Sex differences in CRSwNP: focus on histopathological endotypes and recurrence

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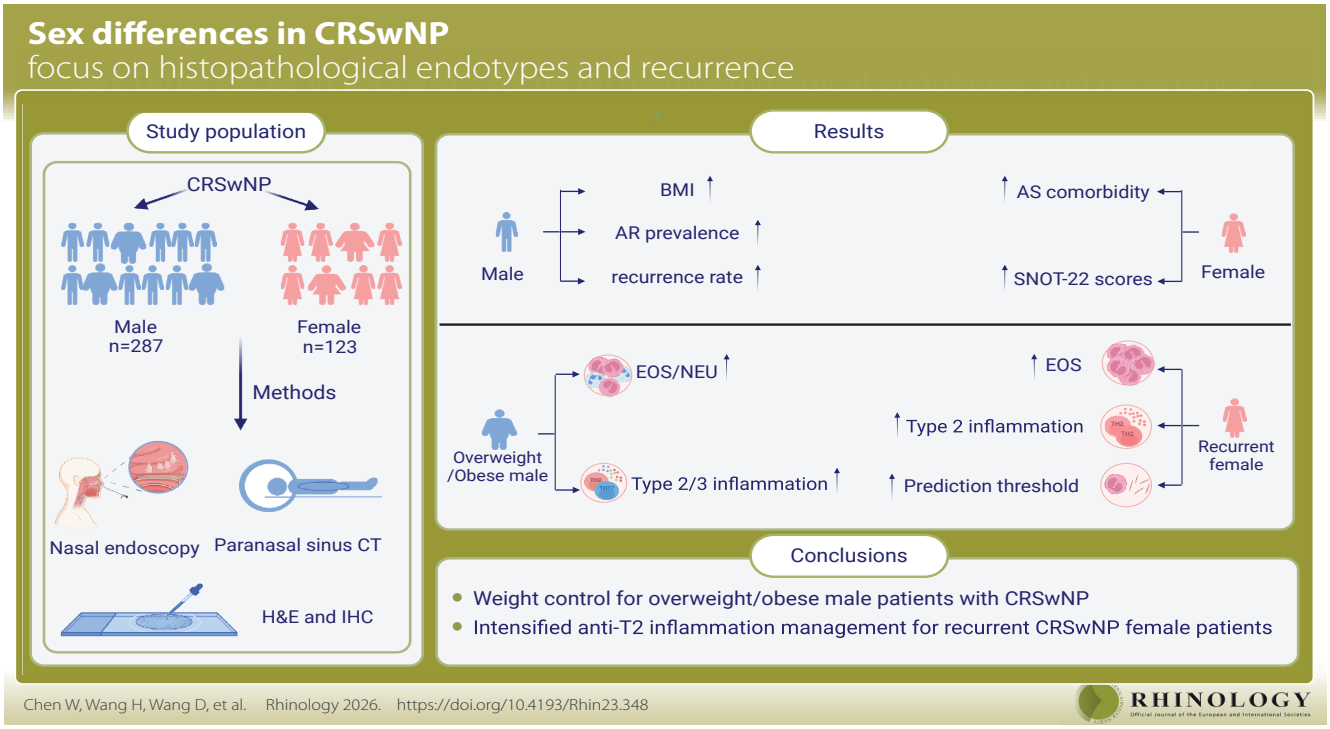

Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) exhibits sex-specific differences in prevalence and clinical presentation. However, the underlying histopathological characteristics and recurrence remain underexplored.

Methodology: A retrospective cohort of 410 CRSwNP patients (287 males, 123 females) undergoing endoscopic sinus surgery between January 2021 and June 2024 was analyzed. Histological evaluation was employed by H&E staining and features of inflammatory profile were identified by immunohistochemistry. Multivariate logistic regression and receiver operating characteristic analyses were performed to assess predictors of recurrence.

Results: Males exhibited higher body mass index (BMI) and greater allergic rhinitis prevalence, while females had more asthma comorbidity and higher SNOT-22 scores. While no significant sex differences were observed in histopathological endotypes, elevated BMI was more likely to exacerbate inflammation in males than females. Additionally, males showed a higher recurrence rate, with male sex being identified as an independent risk factor. However, females who experienced recurrence exhibited more severe eosinophilic and T2 inflammation compared to their male counterparts. Therefore, higher threshold values for tissue eosinophil counts and Charcot-Leyden crystals were required to predict recurrence in female patients.

