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ORIGINAL RESEARCH

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Chronic rhinosinusitis symptoms differentially impact the likelihood of major depressive disorders

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Abstract

Objectives: The extent to which sinonasal symptoms impact the likelihood of major depressive disorders in chronic rhinosinusitis patients with nasal polyposis (CRSwNP) remains incompletely characterized. In this study, we sought to determine whether individual symptom clusters differentially impact the likelihood of depression in a cohort of CRSwNP patients.

Methods: We retrospectively included 77 patients with CRSwNP. The severity of sinonasal symptoms was assessed using the 22-item Sino-Nasal Outcome Test (SNOT-22) and grouped according to a previously validated four-subdomain structure: nasal, otologic/facial pain, sleep, and emotional subdomains. The likelihood of major depressive disorders was assessed using the Patient Health Questionnaire-2 (PHQ-2). The clinical characteristic of symptom severity (nasal polyp size) and disease-specific information, such as the number of previous sinonasal surgeries, were also collected.

Results: The sleep subdomain was most strongly associated with the likelihood of major depressive disorders, followed by the otologic/facial pain subdomain, after controlling for demographics and clinical indicators of symptom severity (nasal polyp size). We found a SNOT-22 score ≥ 30.5 to be an accurate indicator of scoring higher than or equal to 2 on the PHQ-2 in CRSwNP patients. This had a sensitivity of 83.33% and a specificity of 75.47%.

Conclusion: Distinct sinonasal symptom clusters differentially impact the likelihood of depression in CRSwNP patients. Raising awareness for those with severe sinonasal symptomatology might help identify more patients with a higher probability of comorbid depression.

Level of Evidence: 4.

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KEYWORDS
CRS, chronic rhinosinusitis, depression, outcome research, PROM, quality of life, Sino-Nasal Outcome Test 22, SNOT-22

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is a complex disease characterized by persistent inflammation of the paranasal sinuses.[1,2] CRS can be classified based on the presenting phenotype—that is, CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP), which has clinical implications regarding treatment outcome, recurrence rates, and perceived symptom severity.[1–3] Beyond nasal congestion and rhinorrhea, CRS can also manifest itself in symptoms of sleep and emotional disorders, increasing the risk of lost productivity, isolation, or even depression.[4–6] Unsurprisingly, CRS patients' experience of symptom severity gained increasing significance in clinical practice to measure health status and treatment response.[7–10]

There are different tools available for measuring CRS patients' own experience of symptom severity, such as the Sino-Nasal Outcome Test (SNOT-22), a high-quality patient-reported outcome measure (PROM) that assesses sinonasal symptomatology based on 22 questions related to four distinct symptom clusters: (i) nasal, (ii) otologic/facial pain, (iii) emotional, and (iv) sleep-related symptoms.[9,11] Other symptom-specific PROMs, such as the Patient Health Questionnaire-2 (PHQ-2)[12]—a screening tool that evaluates the likelihood for major depressive disorders—are also recommended for periodic screening of adolescents in clinical practice.[13] Indeed, it has been shown that CRS is associated with major depressive disorders and is likely underdiagnosed in many CRS patients.[14] A recent review estimated the prevalence to range between 11% and 40%, depending on the method of diagnosis.[6] Correct and timely diagnosis of comorbid depression is of great importance to improve patient counseling, as this group of patients may not achieve equivalent long-term outcomes after CRS treatment compared to their counterpart group without depression.[6]

Although it has been shown that the overall perceived sinonasal symptomatology (as represented by the SNOT-22) is associated with depression rates in CRS patients,[14] its associations with individual CRS symptom clusters remain incompletely characterized, especially in distinct CRS phenotypes. Investigating individual CRS subpopulations is of great importance, as previous studies have shown that the risk for depression is higher in the subgroup of CRSsNP than CRSwNP.[5] Interestingly, it has also been shown that the quality of life (QoL) differs between subtypes of CRS, as CRSwNP differs from CRSsNP in perceived symptom profile and general health-related QoL.[3,15,16] Furthermore, although demographics and comorbidities (such as asthma) have been taken into account during investigations related to the association between sinonasal symptomatology and the risk for depression, objective parameters related to disease severity (such as the nasal polyp size) have not been considered yet.

