Diagnostic value of serum squamous cell carcinoma antigen and cytokeratin fragment antigen 21-1 for sinonasal inverted papilloma: an exploratory study

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Abstract

Background: Serum tumor markers have not yet been developed for the clinical diagnosis and treatment of sinonasal inverted papilloma (SNIP), one of the most significant sinonasal tumors. Therefore, this study aimed to determine the diagnostic value of serum squamous cell carcinoma antigen (SCCA) and cytokeratin fragment antigen 21-1 (CYFRA 21-1) for SNIP.

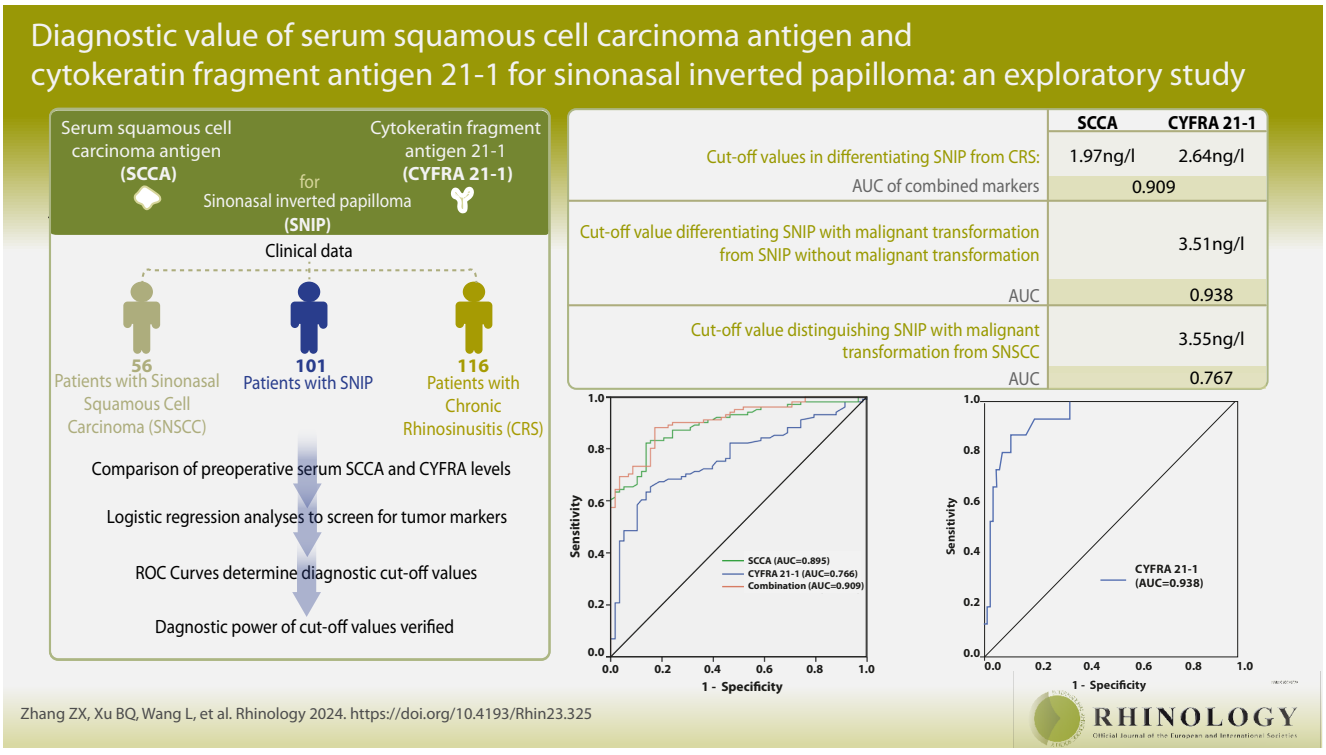
Methods: Clinical data were obtained from 101, 56, and 116 patients with SNIP, sinonasal squamous cell carcinoma (SNSCC), and unilateral chronic rhinosinusitis (CRS), respectively. Preoperative serum SCCA and CYFRA 21-1 levels were compared, and logistic regression analyses were performed to screen serum tumor markers, which may be used to diagnose SNIP. Diagnostic cut-off values were determined using receiver operating characteristic (ROC) curves, and their diagnostic power was verified.

Results: Serum SCCA and CYFRA 21-1 differentiated SNIP from CRS with the cut-off values of 1.97 ng/mL and 2.64 ng/mL and the areas under the ROC curves (AUC) of 0.895 and 0.766, respectively, and the AUC of the combination of the two markers was 0.909. CYFRA 21-1 differentiated SNIP with malignant transformation from that without malignant transformation with a cut-off value of 3.51 ng/mL and an AUC of 0.938. CYFRA 21-1 distinguished SNIP with malignant transformation from SNSCC with a cut-off value of 3.55 ng/mL and an AUC of 0.767.

Conclusions: This study provides novel potential diagnostic tools for SNIP by demonstrating the use of serum SCCA and CYFRA 21-1 in the diagnosis of SNIP.

Key words: sinonasal inverted papilloma, squamous cell carcinoma antigen, cytokeratin fragment antigen 21-1, diagnosis

Graphical abstract



Introduction

Sinonasal inverted papilloma (SNIP) is one of the most common benign tumors of the nasal cavity and sinuses, and its treatment strongly depends on early diagnosis and surgical intervention[1-3]. Serum tumor markers are becoming more widely used for initial screening, diagnosis, and prognostic evaluation of neoplastic diseases[4]. However, for clinical practice, reliable serum tumor markers for SNIP diagnosis have not yet been developed. Previous studies have preliminarily reported differences in serum levels of squamous cell carcinoma antigen (SCCA) between patients with SNIP and those with sinonasal inflammatory diseases, indicating the potential differential diagnostic value of serum SCCA for these patients[5, 6]. However, the small sample size and heterogeneity of these studies hampered the clinical application of serum SCCA, necessitating the increase in the sample size, further classifying the diseases, and specifying the diagnostic cut-off values to enhance the clinical applicability of serum SCCA.

