeces, as a gas molecule, H_2S can diffuse into the bloodstream and be exhaled through expiration. Thus, we aim to determine whether CRC can cause an elevation in the amount of exhaled H_2S. Furthermore, we intend to characterise the increase of H_2S exhalation to develop a convenient and non-invasive method for the diagnosis of CRC. Benefiting from the latest detection instruments, the present pilot cohort study is determined to explore the diagnostic value of oral and nasal H_2S as a potential screening method for CRC.

Methods and patients

Study design

The diagnosis of CRC was made via colonoscopy at the endoscopy centre with pathology confirmation. Patients were recruited from the population who came to our hospital's outpatient department for gastrointestinal discomfort between June 2019 and November 2020 and agreed to undergo colonoscopy examination. During this period, we also recruited a number of CRC-diagnosed patients from the surgical department. Informed consent was voluntarily signed when making an appointment for colonoscopy. Exhalation test was conducted immediately after colonoscopy, which takes about 5 min. Patients who did not meet the following exclusion criteria were included in this study: (1) use gastrointestinal motility drugs, psychotropic drugs, acid suppressants, immunosuppressants, hormonal therapy, intestinal microecological agents, antidiarrhoeal drugs, antibiotics, probiotics or laxatives consecutively for more than 3 days within 2 weeks of the examination; (2) serious systemic diseases, such as cardiac or pulmonary insufficiency, abnormal liver or kidney function; (3) history of gastrointestinal or abdominal surgery; (4) without the ability to complete respiratory expiration examination; (5) IBD or new pathology other than CRC, such as adenoma, lymphoma or stromal tumours.[4] Patients with normal colonoscopy results were included in control group.

Exhaled H_2S determination

Exhaled oral and nasal H_2S detection was conducted by the Nanocoulomb breath analyser DA6000 (Wuxi Sunvou Medical Electronics Co., Wuxi, China). The concentration of H_2S was measured as one part per billion (ppb). The technical parameters and specific detection process of the equipment were consistent as previously published.[12]

Statistical method

Graphpad Prism V.7.0 software was used for statistical analysis. The diagnostic accuracy of exhaled H_2S levels was evaluated using ROC curve analysis. Differences among the different groups were analysed by the non-parametric Mann-Whitney U test for binary variables or the respective Kruskal-Wallis omnibus test for several independent groups. Continuous variables in the measurement data were represented as the mean±SD. Data were shown as mean±SEM in the figures. Statistical analysis of $p<0.05$ was considered significant.

RESULTS

Exhaled H_2S increased significantly in patients with CRC

A total of 57 patients with CRC and 80 people with normal colonoscopy results were included in the present study. As shown in table 1, the patients with CRC exhibited a relatively older age profile, with a higher proportion of males. In order to comprehensively explore the diagnostic value of exhaled H_2S, via both oral and nasal expiration, H_2S levels were compared between controls and patients with CRC. The nasal and oral H_2S levels in patients with CRC were 20.02±15.82 and 47.51±27.78 ppb, respectively. For those with normal colonoscopy results, the H_2S levels of nasal and oral exhalation are only 10.41±4.45 and 26.32±19.07. Oral H_2S was consistently higher than nasal H_2S in both CRC ($p<0.05$) and control groups ($p<0.05$) (figure 1A). Comparison between same site H_2S showed that the oral and nasal H_2S of patients with CRC were significantly higher than that of the control (figure 1B,C), which prompted exhaled H_2S as a potential indicator for the diagnosis of CRC.

Table 1 Results of exhaled determination in the observation and control group

	CRC group	Control group	P value
Number of people (male/female)	57 (37/20)	80 (38/42)	0.044
Age	60±14.14	54±15.45	0.027
Nasal exhaled H_2S (ppb)	20.02±15.82	10.41±4.45	<0.001
Oral exhaled H_2S (ppb)	47.51±27.78	26.32±19.07	<0.001

Statistically significant difference between groups, $p < 0.05$.
Data represented as mean±SEM.