Thus, in this study, we sought to characterize the association between patients' self-perceived sinonasal symptom clusters and overall severity (as represented by the SNOT-22 and its four subdomains) and the likelihood for major depressive disorders in a distinct cohort of CRSwNP patients, whereas also accounting for clinical characteristics.

2 | MATERIAL AND METHODS

2.1 | Study design and patient selection

This was a cross-sectional study to investigate the impact of sinonasal symptom clusters and overall symptom severity on the likelihood for major depressive disorders in a distinct cohort of adult patients (≥18 years) diagnosed with CRSwNP based on consensus guidelines established criteria.[1] Demographic information (age, gender), self-reported asthma (physician-diagnosed), and allergy status (self-reported) were collected in all patients. We also documented the nasal polyp score (NPS) assessed during clinical examination and disease-specific information such as the number of prior endoscopic sinus surgeries. This study was approved by the Ethics Committee of the Medical University of Vienna (EK-Nr.: 2325/2020) and included all CRSwNP patients who had completed below-mentioned PROMs between September 22, 2020, and February 1, 2021.

2.2 | Patient-reported outcome measures

All patients completed PHQ-2, a two-item PROM developed as a screening tool for major depressive disorders. Answers are Likert-scale grades ranging from 0 (not at all) to 3 (nearly every day), with a higher score representing a higher likelihood of suffering from depression.[12,17] Furthermore, they also completed the SNOT-22, a validated and widely used 22-item PROM that assesses disease-specific symptomatology of CRS patients. In this study, we use the same four-subdomain structure of the SNOT-22, which has previously been validated in a large cohort of CRS patients[11]: (i) nasal symptoms (Items 1–6, 21, and 22), (ii) emotional symptoms (Items 19 and 20), (iii) sleep-related symptoms (Items 11–18), and (iv) otologic/facial pain symptoms (Items 7–10). Answers are Likert-scale grades, ranging from 0 (no symptoms) to 5 (highest symptoms possible). Responses from individual items are summed, resulting in higher scores representing more significant QoL impairments.

2.3 | Nasal polyp score (NPS)

The endoscopic staging of nasal polyps was performed based on the Gevaert "nasal polyp" scoring method.[18] Each nostril was scored on a scale of 0–4: 0 = no visible nasal polyps, 1 = small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = nasal polyps reaching below the lower border of the middle turbinate; 3 = large nasal polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4 = large nasal polyps causing complete obstruction of the inferior nasal cavity. Scores from both nostrils were added to the final "NPS score" (range: 0–8).

2.4 | Statistical analysis

Analyses were performed with the statistical software SPSS 26.0 (Chicago, IL, USA) and GraphPad Prism 9.1.0 (GraphPad Software, Inc., La Jolla, CA). Continuous variables are presented as mean ± SD. Categorical variables are presented as absolute numbers (percentage). Pearson's *r* was used for bivariate correlation analysis between individual SNOT-22 items and the PHQ-2 score. Univariate and multivariable linear regressions were used to associate (i) the outcome of the likelihood of major depressive disorders, as represented by the PHQ-2 score, with each of the four SNOT-22 subdomains individually, whereas controlling for demographics (age and gender), disease-specific characteristics (asthma and number of previous sinus surgeries), and objective measures of disease severity (nasal polyp size), and (ii) the outcome of the PHQ-2 score with the overall perceived sinonasal symptom severity, as represented by the SNOT-22, whereas also controlling for objective measures of disease severity (nasal polyp size), demographics (age and gender), and disease-specific characteristics (asthma and number of previous sinus surgeries). Finally, to assess the diagnostic accuracy of the SNOT-22 to detect patients who score 2 points or higher in the PHQ-2, we plotted receiver operating characteristics (ROC) curves and calculated the area under the ROC curves (AUC) to determine the diagnostic accuracy. AUC values were interpreted as follows: 0.9–1 = excellent, 0.8–0.9 = very good, 0.7–0.8 = good, and 0.6–0.7 = sufficient accuracy.[19] The α level was set at .05.