Serum cytokeratin fragment antigen 21-1 (CYFRA 21-1) has been confirmed to be of diagnostic value in several types of head and neck squamous cell carcinomas (HNSCC)[7, 8]. However, investigations comparing the differences in serum CYFRA 21-1 levels and its diagnostic value in SNIP, sinonasal squamous cell carcinoma (SNSCC), and sinonasal inflammatory diseases remain elusive. Additionally, further explorative studies are necessary to determine whether CYFRA 21-1, as an important tumor marker for epithelial malignant tumors, has diagnostic importance in SNIP with malignant transformation.

Thus, this study aimed to investigate the diagnostic value of serum tumor markers (SCCA and CYFRA 21-1) for SNIP, discover novel serum tumor markers for potential use in the diagnosis of SNIP, and establish cut-off values for clinical decision-making.

Materials and methods

Study population

This single-center retrospective study was approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University (ID: QYFY WZLL 28172). By browsing our center's pathology database, we included patients who presented with SNIP, SNSCC, or unilateral chronic rhinosinusitis with/without nasal polyps (CRSw/sNP) between October 2018 and June 2023. The inclusion criteria were as follows: 1) Patients with SNIP, SNSCC, or unilateral CRSw/sNP diagnosed by surgical pathology; of these, those with SNIP or SNSCC who met the diagnostic criteria of the European position paper on endoscopic management of tumors of the nose, paranasal sinuses, and skull base (2010) [1] and those with unilateral CRSw/sNP who met the diagnostic criteria of European position paper on rhinosinusitis and nasal polyps (2012)[9]; 2) those whose blood tests for serum SCCA and CYFRA 21-1 were completed within 7 days before surgical intervention; 3) those with complete clinical data.

The exclusion criteria were as follows: 1) Patients with fungal sinusitis or odontogenic maxillary sinusitis; 2) those who indicated co-morbidity with other sinonasal diseases such as sinus cysts, antrochoanal polyps, cystic fibrosis, ciliary dyskinesia, and other sinonasal tumors; 3) those with SNIP with metachronous malignant transformation and those with recurrent SNSCC; 4) those who indicated co-morbidity with immunodeficiency; 5) pregnant patients; 6) those who indicated co-morbidity with other tumors elsewhere or a history of other tumors; 7) those who indicated co-morbidity with skin diseases affecting serum SCCA.

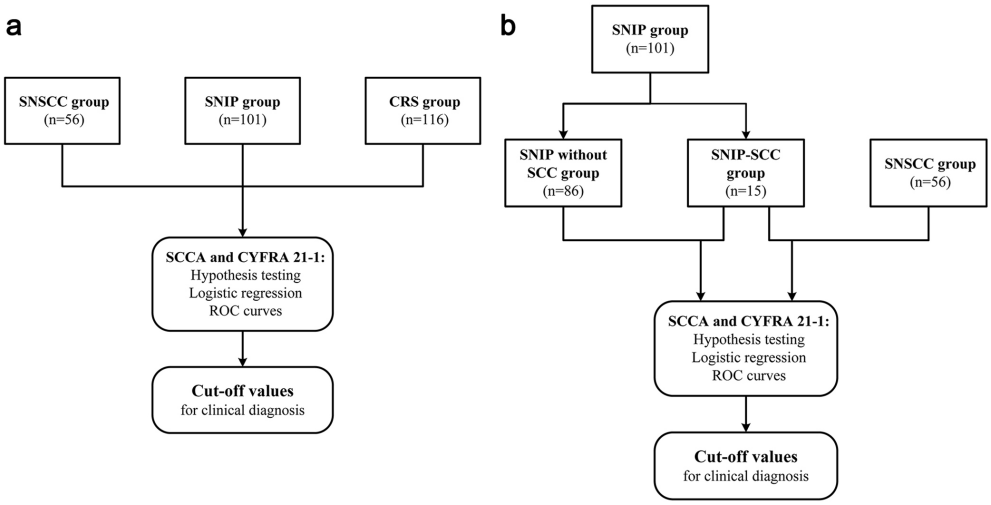


Figure 1. The framework of this study design. a The study flowchart of SCCA and CYFRA 21-1 for the diagnositic value in SNIP patients. b The study flowchart of SCCA and CYFRA 21-1 for the diagnositic value in SNIP with malignant transformation patients. CRS, chronic rhinosinusitis; CYFRA 21-1; cytokeratin fragment antigen 21-1; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNIP-SCC, SNIP with squamous cell carcinoma transformation; SNIP without SCC, SNIP without squamous cell carcinoma transformation; SNSCC, sinonasal squamous cell carcinoma.

Table 1. Preoperative serum tumor markers among SNIP, SNSCC, and CRS groups.