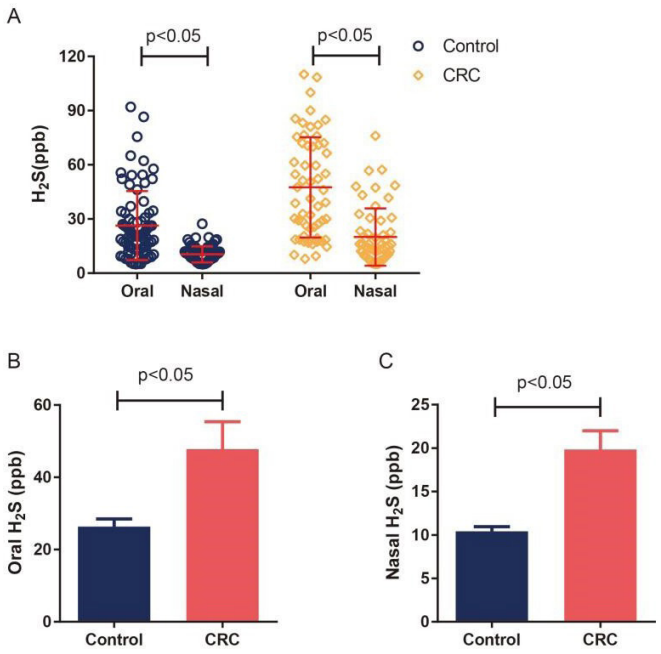

Figure 1 Exhaled hydrogen sulfide (H_2S) comparison between the control group and patients with colorectal cancer (CRC). (A) Comparison of H_2S in different sampling sites within the same group. Comparison of (B) oral H_2S and (C) nasal H_2S between two groups. Data represented as mean±SEM.

Diagnostic value of exhaled H_2S

ROC curve analysis was used to evaluate the diagnostic value of exhaled H_2S. The AUC of oral H_2S was 0.73 (figure 2A). As shown in table 2, with oral exhaled H_2S>16.4 ppb as cut-off value, the sensitivity of predicting CRC was 91% (specificity=33%). Comparatively, the AUC of nasal H_2S was 0.71 (figure 2B). A cut-off value of nasal exhaled H_2S>16.6 ppb has an ideal specificity of 90% in predicting CRC (sensitivity=36%).

Correlation between exhaled H_2S and clinicopathological features

The correlation between exhaled H_2S and tumour clinicopathological features was further explored to determine the characteristics of exhaled H_2S in patients with CRC (table 3). Results showed that exhaled H_2S in female is generally lower than that of male (figure 3A). As age increases, the amount of nasal H_2S showed an increasing trend, while the oral H_2S was the opposite (figure 3B). It was worth noting that the oral H_2S of Stage I&II CRC is significantly higher than that of the people with normal colonoscopy results (figure 3C). A higher level of exhaled H_2S was associated with malignant tumours of the right colon and was often accompanied with deeper infiltration depth, lymph node metastasis and occurrence of metastatic cancerous nodules (figure 4A–D). The excretion of H_2S was relatively decreased in patients with vascular or nerve invasion (figure 4E,F).

DISCUSSION

In recent years, the physiological role and pathological mechanisms of H_2S in gastrointestinal diseases have gained significant attention. Studies have shown that H_2S plays an important role in the occurrence and development of IBD[13] and CRC.[14] Currently, H_2S has been regarded as a potential therapeutic target for CRC, but research focusing on exhaled H_2S as an indicator for the diagnosis of CRC is rare. In this study, we revealed that patients with CRC produce more H_2S and exhaled H_2S, hinting to its potential as a non-invasive screening method for CRC in the future.

Endogenous H_2S promotes the occurrence of CRC by inhibiting autophagy and apoptosis.[15] Moreover, H_2S enhance the antioxidant defence and DNA protection of cancer cells, which promotes proliferation, metastasis and differentiation of CRC.[14 16] Epidemiological investigation showed that the concentration of SRB in the intestine and H_2S within the intestinal lumen and faeces of patients with CRC were 3–4 times higher than those with normal colonoscopy results.[17] A follow-up study found that the H_2S ion current test for colon cancer epithelium, peripheral epithelium and distal epithelium showed a high-to-low voltage change, which was prominent among patients with CRC.[18] These findings indicated that H_2S is closely related to the oncogenesis and progression of CRC.