Conclusions: These findings underscore the necessity for sex tailored therapeutic strategies, particularly emphasizing weight control in male patients and intensified anti-T2 inflammation management in female patients with recurrent CRSwNP. Further research is needed to investigate the underlying causes and to offer evidence-based treatment guidelines.

Key words: chronic rhinosinusitis with nasal polyps, sex, eosinophils, endotype, recurrence

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of nasal and paranasal mucosa characterized by high morbidity, frequent disease flares, and progressive bilateral polyp growth [1,2]. Individuals with CRSwNP have persistent and debilitating symptoms profoundly impact patients' health-related quality of life (HRQoL).

Sex- and sex-related factors have been shown to influence disease development and severity, clinical presentation, therapeutic effects, and prognosis across a wide range of diseases [3,4]. How-ever, there is limited information on the impact of sex in patients with CRSwNP. Previous studies have reported a higher prevalence of CRSwNP in males compared to females [5-7], while females exhibit more severe subjective symptom burdens [8,9], and are more likely to take sick leave [10]. A meta-analysis including 103,499 CRS patients demonstrates that females have worse pre- and postoperative SNOT-22 scores, but there are no significant sex differences of disease burden on imaging or endoscopy [8]. The discrepancy between subjective symptoms and objective manifestations in CRSwNP patients prompt us to investigate sex-specific differences in pathological endotypes, aiming to refine personalized management strategies.

Although the application of extended endoscopic sinus surgery (ESS) and the advent of type 2 (T2) biologics have significantly improved nasal polyp (NP) size, CT score, visual analogue scale score, and HRQoL in CRSwNP patients, some individuals still experience recurrence [2,11,12]. Consequently, numerous biomarkers have been reported to predict NP recurrence [11,13-15]. Our previous studies have demonstrated that Charcot-Leyden crystals (CLCs) and elevated body mass index (BMI) serve as predictors for relapse, and increased BMI impairs the predictive capability of conventional predictors [16,17]. However, whether sex differences influence NP recurrence and predictive efficiency of current predictors remain elucidated.

This study aims to investigate sex differences in histopathological endotypes and disease recurrence, thereby facilitating sex-specific personalized therapeutic strategies for CRSwNP patients.

Materials and methods

Subjects

A retrospective cohort of 410 bilateral CRSwNP patients undergoing ESS at The Third Affiliated Hospital of Sun Yat-sen University from January 2021 to June 2024 was analyzed. Patients were stratified by sex (287 males, 123 females). The study was approved by the Ethics Committee (II2023-117-03), and written informed consent was obtained from all participants. CRSwNP was diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 and EPOS 2020 guidelines [18,19]. Allergic rhinitis (AR) and asthma were diagnosed based on ARIA 2010 and GINA 2014 guidelines, respectively [20,21]. Participants did not use oral corticosteroids or antibiotics within one month prior to surgery, with an extended restriction of four months for any biologic use. Patients with allergic fungal rhinitis, cystic fibrosis, immunodeficiency, coagulation disorder, eosinophilic granulomatous polyangiitis or pregnancy were excluded from the study.

Histological evaluation

NP specimens were collected during ESS for histopathological analysis. Tissue sections were subjected to hematoxylin-eosin (H&E) staining following established protocols [22,23]. Eosinophilic chronic rhinosinusitis with nasal polyposis (Eos CRSwNP) was defined as >10% eosinophils among total inflammatory cells [23]. CLCs were identified by their hexagonal bipyramidal crystalline morphology in H&E-stained slides [16,24].

Immunohistochemistry (IHC)

Serial 4-μm paraffin-embedded sections were subjected to deparaffinization and rehydration. Antigen retrieval was performed using citrate buffer (pH 6.0, 95°C, 20min) prior to 1h blocking with 5% BSA. Primary antibody (Table S1) incubation was conducted at 4°C for 12-16h in humidified chambers. Signal development employed HRP-conjugated species-specific $F(ab')_2$ fragments (Boster Biological, #SV0002), and color development was achieved with 3, 3-diaminobenzidine (Vector Labs, SK-4105). Species and subtype matched antibodies were used as controls. Five random high-power field (HPF, 400×) were captured, and the mean number of positive cells was counted.