	SNIP group (n=101)	SNSCC group (n=56)	CRS group (n=116)	P	P[a]	P[b]	P[c]
Gender (male)	70 (69.31%)	38 (67.86%)	66 (56.90%)	0.272	NA	NA	NA
Age, years*	55.01±12.66	61.86±11.29	48.24±14.93	<0.001	0.011	0.003	<0.001
Smoking dependence	38 (37.62%)	20 (35.71%)	32 (27.59%)	0.431	NA	NA	NA
Alcohol dependence	20 (19.80%)	10 (17.86%)	12 (10.34%)	0.298	NA	NA	NA
Occupational exposure	3 (2.97%)	3 (5.36%)	2 (1.72%)	0.187	NA	NA	NA
SCCA #	3.90±5.31	2.04±2.21	1.28±0.68	<0.001	<0.001	<0.001	0.005
CYFRA 21-1#	2.61±1.65	2.86±2.53	1.61±0.69	<0.001	0.377	<0.001	<0.001

* $\bar{X} \pm s$; # $M \pm Q_R$; [a] comparison between SNIP and SNSCC groups; [b] comparison between SNIP and CRS groups; [c] comparison between SNSCC and CRS groups; CRS, chronic rhinosinusitis; CYFRA 21-1, cytokeratin fragment antigen 21-1; NA, not applicable; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNSCC, sinonasal squamous cell carcinoma.

Table 2. Logistic regression for distinguishing SNIP from CRS.

							95% CI for OR	
		β	se	Wald	P	OR	Lower	Upper
SCCA	Model 1[a]	1.507	0.295	26.084	<0.001	4.513	2.531	8.048
	Model 2[b]	1.658	0.335	24.483	<0.001	5.251	2.722	10.128
CYFRA 21-1	Model 1[a]	1.180	0.253	21.693	<0.001	3.254	1.980	5.346
	Model 2[b]	1.155	0.268	18.617	<0.001	3.173	1.878	5.362

[a] No adjustment variable; [b] aadjusted for gender, age, and smoking dependence; β, slope parameter; CI, confidence interval; CRS, chronic rhinosinusitis; CYFRA 21-1, cytokeratin fragment antigen 21-1; OR, odds ratio; SCCA, squamous cell carcinoma antigen; se, standard error; SNIP, sinonasal inverted papilloma.

Data collection

Clinical data including gender, age, smoking dependence, alcohol dependence, occupational exposure[10, 11] (including welding dust, wood dust, industrial carcinogens, and heavy metals, etc.), pathological diagnosis, and preoperative serum tumor marker (SCCA and CYFRA 21-1) levels were collected from patients with SNIP, SNSCC, and CRS, individually.

The pathology results were reviewed by a pathologist with more than 20 years of experience in sinonasal pathology to ensure the accuracy of the pathology results.

Serum tumor marker test specimens were gathered from the venous blood of the patients, and the samples were centrifuged at 1000 rpm for 10 minutes. The separated serum was tested by the Roche automatic biochemical analyzer (Roche cobase801, Germany), and the results of serum SCCA and CYFRA 21-1 were recorded.

Study design

Clinical characteristics including gender, age, smoking dependence, alcohol dependence, and preoperative serum tumor marker (SCCA and CYFRA 21-1) levels were compared between SNIP, SNSCC, and CRS groups. Logistic regression and receiver operating characteristic (ROC) curves were used to analyze the diagnostic potential of serum tumor markers to distinguish SNIP from SNSCC/CRS and determine diagnostic cut-off values. SNIP group was sub-divided into SNIP with squamous cell carcinoma transformation (SNIP-SCC) group and SNIP without squamous cell carcinoma transformation (SNIP without SCC) group. Preoperative serum tumor marker levels were compared between SNIP-SCC, SNIP without SCC, and SNSCC groups; logistic regression and ROC curves were used to analyze the diagnostic ability of serum tumor markers to distinguish SNIP-SCC from SNIP without SCC/SNSCC and determine diagnostic cut-off values. Figure 1 presents this study's design.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences version 26.0 (IBM, Corp, Armonk, NY, USA). Normality tests were performed for quantitative data. Quantitative data of normal distribution were demonstrated using mean ± standard deviation ($\bar{x} \pm s$); one-way analysis of variance was used for comparisons between three groups; Stu-

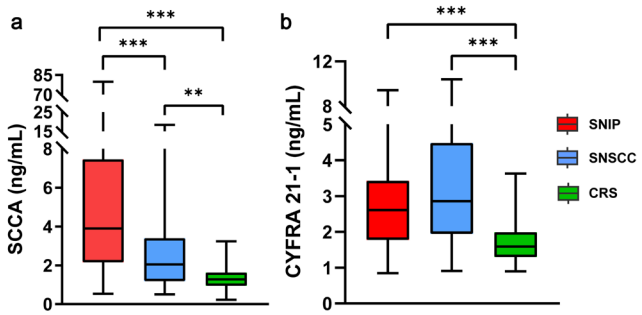


Figure 2. Serum tumour markers levels among the SNIP, SNSCC and CRS groups. a Comparison of serum SCCA levels among the SNIP, SNSCC and CRS groups. b Comparison of serum CYFRA 21-1 levels among the SNIP, SNSCC and CRS groups. CRS, chronic rhinosinusitis; CYFRA 21-1; cytokeratin fragment antigen 21-1; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNSCC, sinonasal squamous cell carcinoma.

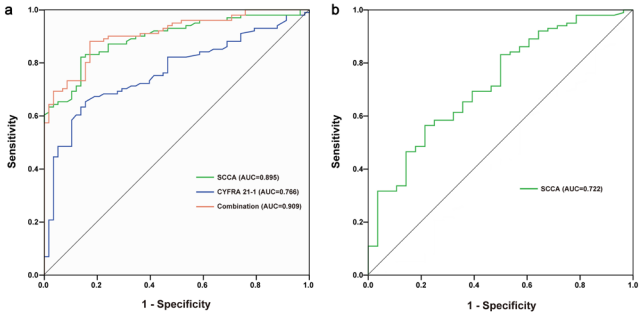


Figure 3. ROC curves of serum tumour markers for predicting SNIP. a ROC curves of SCCA and CYFRA 21-1 for distinguishing SNIP from CRS. b ROC curve of SCCA for distinguishing SNIP from SNSCC. AUC, area under the curve; CRS, chronic rhinosinusitis; CYFRA 21-1; cytokeratin fragment antigen 21-1; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNSCC, sinonasal squamous cell carcinoma.