TABLE 1 Study participants' characteristics

Characteristics	Study participants (*N* = 77)
Demographics	
Age, years	47.6 ± 13.1 (19–53)
Gender, female	29 (37.7%)
Asthma	47 (61.1%)
Allergy	41 (53.2%)
CRS-specific characteristics	
Number of previous surgeries	1.8 ± 1.3 (0–6)
Nasal polyp score	2.5 ± 2.5 (0–8)
Patient-reported outcome measures	
Sino-Nasal Outcome Test 22 (SNOT-22)	30.4 ± 22.6 (0–83)
Patient Health Questionnaire-2 (PHQ-2)	0.9 ± 1.3 (0–5)

Note: Continuous variables are presented as mean ± SD (range), and categorical variables are presented as absolute number (percentage).
Abbreviation: CRS, Chronic rhinosinusitis.

3 | RESULTS

3.1 | Study participants

A total of 77 patients with CRSwNP (37.7% female and 62.3% male) was included with a mean age of 47.6 years (standard deviation, SD = 13.1). The characteristics of the study patients are summarized in Table 1. Of these patients, 11(14.3%) had no prior functional

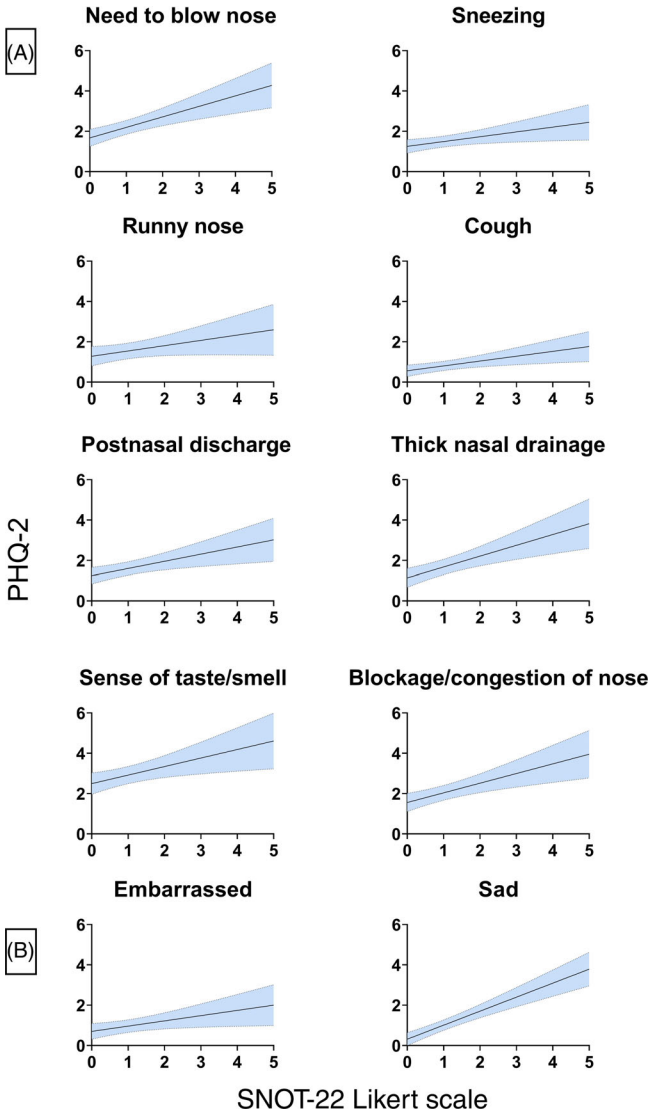

FIGURE 1 Scatter plot with simple linear regression fit and 95% confidence interval bands for the association between the PHQ-2 and individual item scores from the (A) nasal and (B) emotional subdomains. PHQ-2, Patient Health Questionnaire-2; SNOT-22, 22-item Sino-Nasal Outcome Test