Classification of NPs based on endotype

Cellular endotype stratification [17]: The eosinophil-dominant (Eos^{high}) cellular endotype was diagnosed as eosinophil proportion>10% of total infiltrating inflammatory cells. The neutrophil-predominant (Neu^{high}) endotype was defined by myeloperoxidase (MPO)-positive neutrophil counts>10/HPF [23,25]. Therefore, four cellular endotypes were categoried: $Eos^{high}Neu^{high}$, $Eos^{high}Neu^{low}$, $Eos^{low}Neu^{high}$, and $Eos^{low}Neu^{low}$.

Cytokine profile classification [17]: Cytokine profiles of T1, T2, and T3 were characterized by the detection of interferon-γ (IFN-γ)+, interleukin-5 (IL-5)+, and interleukin-17A (IL-17A)+ cells, respectively. Based on the median cut-off value of each cytokine, cytokine endotypes were classified as: $IL\text{-}5^{high}IL\text{-}17^{high}$, $IL\text{-}5^{high}IFN\text{-}\gamma^{high}$, $IL\text{-}5^{high}IL\text{-}17^{high}IFN\text{-}\gamma^{high}$, $IL\text{-}17^{high}IFN\text{-}\gamma^{high}$, $IL\text{-}17^{high}$, $IL\text{-}5^{high}$, $IFN\text{-}\gamma^{high}$, and All^{low}.

Follow-up and postoperative evaluation

Follow-up was conducted at 1 week, 1 month, 3 months, 6 months, and 1 year after ESS. Daily nasal irrigation (0.9% saline solution), intranasal budesonide spray (Rhinocort Aqua, AstraZeneca, Sweden) 128 μg twice a day, and oral clarithromycin 250 mg daily were administered for 3 months. Recurrence was

Table 1. Demographic data and baseline characteristics of participants by sex group.

Variables	Male	Female	P_{adj} Value
n (%)	287 (70.00%)	123 (30.00%)	-
BMI (kg/m²)	23.43 [21.43, 25.68]	21.77 [19.49, 24.01]	**< 0.001**
Age (years)	39.00 [30.00, 52.00]	35.00 [28.00, 49.00]	0.823
Asthma (%)	19 (6.62%)	21 (17.07%)	**< 0.001**
Allergic rhinitis (%)	109 (37.98%)	30 (24.39%)	**0.019**
AERD (%)	1 (0.35%)	1 (0.81%)	0.512
Specific IgE + (%)	112 (39.02%)	40 (32.52%)	0.638
Total IgE + (%)	155 (54.01%)	62 (50.41%)	0.778
Total IgE (IU/ml)	59.00 [24.00, 193.00]	92.00 [35.50, 196.00]	0.688
PB EOS (%)	4.50 [2.40, 7.00]	3.10 [1.80, 5.90]	**0.029**
PB EOS (10^9/L)	0.30 [0.15, 0.45]	0.19 [0.11, 0.39]	**0.017**
PB NEU (%)	53.60 [48.10, 58.00]	54.60 [49.00, 60.90]	0.442
PB NEU (10^9/L)	3.43 [2.81, 4.27]	3.51 [2.69, 4.28]	0.439
SNOT-22 scores			
Rhinologic	15.00 [10.00, 20.00]	16.00 [11.00, 22.00]	0.341
Extranasal rhinologic	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.236
Ear/facial	0.00 [0.00, 3.00]	0.00 [0.00, 3.00]	0.315
Sleep	3.00 [0.00, 9.00]	4.00 [1.00, 10.00]	0.080
Psychological	3.00 [0.00, 8.00]	7.00 [2.00, 13.00]	**0.001**
Total scores	24.00 [15.00, 39.00]	33.00 [21.00, 44.00]	**0.024**
Lund-Kennedy scores			
Nasal polyp	4.00 [2.00, 4.00]	2.00 [2.00, 4.00]	**0.044**
Mucosal edema	4.00 [2.00, 4.00]	4.00 [2.00 4.00]	0.990
Discharge	2.00 [2.00, 4.00]	2.00 [2.00, 4.00]	0.315
Crusting	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.729
Scar	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.999
Total scores	9.00 [6.00, 12.00]	8.00 [6.00, 10.00]	0.183