dent's t-tests were used for comparisons between two groups. Median ± interquartile range ($M \pm Q_R$) was used to determine quantitative data of non-normal distribution, Kruskal–Wallis H tests were used for comparisons between three groups, and Mann–Whitney U tests were used for comparisons between two groups. Frequencies and proportions were used to determine qualitative data; the χ^2 test was used for comparisons between groups. Logistic regression was used to analyze the risk factors associated with the diagnosis of SNIP, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. ROC curves were constructed to assess the potential of preoperative serum tumor markers to diagnose SNIP. These tests were two-tailed, and P<0.05 was considered statistically significant.

Results

Clinical data and preoperative serum tumor marker characteristics

This study involved 273 patients, including 101, 56, and 116 patients with SNIP, SNSCC, and CRS, respectively.

The SNIP group included 86 patients with SNIP without SCC (85.15%) and 15 patients with SNIP-SCC (14.85%), with an average age of 55.01±12.66 years old and 70 males (69.31%) and 31 females (30.69%). The SNSCC group included 24 patients with lowly-differentiated SCC (42.86%), 22 with moderately-differentiated SCC (39.29%), and 10 with highly-differentiated SCC (17.85%), with an average age of 61.86±11.29 years and 38 males (67.86%) and 18 females (32.14%). The CRS group included 68 patients with unilateral CRSwNP (58.62%) and 48 with unilateral CRSsNP (41.38%), with an average age of 48.24±14.93 years and 66 males (56.90%) and 50 females (43.10%). Tables S1-S4 demonstrate further clinical characteristics of the SNIP, SNIP-SCC, SNSCC, and CRS groups, respectively, including the involved sinuses, the clinical stage of tumors, the originating site and dysplasia characteristics of SNIP, the differentiation characteristics of SCC, and the phenotypes and endotypes of CRS.

As presented in Table 1, no statistically significant differences were observed in gender (P=0.272), smoking dependence (P=0.431), alcohol dependence (P=0.298), and occupational exposure (P=0.187) among the three groups. The differences in age, preoperative serum SCCA, and CYFRA 21-1 among the three groups were statistically significant (P<0.001). Figure 2 depicts the preoperative serum SCCA and CYFRA 21-1 levels and differences among the SNIP, SNSCC, and CRS groups.

Diagnostic predictive value of preoperative serum tumor markers for SNIP and CRS

As presented in Table 2, SNIP and CRS were used as dependent variables and preoperative serum SCCA and CYFRA 21-1 were used as independent variables in logistic regression analysis, and the results revealed that serum SCCA and CYFRA 21-1 were risk factors for the diagnosis of SNIP (SCCA, OR=4.513, 95% CI: 2.531–8.048, P<0.001; CYFRA 21-1, OR=3.254, 95% CI: 1.980–5.346, P<0.001). The regression model 2 adjusted for gender, age, and smoking dependence; elevated SCCA or CYFRA 21-1 remained a risk factor for the diagnosis of SNIP (SCCA, OR=5.251, 95% CI: 2.722–10.128, P<0.001; CYFRA 21-1, OR=3.173, 95% CI: 1.878–5.362, P<0.001).

Figure 3a exhibits the ROC curves for serum tumor markers to distinguish SNIP from CRS. The area under the curve (AUC) for SCCA was 0.895 (95% CI: 0.846–0.943), with a diagnostic cut-off value of 1.97 ng/mL, a sensitivity of 0.812, a specificity of 0.862, and a maximal Youden's index of 0.674. The AUC for CYFRA 21-1 was 0.766 (95% CI: 0.692–0.840), with a diagnostic cut-off value of 2.64 ng/mL, a sensitivity of 0.485, a specificity of 0.948, and a maximal Youden's index of 0.433. The AUC of the combined SCCA and CYFRA 21-1 prediction curve was 0.909 (95% CI:

Table 3. Logistic regression for distinguishing SNIP-SCC from SNIP without SCC.

							95% CI for OR	
		β	se	Wald	P	OR	Lower	Upper
CYFRA 21-1	Model 1[a]	1.366	0.340	16.184	<0.001	3.921	2.015	7.629
	Model 2[b]	1.459	0.375	15.107	<0.001	4.300	2.061	8.974

[a] No adjustment variable; [b] adjusted for gender and age; [c] adjusted for gender, age, smoking dependence, and alcohol dependence; β, slope parameter; CI, confidence interval; CYFRA 21-1, cytokeratin fragment antigen 21-1; OR, odds ratio; se, standard error; SNIP, sinonasal inverted papilloma; SNIP-SCC, SNIP with squamous cell carcinoma transformation; SNIP without SCC, SNIP without squamous cell carcinoma transformation.

Table 4. Logistic regression for distinguishing SNIP-SCC from SNSCC.

							95% CI for OR	
		β	se	Wald	P	OR	Lower	Upper
SCCA	Model 1[a]	0.133	0.082	2.604	0.107	1.142	0.972	1.341
	Model 2[b]	0.173	0.097	3.176	0.075	1.189	0.983	1.439
CYFRA 21-1	Model 1[a]	0.331	0.162	4.163	0.041	1.393	1.013	1.915
	Model 2[b]	0.370	0.172	4.693	0.031	1.448	1.034	2.029

[a] No adjustment variable; [b] adjusted for gender and age, smoking dependence, and occupational exposure; β, slope parameter; CI, confidence interval; CYFRA 21-1, cytokeratin fragment antigen 21-1; OR, odds ratio; se, standard error; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNIP-SCC, SNIP with squamous cell carcinoma transformation; SNSCC, sinonasal squamous cell carcinoma.