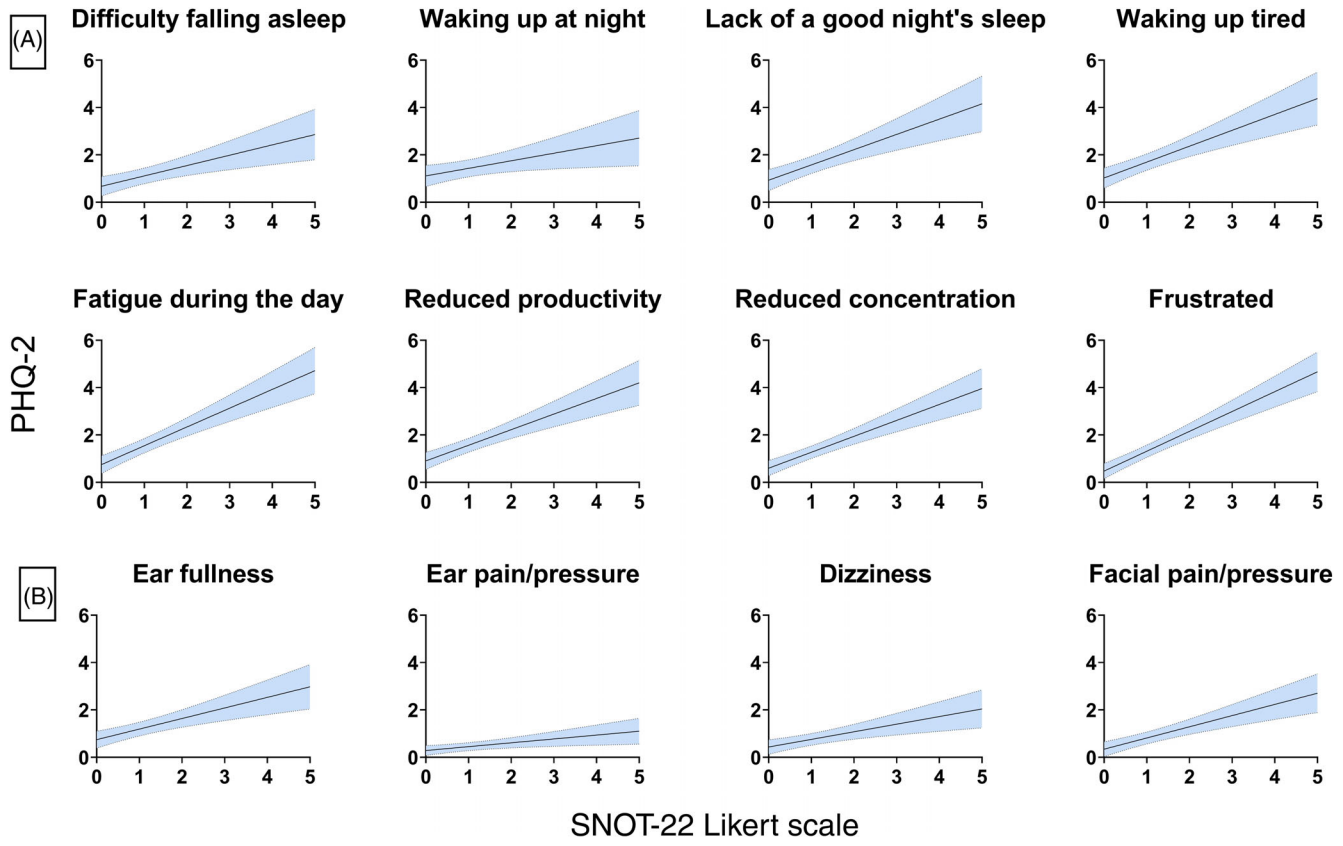

FIGURE 2 Scatter plot with simple linear regression fit and 95% confidence interval bands for the association between the PHQ-2 and individual item scores from the (A) sleep and (B) otologic/facial pain subdomains. PHQ-2, Patient Health Questionnaire-2; SNOT-22, 22-item Sino-Nasal Outcome Test