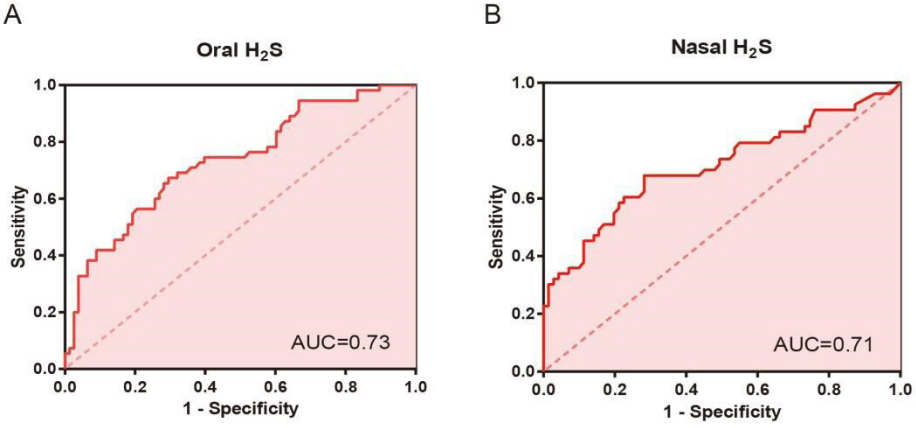

Figure 2 ROC curve of (A) oral and (B) nasal exhaled hydrogen sulfide (H_2S).

Table 2 Results of exhaled hydrogen sulfide (H_2S) ROC curve analysis

	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio
Oral H_2S>16.4	0.91 (0.80 to 0.97)	0.33 (0.23 to 0.45)	1.36
Oral H_2S>54.3	0.42 (0.28 to 0.56)	0.90 (0.81 to 0.95)	4.08
Nasal H_2S>6.85	0.91 (0.80 to 0.97)	0.23 (0.15 to 0.36)	1.19
Nasal H_2S>16.6	0.36 (0.23 to 0.50)	0.90 (0.81 to 0.96)	3.64

After clarifying the crucial role of H_2S in CRC, many researchers continued to explore the specific methods for H_2S detection in CRC. In terms of treatment, aminooxyacetic acid (AOAA) is a traditional CBS inhibitor and has been extensively used in the field of H_2S biology. In colon cancer cell lines, AOAA treatment inhibits H_2S production, cell migration and cell growth, closely mimicking the effect of CBS silencing.[9 19] In vivo, AOAA exhibited remarkable inhibition of HCT116 cell xenografts[19] and the proliferation of patient-derived colon tumour xenografts.[20] However, since H_2S is very susceptible to pH changes and can easily be degraded by thiol methyltransferase and rhodanase, the traditional detection assays, such as the methylene blue method, the monobromobimane method and sulfide selective electrodes, cannot achieve a high repeatable conclusion in the diagnosis of CRC. Compared with detections of H_2S in human peripheral blood and faeces, exhaled H_2S is a more reliable, sensitive and accurate detection method.[12] The screening results from the general population showed that H_2S exhalation volume is relatively stable. This means that an abnormal increase in H_2S exhalation may indicate the occurrence of the disease.[21]

Table 3 Distribution of patients with CRC per clinicopathological feature

Clinicopathological feature	Number
Primary tumour (T)	
Tis+T1	4
T2	5
T3	19
T4	19
Lymph node metastasis (N)	
N0	23
N1	11
N2	13
Distant metastasis (M)	
M0	44
M1	3
TNM stage	
I	5
II	17
III	22
IV	3
Vascular invasion	
Positive	15
Negative	32
Nerve invasion	
Positive	9
Negative	38
Cancerous nodule	
Positive	7
Negative	40

CRC, colorectal cancer.

Excess H_2S can be excreted through pulmonary respiration, which is the theoretical basis for the determination of exhaled H_2S in the diagnosis of CRC. However, its content may be affected by other factors, including nasal cavity, oral cavity and narrow airway. Previous study reported that the H_2S concentration in mouth-exhaled air of healthy adults was about 8–16 ppb,[22] which is much higher than nasal-exhaled H_2S (1-4ppb).[21] Consistently, we found that oral H_2S was significantly higher than nasal H_2S in patients with CRC (figure 1A). Endogenous H_2S has been proven to contribute to the pathophysiology of various airway diseases, including chronic obstructive pulmonary disease, asthma and pulmonary fibrosis.[23]

The Fecal Immunochemical Test (FIT) is a well-established CRC screening method known for its reliability, boasting a high sensitivity of 0.83 (95% CI 0.76 to 0.88) and specificity of 0.90 (95% CI 0.87 to 0.92),[24] with an impressive AUC of up to 0.93.[25] Nevertheless, FIT is not without its limitations. For instance, its sensitivity for early-stage cancer is relatively low, standing at 40%.[26] Additionally, a single study reported FIT's sensitivity for proximal CRC is notably lower than for distal CRC, with a significant difference (71.1% vs 94.2%, p<0.001).[27] Furthermore, the participation rate in FIT screening hovers around 50%.[28 29] In contrast, exhaled H_2S analysis offers a breakthrough by addressing the limitations associated with bleeding and eliminating the influence of other haemorrhagic conditions on FIT results, such as haemorrhoids. Moreover, H_2S breath detection is more convenient than FIT, as it eliminates the need for retaining stool samples, enhancing patient compliance and the potential for improved diagnostic accuracy through multiple tests. In terms of health economics, H_2S also holds advantages, including cost-effective consumables and labour costs, making it a viable option for broader applications. Our results demonstrated that