0.865–0.953), with a sensitivity of 0.881, a specificity of 0.828, and a maximal Youden's index of 0.709.

Diagnostic predictive value of preoperative serum tumor markers for SNIP and SNSCC

As presented in Table S5, SNIP and SNSCC were used as dependent variables, and preoperative serum SCCA was used as an independent variable in logistic regression analysis. The results demonstrated that serum SCCA was a risk factor for the diagnosis of SNIP (OR=1.192, 95% CI: 1.020–1.393, P=0.027). The regression model 2 adjusted for gender, age, smoking dependence, and occupational exposure; elevated SCCA remained a risk factor for the diagnosis of SNIP (OR=1.197, 95% CI: 1.020–1.405, P=0.028). Figure 3b depicts the ROC curve for SCCA to distinguish SNIP from SNSCC. The AUC for SCCA was 0.722 (95% CI: 0.617–0.826), with a diagnostic cut-off value of 3.43 ng/mL, a sensitivity of 0.564, a specificity of 0.786, and a maximal Youden's index of 0.350.

Diagnostic predictive value of preoperative serum tumor markers for SNIP-SCC and SNIP without SCC

As presented in Table S6, there were no statistically significant differences in gender (P=0.714), smoking dependence (P=0.433), alcohol dependence (P=0.154), occupational exposure (P=0.361), and preoperative SCCA level (P=0.789) between the SNIP-SCC and the SNIP without SCC groups. The age (P=0.049) and preoperative CYFRA 21-1 level (P<0.001) in the SNIP-SCC group were significantly higher than those in the SNIP without SCC group. Figure 4a depicts the preoperative serum SCCA and CYFRA 21-1 levels and differences between the SNIP-SCC group and SNIP without SCC group.

As presented in Table 3, SNIP-SCC and SNIP-without SCC were used as dependent variables, and preoperative serum CYFRA 21-1 was used as an independent variable in logistic regression analysis. The results revealed that serum CYFRA 21-1 was a risk factor for the diagnosis of SNIP-SCC (OR=3.921, 95% CI: 2.015–7.629, P<0.001). The regression model 2 adjusted for gender, age, smoking dependence, and occupational exposure; elevated CYFRA 21-1 remained a risk factor for the diagnosis of SNIP-SCC (OR=4.300, 95% CI: 2.061–8.974, P<0.001).

Figure 4b depicts the ROC curve for CYFRA 21-1 to distinguish SNIP-SCC from SNIP without SCC. The AUC for CYFRA 21-1 was 0.938 (95% CI: 0.884–0.992), with a diagnostic cut-off value of 3.51 ng/mL, a sensitivity of 0.867, a specificity of 0.895, and a maximal Youden's index of 0.762.

Diagnostic predictive value of preoperative serum tumor markers for SNIP-SCC and SNSCC

As presented in Table S7, no statistically significant differences were observed in terms of gender (P=0.709), age (P=0.793),

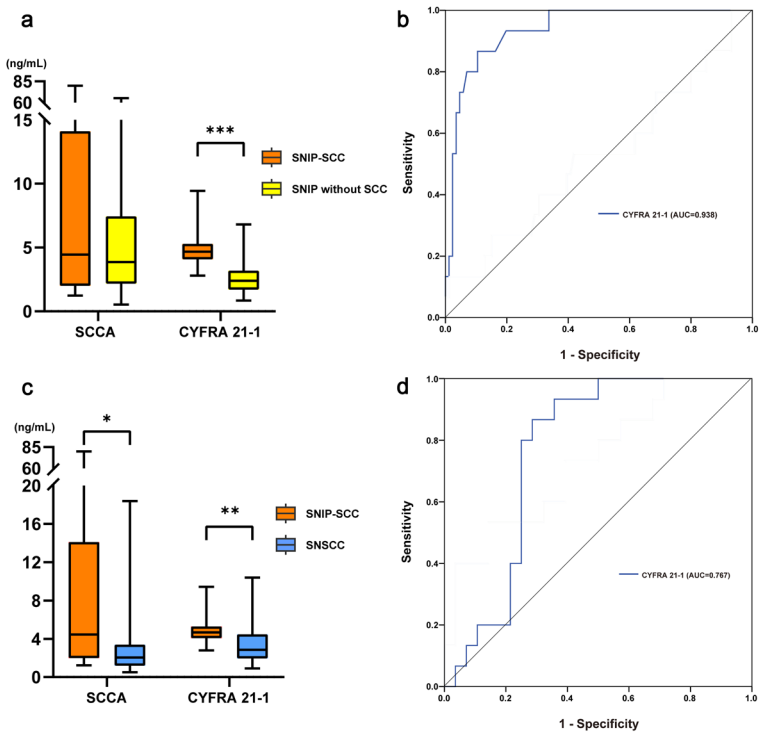


Figure 4. The diagnositic value of serum toumor makers in SNIP with malignant transformation patients. a) Comparison of serum SCCA and CYFRA 21-1 levels among the SNIP with/without SCC transformation groups. b) ROC curve of CYFRA 21-1 for identifing SNIP with/without SCC transformation. c) Comparison of serum SCCA and CYFRA 21-1 levels between the SNIP with SCC transformation and SNSCC groups. d) ROC curve of CYFRA 21-1 for distinguishing SNIP with SCC transformation from SNSCC. AUC, area under the curve; CYFRA 21-1; cytokeratin fragment antigen 21-1; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNIP-SCC, SNIP with squamous cell carcinoma transformation; SNSCC, sinonasal squamous cell carcinoma.