TABLE 2 Associations between individual Sino-Nasal Outcome Test 22 (SNOT-22) subdomains with the Patient Health Questionnaire-2 (PHQ-2)

	Univariate analysis		Multivariable analysis[a]	
	β [95% CI]	*p* value*	β [95% CI]	*p* value*
Nasal subdomain	**.441 [.235 - .648]**	**<.001**	**.498 [.237 - .759]**	**<.001**
Otologic/facial pain subdomain	**.526 [.331 - .722]**	**<.001**	**.545 [.326 - .764]**	**<.001**
Sleep subdomain	**.590 [.404 - .775]**	**<.001**	**.595 [.387 - .804]**	**<.001**
Emotional subdomain	**.497 [.297 - .697]**	**<.001**	**.498 [.276 - .721]**	**<.001**

Note: *Bold values of *p* are significant.
Abbreviations: β = Linear regression coefficient; CI, confidence interval.
[a]Adjusting for age, gender, asthma, number of previous surgeries, and nasal polyp score.

endoscopic sinus surgery (FESS), 25 (32.5%) had a history of one FESS, and 41 (28.6%) had a history of equal or more than two sinus surgeries. Regarding comorbidities, 47 (61.1%) had a diagnosis of asthma and 41 (53.2%) had a history of allergy.

3.2 | CRS symptoms differentially impact the likelihood of major depressive disorders

Previous studies provided the first evidence that CRS symptom subdomains—that is, nasal, otologic/facial pain, sleep, and emotional symptoms—differentially impact the general health-related QOL. We were therefore first interested in investigating a formal association between these CRS symptom clusters and the likelihood for major depressive disorders, represented by the PHQ-2 score, whereas also controlling for demographics (age and gender) and clinical characteristics (asthma, number of previous surgeries, NPS) using a linear regression model.

On an individual SNOT-22 item level, the PHQ2 was most strongly correlated with #Item 18 "Frustrated" (r = .701, p < .001), followed by #Item 19 "Sad" (r = .631, p < .001; Figures 1 and 2). In univariate analysis, all four subdomains were positively associated with the PHQ2 score: nasal (β = .441, p < .001), otologic/facial pain (β = .526, p < .001), sleep (β = .590, p < .001), and emotional

TABLE 3 Associations between the Sino-Nasal Outcome Test 22 (SNOT-22) with the Patient Health Questionnaire-2 (PHQ-2)

	Univariate analysis		Multivariable analysis	
	β [95% CI]	*p* value*	*β* [95% CI]	*p* value*
Age	−.103 [−.332 - .126]	.372	−.081 [−.276 - .113]	.406
Gender	−.071 [−.301 - .158]	.538	−.029 [−.224 - .167]	.771
Asthma	−.133 [−.361 - .095]	.251	−.109 [−.302 - .085]	.265
Number of previous surgeries	−.036 [−.266 - .194]	.758	.023 [−.166 - .211]	.812
Nasal polyp score	.173 [−.054 - .399]	.133	−.158 [−.390 - .074]	.178
SNOT-22	**.608 [.426 - .791]**	**<.001**	**.695 [.477 - .913]**	**<.001**

Note: *Bold values of *p* are significant.
Abbreviations: β = Linear regression coefficient; CI, confidence interval.

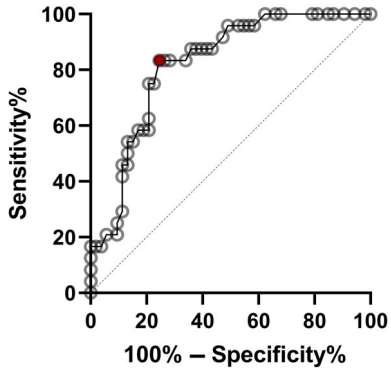

FIGURE 3 Receiver operating characteristic curve for the SNOT-22 score as an indicator to score ≥ 2 on the PHQ-2. The cutoff of 30.5 (red point) maximizes the sum of sensitivity (3.33%) and specificity (75.47%). PHQ-2, Patient Health Questionnaire-2; SNOT-22, 22-item Sino-Nasal Outcome Test

(β = .497, p < .001) subdomains. In multivariable analysis, we found the strongest associations between the sleep (β = .595, p < .001) and the otologic/facial pain subdomains (β = .545, p < .001) with the PHQ2 score, followed by the emotional and the nasal subdomains (both β = .498, p < .001; Table 2).