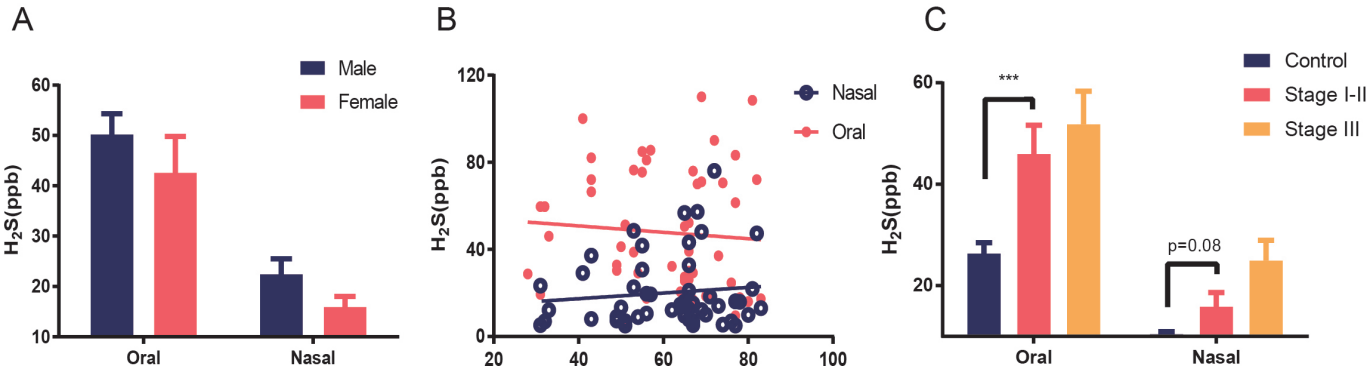

Figure 3 The variation of exhaled hydrogen sulfide (H_2S) in different (A) gender, (B) age and (C) TNM stage.