smoking dependence (P=0.484), alcohol dependence (P=0.252), and occupational exposure (P=0.663) between the SNIP-SCC group and the SNSCC group. The preoperative serum SCCA (P=0.013) and CYFRA 21-1 (P=0.004) levels in the SNIP-SCC group were significantly higher than those in the SNSCC group. Figure 4c depicts the preoperative serum SCCA and CYFRA 21-1 levels and differences among the SNIP-SCC and SNSCC groups. As presented in Table 4, SNIP-SCC and SNSCC were used as dependent variables, and preoperative serum SCCA and CYFRA 21-1 were used as independent variables in logistic regression analysis. The results revealed that serum CYFRA 21-1 was a risk factor for the diagnosis of SNIP-SCC (OR=1.393, 95% CI: 1.013–1.915, P=0.041) and that serum SCCA was not significantly associated with SNIP-SCC (P=0.107). The regression model 2 adjusted for gender, age, smoking dependence, and occupational exposure; elevated CYFRA 21-1 remained a risk factor for the diagnosis of SNIP-SCC (OR=1.448, 95% CI: 1.034–2.029, P=0.031). Figure 4d depicts the ROC curve for CYFRA 21-1 to distinguish between SNIP-SCC and SNSCC. The AUC for CYFRA 21-1 was 0.767 (95% CI: 0.624–0.909), with a diagnostic cut-off value of 3.55 ng/mL, a sensitivity of 0.867, a specificity of 0.714, and a maximal Youden's index of 0.581.

Discussion

In this study, we compared serum SCCA and CYFRA 21-1 levels between patients with SNIP, SNSCC, and unilateral CRSw/sNP and discovered that elevated serum SCCA and serum CYFRA 21-1 were risk factors for the diagnosis of SNIP and SNIP-SCC, respectively.

SCCA, a tumor-associated antigen, was first isolated from cervical squamous cell carcinoma[12]. Although it is expressed in normal squamous epithelium, its levels are significantly elevated in the serum of patients with certain malignancies[13]. Previous studies have confirmed the diagnostic use of serum SCCA in cervical squamous cell carcinoma, oral cavity cancer, non-small cell lung cancer, esophageal adenocarcinoma, hepatocellular carcinoma, and other malignant tumors[14]. Recent research has revealed that SCCA has varied expression levels in inflammatory skin diseases such as atopic dermatitis, psoriasis, and lichen planus[15-17].

Yamashita et al. reported that 83.3% of patients with SNIP exhibited higher serum SCCA levels than the upper limit of normal (1.5 ng/mL); however, in the sinonasal inflammatory disease group, the percentage was only 5.3%[18]. Postoperative serum SCCA levels significantly declined in patients with SNIP and were not associated with SNIP recurrence rates[6]. Additionally, serum SCCA has been reported to be high in HNSCC, such as squamous cell carcinoma of the oral cavity, larynx, oropharynx, and hypopharynx[19]. Considering that SNSCC is also a significant HNSCC, it is necessary to explore the differences in serum SCCA levels between patients with SNSCC and those with SNIP. This study has the largest sample size in the field investigating serum SCCA levels in patients with SNIP. We demonstrated that serum SCCA levels were statistically different between patients with SNIP and those with CRS and between patients with SNIP and those with SNSCC. Using the ROC curves, we determined that the cut-off value of 1.97 ng/mL for SCCA was a reliable indicator to distinguish SNIP from CRS. Our findings further expand the

clinical applicability of serum SCCA in the diagnosis of sinonasal diseases.

A previous study has revealed a decline in postoperative serum SCCA levels in patients with SNIP compared to preoperative levels[18], suggesting that SNIP tissue is a potential source of serum SCCA. In this study, we further divided patients with SNIP into SNIP-SCC and SINP without SCC groups, and there was no statistically significant difference in serum SCCA levels between the two groups, suggesting that elevated serum SCCA levels in patients with SNIP are more likely to originate from the influence of the benign solid (non-malignant) portion of the tumor. SCCA levels were higher in patients with SNSCC than in those with CRS, which is consistent with findings in other HNSCCs[20, 21]. Additionally, we observed that patients with SNIP had higher serum SCCA levels than those with SNSCC, suggesting that higher SCCA can be produced and released in SNIP tumor tissues than in SNSCC tumor tissues.

Cytokeratin, one of the structural proteins of epithelial cells, is extensively present in epithelial tissues. When epithelial cells are degraded by proteases, fragments of cytokeratin are released into the bloodstream, of which the soluble fragment binds specifically to two strains of monoclonal antibodies, KS19-1 and BM19-21, to form CYFRA 21-1[22, 23]. CYFRA 21-1 is widely distributed in epithelial cells and serves as a significant marker for the diagnosis and prognosis of non-small cell lung cancer(24). Serum CYFRA 21-1 levels have recently been reported to be associated with the diagnosis and prognosis of HNSCC such as nasopharyngeal carcinoma, oral cavity carcinoma, laryngeal carcinoma, and hypopharyngeal carcinoma[21, 25-27]. No previous studies have examined the differences in serum CYFRA 21-1 in SNIP, SNSCC, CRS, and other sinonasal diseases; which makes this the first exploratory study to investigate the diagnostic value of CYFRA 21-1 in sinonasal diseases. In this study, we demonstrated that serum CYFRA 21-1 levels were significantly higher in patients with SNIP and SNSCC than in those with CRS, suggesting that this tumor marker was a potential tool for differentiating neoplastic lesions from inflammatory lesions in sinonasal diseases.