3.3 | Sinonasal symptom severity is independently associated with the likelihood of major depressive disorders

Because we found all four SNOT-22 subdomains to be differentially but independently associated with a higher risk for major depressive disorders, we sought to evaluate whether the patients' self-perceived overall symptom severity, as represented by the SNOT-22, was an independent predictor of PHQ-2 scores, whereas also accounting for demographics (age and gender), disease-specific variables (asthma and number of previous surgeries), and objective measures of disease severity such as the nasal polyp size (Table 3).

Univariate regression analysis revealed that the SNOT-22 (β = .608, p < .001) was positively associated with the PHQ-2 score. In multivariable analysis, the SNOT-22 (β = .695, p < .001) remained independently associated with the PHQ-2 score.

3.4 | The SNOT-22 is an accurate indicator for higher risk of major depressive disorders in CRSwNP patients

Our observation of the independent association of the SNOT-22 with the PHQ-2 score, whereas also accounting for the general health-related QoL and objective measures of disease severity, prompted us to investigate whether the SNOT-22 can be used as an accurate indicator to identify CRSwNP patients who are at risk for depression (defined as PHQ-2 scores ≥ 2[17]) by calculating a ROC curve.

The AUC of 0.820 (95% confidence interval [CI] [.727 - .914], p < .001) indicates a good diagnostic accuracy for the SNOT-22. The cutoff of >30.5 maximized the sum of sensitivity and specificity to detect CRSwNP patients who score ≥ 2 on the PHQ-2 with a sensitivity of 83.33% and a specificity of 75.47% (Figure 3).

4 | DISCUSSION

CRS is a common health problem with a significant impact on the QoL of affected individuals.[1,2] Beyond economic losses, untreated CRS can lead to various symptoms that differentially affect everyday life, causing isolation, frustration, or even depression.[7,8] As previous studies have shown that depression is more common among CRS patients compared to the general population and that depressed mood modulates the impact of disease-specific symptom severity on general health-related QoL,[5,6,20] it is of great importance to further understand the drivers of a higher risk for major depressive disorders in CRS patients. In this study, we sought to understand the impact of patient self-perceived symptom severity (as represented by the SNOT-22) and clinical characteristics (such as demographics and nasal polyp size) on the likelihood for major depressive disorders in a distinct cohort of patients with CRSwNP. We found that patients' self-perceived sinonasal symptom severity, but not clinical severity of disease (such as the nasal polyp size), was independently associated with

the likelihood for major depressive disorders. Most importantly, we found that different CRS-symptom clusters were differentially associated with a higher risk for depressive disorders, with the sleep and otologic/facial pain subdomain showing the strongest associations with the PHQ-2 score.

The patients' self-perceived disease severity has gained significant importance in recent years. Previous studies have shown that disease-specific measures of QoL are helpful to predict medical and surgical treatment outcomes. The SNOT-22 has established itself as one of the most popular, disease-specific PROMs for patients with CRS, reflected in its worldwide use and numerous translations.[9,10] Indeed, we have previously confirmed that the SNOT-22 is a high-quality PROM regarding its psychometric properties.[21] In this study, we found that only the self-perceived sinonasal symptom severity, but not clinical parameters such as the nasal polyp size, or the general health-related QoL, was independently associated with the PHQ-2 score. Consistent with our results, a previous study has also demonstrated an association between the SNOT-22 and the risk for major depressive disorders. The authors reasonably suggested that depression should be considered during history taking and that the treating physician should more actively ask about underlying depressive symptoms.[14] Because the PHQ-2 only consists of two items, it can be analyzed quickly during clinical practice and may allow the identification of more CRS patients that are at higher risk for major depressive disorders. Notably, it is recommended to use more comprehensive PROMs, such as the PHQ-9 (the PHQ-2 consists of the first two questions of the PHQ-9) in those patients who screened positive using the PHQ-2 to make criteria-based diagnoses of depressive disorders.[17,22]