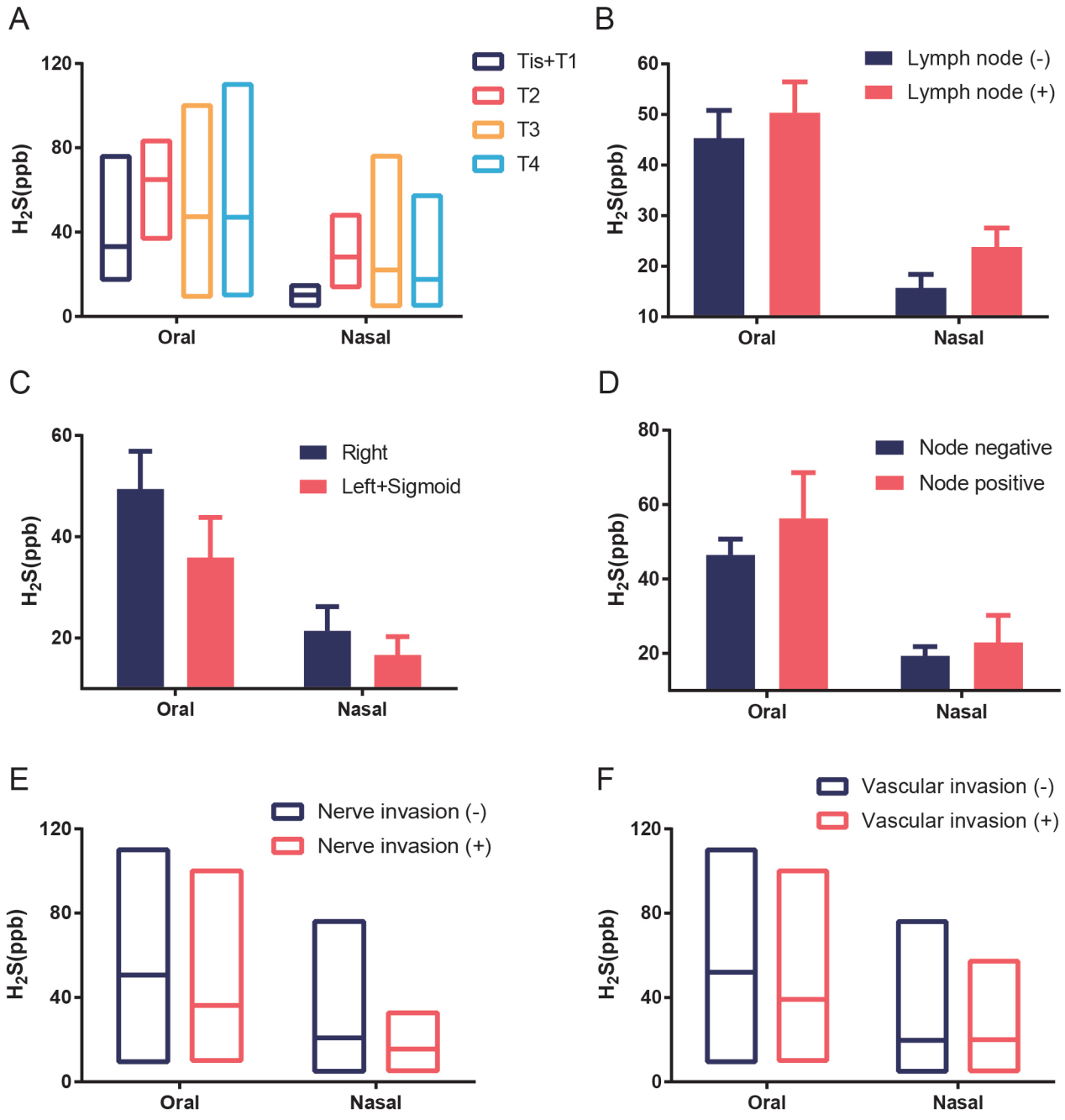

Figure 4 Correlation between exhaled hydrogen sulfide (H_2S) and clinicopathological features. Data represented as Mean±SEM. ***P<0.01.

H_2S exhalation in right colon cancer is higher than in left colon cancer, and oral H_2S exhalation in stages I and II CRC is significantly higher than in the control population (figure 4C). These findings suggested that H_2S analysis may offer good sensitivity for proximal colon cancer and early-stage CRC, addressing specific shortcomings of FIT. As a novel screening method, exhalation test provides an alternative approach to CRC screening, with the potential to complement FIT's limitations and potentially serve as a reference for recommending colonoscopy testing.

Patients with right colon cancer exhaled more H_2S than those with left colon cancer, which may be related to the variation of gut microbiota distribution in different colon segments (such as fusobacterium nucleatum).[23] In general, exhaled H_2S is positively correlated with tumour progression. A higher concentration of exhaled H_2S may be indicative of a more advanced tumour progression. Interestingly, we noted that the H_2S exhalation of T2 tumours is particularly high, which indicated that H_2S may play an important role during the early progression of tumorigenesis.[12]

Our research has certain limitations. First, the subjects underwent breath testing after intestinal preparation, which may result in changes in exhaled H_2S and may not fully align with real-world tumour screening conditions. Second, H_2S exhalation can vary based on gender and age, potentially necessitating different detection thresholds for populations with distinct characteristics. Third, breath testing reflects overall metabolism, potentially including individuals with metabolic or respiratory conditions unrelated to CRC. Additionally, considering several exclusion criteria were implemented for patient selection and small sample size of the present study, further detailed research is needed to establish the feasibility of H_2S as a mass-screening tool for CRC.

CONCLUSION

The present pilot study explored the value of oral and nasal H_2S in the diagnosis of CRC. The amount of exhaled H_2S from CRC is significantly higher than that of people with normal colonoscopy results, especially in oral exhaled H_2S. Exhalation H_2S analysis is a fast and non-invasive detection method for diagnosing CRC, which has the potential to become a new method for screening CRC in large-scale populations. Due to the small samples of the current study, prospective cohort studies with larger samples are warranted to validate the screening efficacy of H_2S in CRC before its clinical application.

Contributors JC, GH and CH: designed the study, supervised the completion of research . PD and YT: analysed and interpreted the data. PD and PL: wrote this manuscript. YT and HZ conducted the colonoscopy. JC and CH is the guarantor of the study. All authors contributed to the article and approved the submitted version.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethics Committee of Huashan Hospital (471-2019). All subjects signed and provided informed consent prior to study enrolment. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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