Owing to the propensity of SNIP to malignancy, accurate preoperative prediction of SNIP malignant transformation is particularly crucial for the development of surgical plans[28, 29]. Although the degree of bone and soft tissue destruction in computed tomography (CT) and MRI manifestations can initially determine its malignant transformation, accurate preoperative determination remains challenging in some patients with malignant lesions, attributed to the characteristics of focal bone erosion in SNIP, especially when the extent of the malignancy is small[30]. It has been observed in several HNSCCs[21, 31, 32] including laryngeal squamous carcinoma, hypopharyngeal carcinoma, and oropharyngeal carcinoma that CYFRA 21-1 is released into the blood upon necrosis or apoptosis of tumor cells, and its sensitivity and concentration increase with the progression of cancer cells, however, the potential value of its application in sinonasal tumors remains elusive. In our study, we discovered a significant difference in CYFRA 21-1 among patients with SNIP-SCC and those with SNIP without SCC and determined the diagnostic cut-off value of 3.51 ng/mL with strong predictive ability (AUC=0.938), which may provide a flexible and simple tool for the diagnosis of SNIP with malignant transformation. The highly invasive nature of the malignant portion of patients with SNIP-SCC causes the destruction of numerous local epithelial cells and an increased release of CYFRA 21-1 into the bloodstream, which may be the primary cause of the significantly elevated serum CYFR 21-1 levels in those patients.

Although the malignant tissues of SNIP-SCC are also squamous cell carcinomas, they are more locally invasive and less sensitive to radiotherapy than primary SNSCC, and the preoperative differentiation of the malignant tissues can help doctors create more comprehensive treatment plans for these patients[33, 34]. In this study, we discovered that serum CYFRA 21-1 differentiated patients with SNIP-SCC from those with SNSCC, and the cut-off value for diagnosis was 3.55 ng/mL. This finding further enhances the potential of CYFRA 21-1 for usage in clinical settings.

In clinical practice, the normal reference intervals for SCCA and CYFRA 21-1 are usually defined as 0-1.5 ng/mL and 0-3.3 ng/mL, respectively[18, 35, 36]. Two previous studies of East Asian populations found that the median serum SCCA and CYFRA 21-1 in healthy populations were 0.80 ng/mL and 1.49 ng/mL, respectively[37, 38]. Compared to the healthy population, the tumor markers of the tumor population in our study remained significantly elevated, which further enhances the robustness of our findings. Considering that reference intervals and medians for serum SCCA and CYFRA 21-1 in normal populations have been previously established with large samples, and the purpose and scenarios of clinical application of our study, we did not use a control group without any sinonasal lesions, and instead, we used the sinonasal diseases that are most important to be distinguished from SNIP as the control groups. This allowed us to establish the clinical diagnostic cut-off values for the two markers and enhanced the clinical application of our findings, which is an advantage of this study.

Owing to the non-specificity of symptoms and similarity in sinus CT presentation, SNIP is crucial in differentiating unilateral CRSw/sNP from it. Although fungal sinusitis, odontogenic maxillary sinusitis, sinus cysts, and antrochoanal polyps are also common benign sinus lesions, it is not difficult to differentiate SNIP from these diseases by specific manifestations on sinus CT or nasal endoscopy. Thus, we excluded these heterogeneous sinonasal disorders from the study to ensure that our findings better meet the necessity of the clinical practice. Previous studies[1, 11, 21, 39] have indicated differential effects of gender, age, smoking dependence on sinonasal diseases, SCCA, and CYFRA

21-1, and a history of occupational exposure as a risk factor for sinonasal malignancy, thus, we adjusted for these confounders in logistic regression to ensure the robustness of our results. In clinical differentiation scenarios between SNIP and unilateral CRSw/sNP, such as when patients report non-specific symptoms and sinus CT indicates unilateral soft tissue density shadows, our findings offer novel possibilities for clinical decision-making. Furthermore, CYFRA 21-1 can be used to predict whether or not SNIP has undergone a malignant transformation and distinguish SNIP-SCC from SNSCC, guiding preoperative planning and diagnostic and therapeutic protocol development. In our future study plans, we will continue to explore the postoperative and long-term changes of serum SCCA and CYFRA 21-1 in SNIP patients with the hope of revealing the relationship between changes in serum tumor markers and recurrence of SNIP, so as to further enhance the robustness and clinical applicability of our findings.

This study also has some limitations. It was a single-center retrospective study involving only the Chinese population; multicenter studies with large sample sizes involving other ethnic groups are needed to further enhance the generalizability of the findings. This study explored the relationship between serum tumor markers and SNIP, SNSCC, and CRS and established the cut-off values for clinical diagnosis; however, the levels of tumor markers in tissues and the correlation between these levels and serum levels need further investigation. Moreover, whether serum tumor markers can be a tool for the detection of recurrence awaits further prospective studies and long-term follow-up.

Conclusions

This study's findings demonstrated that serum SCCA and CYFRA 21-1 can be used as serum tumor markers for the diagnoses of SNIP and SNIP with malignant transformation, respectively. Additionally, we identified the cut-off values of serum tumor markers for clinical diagnosis, providing a novel, simple, and non-invasive potential tool for the diagnosis of SNIP.

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Authorship contribution

LY, YJ, and ZZ contributed to the study conception and design. Data collection ZZ, BX, SL, LY, and XY. Data analysis were performed by ZZ, BX, and LY. The first draft of the manuscript was written by ZZ, YJ, and LY. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Ethics Statement

This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University (ID: QYFY WZLL 28172).

Conflict of interest

The authors declare that there is no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Baseline clinical characteristics of SNIP patients (n=101).