Data are subjected to binary linear regression analysis, and parameters including asthma, allergic rhinitis, BMI, and age are adjusted. Data are presented as numbers (percentages) or medians (25th-75th percentiles). BMI, body mass index; AERD, aspirin-exacerbated respiratory; PB, peripheral blood; EOS, eosinophil; NEU, neutrophil; SNOT-22, 22-question SinoNasal Outcome Test.

identified through endoscopic confirmation of NPs accompanied by at least one persistent symptom including congestion, rhinorrhea, olfactory dysfunction, or headache/facial pain lasting ≥7 days despite standardized medical therapy and nasal irrigation [26].

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software. Categorical variables are expressed as percentages, and continuous variables are presented as medians (25th and 75th percentiles). Categorical variables were analyzed using the chi-square test. The intergroup variability was evaluated via the Kruskal-Wallis H test. Between-group comparison was performed using the two-tailed Mann-Whitney U test. Multivariate logistic regression models were employed to identify potential predictors of recurrence, with the predictive value of individual biomarkers assessed through the area under the receiver operating characteristic curve (AUC). These models were applied to the entire patient cohort, stratified according to different sex, weight, or recurrence and adjusted for variables including age, BMI, AR and asthma comorbidity. Statistical significance was defined as a two-tailed P value less than 0.05.

Results

Demographics and baseline characteristics

Among 410 CRSwNP patients, 287 (70.0%) were male and 123 (30.0%) were female, a finding consistent with the higher prevalence of CRSwNP in males reported in previous studies [5,18].