The differential impact of CRS symptom subdomains on the general health-related QoL has been described previously.[20,23] In those studies, the authors reported that the otologic/facial pain subdomain was most strongly associated with general health-related QoL in multivariable analysis after controlling for demographics and clinical characteristics in a cohort of CRS patients with and without polyps. The authors hypothesized that four different pathophysiologic mechanisms all have relevant but different impacts on general health-related QoL in patients with CRS.[23] In our analyses, we show that the otologic/facial pain subdomain and the sleep-related symptoms were most strongly associated with the self-perceived sinonasal symptom severity after controlling for clinical characteristics. Our findings further demonstrate that there likely exist four distinct pathophysiological mechanisms in the development of CRS and that each of these processes has a different impact on the likelihood of major depressive disorders in CRSwNP patients. Nonetheless, studies in other CRS phenotypes are further needed to confirm whether our findings can also be related to other pathophysiological mechanisms.

As mentioned above, previous studies provided evidence that depression is more prevalent in CRS patients than in the general population.[5,6] Identifying factors associated with the likelihood of major depressive disorders is even more critical in CRS patients, as this might affect treatment outcomes.[24,25] Furthermore, it has also been shown that comorbid depression is the primary driver of lost productivity.[4] In an intuitive manner, we found that the sleep subdomain was consistently most strongly associated with the likelihood of major depressive disorders. This finding was not surprising, as previous studies provided direct evidence that poor sleep quality is strongly associated with a higher risk for depression.[26,27] Moreover, we also found that self-perceived sinonasal symptomatology (as represented by the SNOT-22) is also an accurate indicator for higher risk of major depressive disorders in CRSwNP patients despite previous evidence that CRSsNP patients are at higher risk of developing symptoms of depression and anxiety than CRSwNP.[5] This is consistent with previous studies showing that self-perceived nasal obstruction is an accurate indicator for a higher risk of depression in CRS patients and that improvements in nasal obstruction directly associate with improvements in depressed mood.[28,29] Our results further underline the importance of performing analysis in both CRS subpopulations separately to understand further the underlying drivers of comorbid depression in CRS.

Regarding the clinical relevance of this study, results might be implemented easily into clinical practice. More awareness needs to be raised for those CRS patients with severe sinonasal symptomatology. Consequently, more frequent screening for depression in CRSwNP patients with higher SNOT-22 scores might identify novel opportunities for multidisciplinary treatment approaches that improve long-term outcomes, also from an economic standpoint.

The present study uses a comprehensive and homogenous data set of patients with CRSwNP to study the association between sinonasal symptoms and the likelihood of major depressive disorders. Nonetheless, this study also has limitations. Although we believe the homogenous cohort of CRSwNP patients to be a strength of our study, the SNOT-22 has been validated for CRS patients in general.[9] Other subtypes, such as CRSsNP patients, were not included in our analysis. Secondly, this was a retrospective study and might be more susceptible to confounding and bias than prospective studies. Future work should focus on the associations between disease-specific and general health-related QoL instruments and the likelihood of major depressive disorders in different subtypes of CRS. Thirdly, we only used the PHQ-2 to screen for the likelihood of major depressive disorders but not for the assumptive physician-based diagnosis of comorbid depression that would have allowed us to elucidate the true prevalence of undiagnosed comorbid depression in CRSwNP patients.

5 | CONCLUSION

Different subgroups of CRS symptoms—especially the sleep- and the otologic/facial pain-related symptoms—may differentially impact the likelihood of major depressive disorders in CRSwNP. Raising awareness for those with severe sinonasal symptomatology might help identify more CRSwNP patients with a higher risk for comorbid depression.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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