Variables		Number of patients (%)
Recurrent patients	Yes	16 (15.84%)
Involved sinuses	Maxillary sinus	79 (78.22%)
	Ethmoidal sinus	81 (80.20%)
	Frontal sinus	52 (51.49%)
	Sphenoid sinus	44 (43.56%)
Combined with sinusitis	Yes	59 (58.42%)
Krouse stage	T1	4 (3.96%)
	T2	25 (24.75%)
	T3	53 (52.48%)
	T4	19 (18.81%)
Originating site	Nasal cavity	9 (8.91%)
	Maxillary sinus	51 (50.50%)
	Ethmoidal sinus	28 (27.72%)
	Frontal sinus	9 (8.91%)
	Sphenoid sinus	4 (3.96%)
Dysplasia	Low-grade	17 (16.83%)
	Intermediate-grade	3 (2.97%)
	High-grade	3 (2.97%)
Malignant transformation	Yes	15 (14.85%)

SNIP, sinonasal inverted papilloma.

Table S2. Baseline clinical characteristics of SNIP-SCC patients (n=15).

Variables		Number of patients (%)
Differentiation characteristics	lowly-differentiated	7 (46.67%)
	moderately-differentiated	5 (33.33%)
	highly-differentiated	3 (20.00%)
Involved sinuses	Maxillary sinus	13 (86.67%)
	Ethmoidal sinus	14 (93.33%)
	Frontal sinus	11 (73.33%)
	Sphenoid sinus	7 (46.67%)
Tumor stage (AJCC 8th stage)	T2	3 (20.00%)
	T3	6 (40.00%)
	T4	6 (40.00%)
Nodal stage (AJCC 8th stage)	N0	13 (86.67%)
	N+	2 (13.33%)
Distant metastatic	Yes	0

SNIP-SCC, sinonasal inverted papilloma with squamous cell carcinoma transformation.

Table S3. Baseline clinical characteristics of SNSCC patients (n=56).

Variables		Number of patients (%)
Differentiation characteristics	lowly-differentiated	24 (42.86%)
	moderately-differentiated	22 (39.29%)
	highly-differentiated	10 (17.85%)
Involved sinuses	Maxillary sinus	36 (64.29%)
	Ethmoidal sinus	46 (82.14%)
	Frontal sinus	30 (53.57%)
	Sphenoid sinus	26 (46.43%)
Tumor stage (AJCC 8th stage)	T2	7 (12.50%)
	T3	26 (46.43%)
	T4	23 (41.07%)
Nodal stage (AJCC 8th stage)	N0	46 (82.14%)
	N+	10 (17.86%)
Distant metastatic	Yes	0

SNSCC, sinonasal squamous cell carcinoma.

Table S4. Baseline clinical characteristics of CRS patients (n=116).

Variables		Number of patients (%)
Phenotypes	CRSwNP	68 (58.62%)
	CRSsNP	48 (41.38%)
Endotypes	Type 2	19 (16.38%)
	Non-type 2	97 (83.62%)
Involved sinuses	Maxillary sinus	98 (84.48%)
	Ethmoidal sinus	71 (61.21%)
	Frontal sinus	23 (19.83%)
	Sphenoid sinus	14 (12.07%)

CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

Table S5. Logistic regression for distinguishing SNIP from SNSCC.

							95% CI for OR	
		β	se	Wald	P	OR	Lower	Upper
SCCA	Model 1[a]	0.176	0.079	4.905	0.027	1.192	1.020	1.393
	Model 2[b]	0.180	0.082	4.828	0.028	1.197	1.020	1.405

[a] No adjustment variable; [b] adjusted for gender, age, smoking dependence, and occupational exposure; β, slope parameter; CI, confidence interval; OR, odds ratio; se, standard error; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNSCC, sinonasal squamous cell carcinoma.

Table S6. Preoperative serum tumor markers between SNIP-SCC group and SNIP without SCC group.

	SNIP-SCC group (n=15)	SNIP without SCC group (n=86)	P
Gender (male)	11 (73.33%)	59 (68.60%)	0.714
Age, years*	60.93±10.29	53.98±12.80	0.049
Smoking dependence	7 (46.67%)	31 (36.05%)	0.433
Alcohol dependence	5 (33.33%)	15 (17.44%)	0.154
Occupational exposure	1 (6.67%)	2 (2.33%)	0.361
SCCA #	4.45±12.10	3.87±5.27	0.789
CYFRA 21-1#	4.68±1.22	2.40±1.48	<0.001

* $\bar{X} \pm s$; # $M \pm Q_R$; CYFRA 21-1, cytokeratin fragment antigen 21-1; SCCA, squamous cell carcinoma antigen; SNIP, sinonasal inverted papilloma; SNIP-SCC, SNIP with squamous cell carcinoma transformation; SNIP without SCC, SNIP without squamous cell carcinoma transformation.

Table S7. Preoperative serum tumor markers between SNIP-SCC group and SNSCC group.

	SNIP-SCC group (n=15)	SNSCC group (n=56)	P
Gender (male)	11 (73.33%)	38 (67.86%)	0.709
Age, years*	60.93±10.29	61.86±11.29	0.793
Smoking dependence	7 (46.67%)	20 (35.71%)	0.484
Alcohol dependence	5 (33.33%)	10 (17.86%)	0.252
Occupational exposure	1 (6.67%)	3 (5.36%)	0.663
SCCA #	4.45±12.10	2.04±2.21	0.013
CYFRA 21-1#	4.68±1.22	2.86±2.53	0.004

* $\bar{X} \pm s$; # $M \pm Q_R$; CYFRA 21-1, cytokeratin fragment antigen 21-1; SCCA, squamous cell carcinoma antigen; SNIP-SCC, sinonasal inverted papilloma with squamous cell carcinoma transformation; SNSCC, sinonasal squamous cell carcinoma.