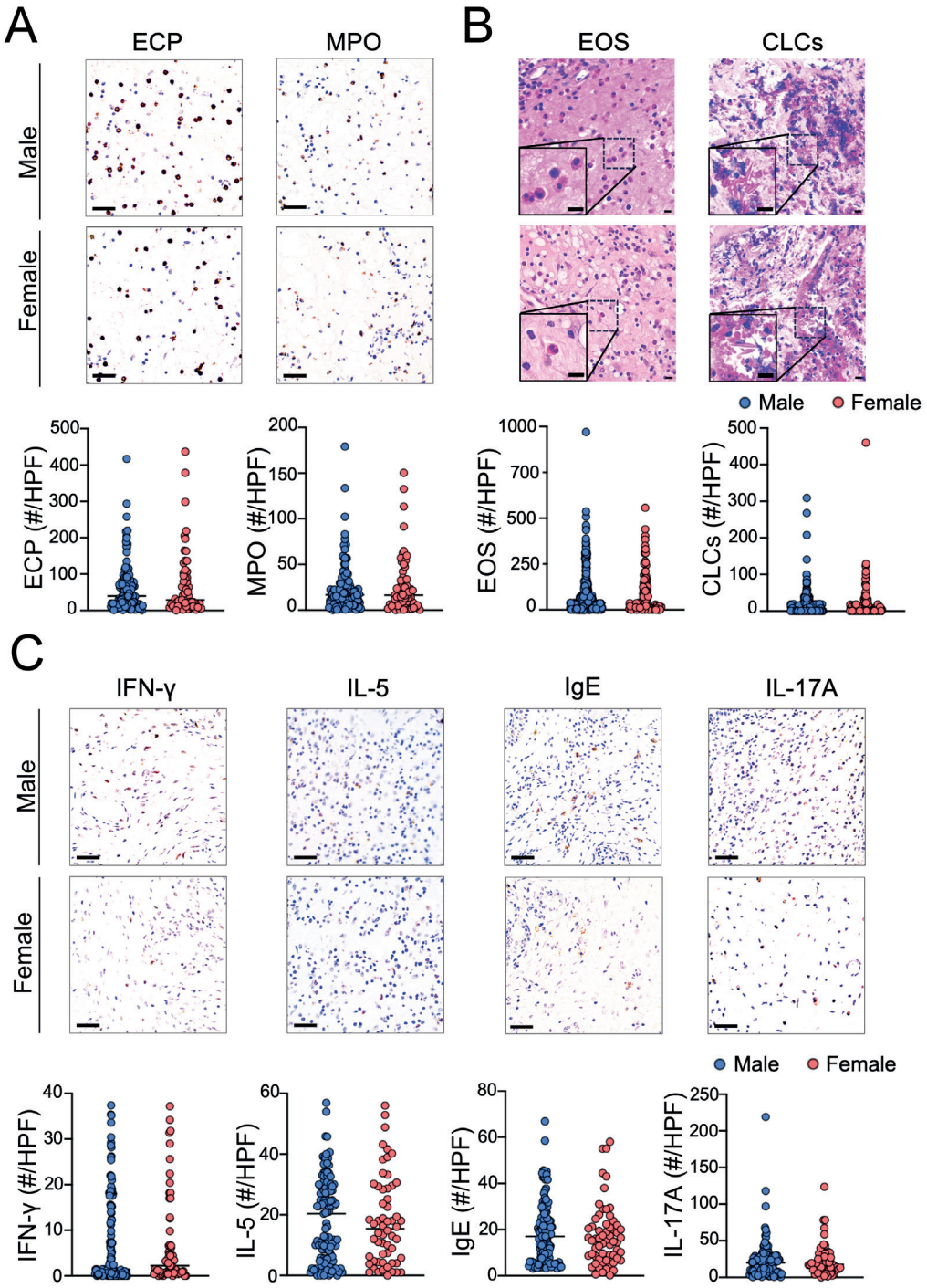

Figure 1. No sex-based differences in inflammatory profiles of CRSwNP patients. (A) Representative photomicrographs and quantitative analysis of ECP+ eosinophils and MPO+ neutrophils in CRSwNP individuals by sex category. (B) Representative photomicrographs stained by H&E and quantitative analysis of EOS and CLCs in CRSwNP subjects by sex group. (C) Representative photomicrographs and quantitative analysis of IFN-γ$^+$, IgE$^+$, IL-5$^+$ and IL-17A$^+$ cells in CRSwNP individuals by sex category. Original magnification x400. CRSwNP, chronic rhinosinusitis with nasal polyps; H&E, hematoxylin and eosin staining; EOS, eosinophil; CLCs, Charcot-Leyden crystals; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL-5, interleukin-5; IL-17A, interleukin-17A.

Demographic and clinical characteristics were analyzed by sex (Table 1). Although age was comparable across sex groups, males (23.43 [IQR: 21.43-25.68]) had a higher BMI than their female counterparts (21.77 [IQR: 19.49–24.01], P_{adj}<0.001). We examined sex-based differences in comorbidities, including AR, asthma, and aspirin-exacerbated respiratory disease (AERD), among

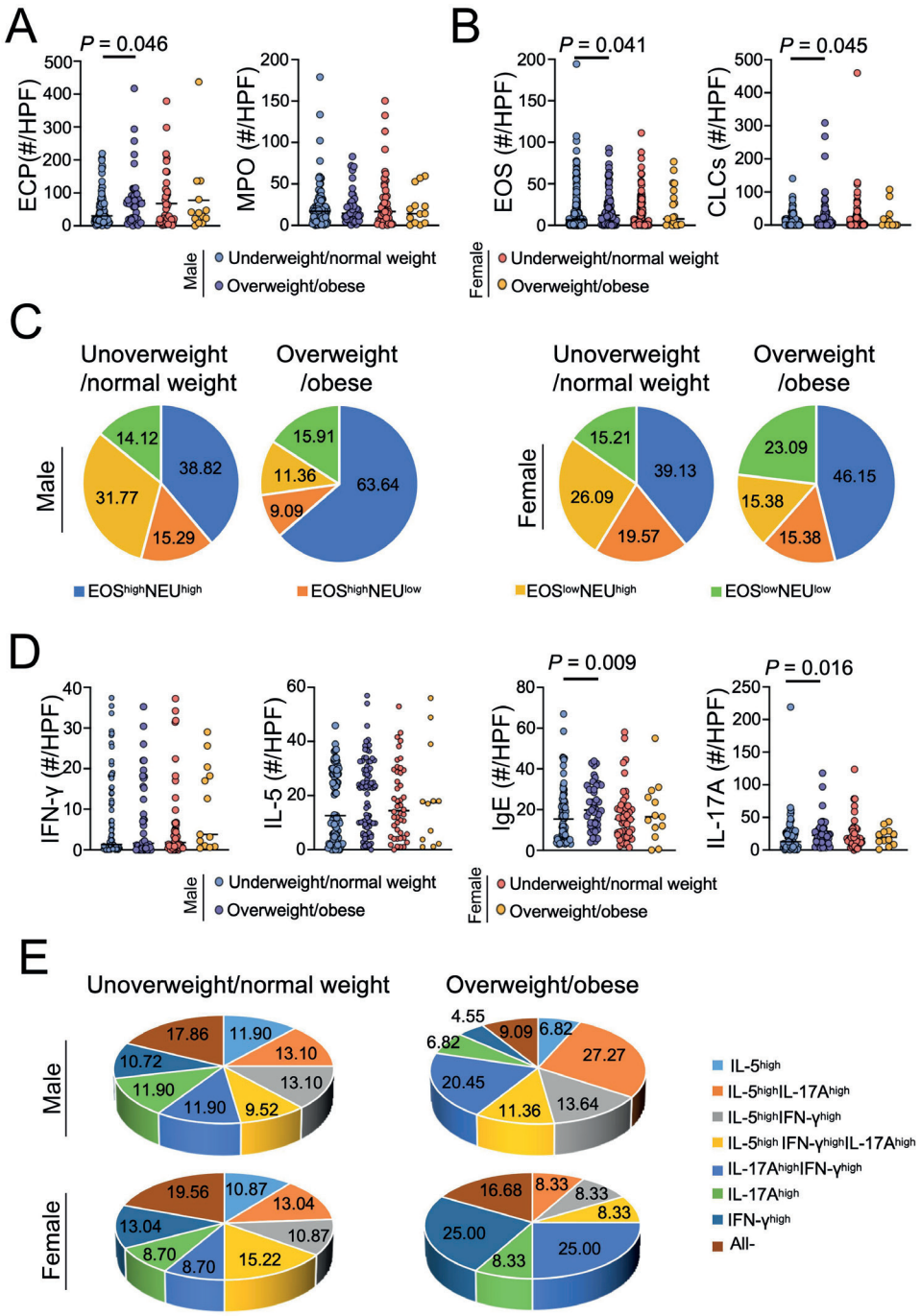

Figure 2. Male-specific predominance of BMI-aggravated inflammation. (A) Quantitative analysis of ECP+eosinophils and MPO+ neutrophils in CRSwNP individuals grouped by BMI across both sexes. (B) Quantitative analysis of EOS and CLCs in CRSwNP subjects grouped by BMI across both sexes. (C) Patterns of eosinophils/neutrophils in CRSwNP patients grouped by BMI across both sexes. (D) Quantitative analysis of IFN-γ$^+$, IgE$^+$, IL-5$^+$ and IL-17A$^+$ cells in CRSwNP individuals grouped by BMI across both sexes. (E) Patterns of T1/T2/T3 cytokine expression in samples from patients with CRSwNP grouped by BMI across both sexes. Underweight/normal weight, BMI of 24.9 kg/m^2 or less; Overweight/obese, BMI of 25kg/m^2 or greater. BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; MPO, myeloperoxidase; CLCs, Charcot-Leyden crystals; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL-5, interleukin-5; IL-17A, interleukin-17A; T1, type 1 inflammation; T2, type 2 inflammation; T3, type 3 inflammation (Specific definition provided in the Methods section).

CRSwNP patients. Males showed higher AR prevalence (37.98% vs. 24.39%, P_{adj}=0.019), whereas females exhibited greater asthma rates (17.07% vs. 6.62%, P_{adj}<0.001). No sex-based difference was observed in AERD prevalence. The percentage of specific IgE and the levels of total IgE were comparable in these two groups, suggesting that male and female CRSwNP patients have

Table 2. The histopathological features of CRSwNP subjects grouped by recurrence across both sexes.

	Non-recurrence			Recurrence		
Variables	Male	Female	P value	Male	Female	P value
n (%)	74 (65.49)	39 (34.51)	-	56 (71.79)	22 (28.21)	-
Tissue EOS (%)*	7.30 [1.90, 24.20]	5.80 [1.60, 16.90]	0.289	35.10 [12.33, 55.98]	49.25 [22.23, 66.30]	**0.026**
EOS (/HPF)*	10.70 [2.20, 38.20]	8.60 [1.80, 28.60]	0.442	77.55 [37.93, 155.98]	139.00 [76.13, 250.28]	**0.003**
CLCs (/HPF)*	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.203	12.10 [2.30, 26.80]	17.05 [4.28, 47.20]	**0.049**
Eos CRSwNP (%)	57 (42.22)	30 (40.00)	0.422	124 (81.58)	45 (93.75)	**0.042**
ECP (/HPF)	24.10 [13.65, 57.65]	17.80 [8.40, 28.00]	**0.039**	68.80 [29.20, 97.60]	96.70 [62.55, 163.70]	**0.034**
MPO (/HPF)	15.20 [6.25, 30.00]	14.60 [3.70, 37.30]	0.832	18.60 [10.80, 29.20]	20.80 [8.05, 38.45]	0.495
IL-17A (/HPF)	14.00 [5.20, 28.35]	17.00 [10.00, 28.65]	0.407	20.80 [10.43, 28.35]	22.30 [13.68, 32.53]	0.579
IFN-γ (/HPF)	1.80 [0.40, 14.60]	3.20 [0.60, 12.60]	0.682	1.20 [0.40, 7.35]	2.20 [0.80, 6.60]	0.318
IgE (/HPF)	13.00 [5.90, 23.75]	10.20 [5.60, 18.60]	0.203	20.20 [12.18, 29.25]	21.50 [15.85, 32.75]	0.262
IL-5 (/HPF)	10.20 [3.60, 28.00]	9.45 [3.68, 16.10]	0.171	23.05 [10.65, 30.00]	29.90 [19.83, 40.95]	**0.011**

Data are subjected to binary linear regression analysis, and parameters including asthma, allergic rhinitis, BMI, and age are adjusted. Data are presented as medians (25th-75th percentiles). EOS, Eosinophil; CLCs, Charcot-Leyden Crystals; ECP, Eosinophil Cationic Protein; MPO, Myeloperoxidase; IgE, Immunoglobulin E; IL-17A, Interleukin-17A; IFN-γ, Interferon-gamma; IL-5, Interleukin-5; NEU, Neutrophils; HPF, per high-power field. *, of the 410 patients, nasal polyps from 210 patients with non-recurrence (135 males and 75 females) and 200 patients with recurrence (152 males and 48 females) were undergone H&E staining for detecting EOS and CLCs.

similar atopy status. Both the percentage (4.50% [IQR: 2.40-7.00] vs. 3.10% [IQR: 1.80-5.90], P_{adj}=0.029) and absolute number (0.30 [IQR: 0.15-0.45]*10^9/L vs. 0.19 [IQR: 0.11-0.39]*10^9/L, P_{adj}=0.017) of peripheral blood eosinophils were higher in males compared to their female counterparts, whereas neutrophil proportion and counts did not differ significantly between the two groups. In addition, compared with females, males exhibited greater Lund-Kennedy polyp scores (4.00 vs. 2.00, P_{adj}=0.044), whereas scores for mucosal edema, discharge, crusting, and scar, as well as total scores were comparable between the two groups. However, compared with males, females reported higher psychological symptom scores (7.00 vs. 3.00, P_{adj}=0.001) and SNOT-22 scores (24.00 vs. 33.00, P_{adj}=0.024), indicating that female patients with CRSwNP experience a greater subjective disease burden than males.

Together, these findings imply that the BMI, comorbidities, and systemic inflammatory cell profiles in CRSwNP vary between sex and that female patients exhibit worse preoperative subjective disease burden.

No sex-based differences in inflammatory endotypes of CRSwNP patients

CRSwNP exhibits distinct inflammatory patterns associated with steroid insensitivity and recurrence, but sex differences in cellular/cytokine endotypes remain underexplored. Therefore, inflammatory profiles were analyzed between male and female patients. Numbers of eosinophil cationic protein (ECP)-positive eosinophils and myeloperoxidase (MPO)-positive neutrophils in NP tissues showed no significant differences between sex (Figure 1A). Additionally, H&E-staining further confirmed comparable numbers of eosinophils and their hyperactivated products - CLCs between the two groups (Figure 1B). In addition to cellular endotypes, patterns of cytokine endotype were also analyzed between sex. IFN-γ, IgE and IL-5, as well as IL-17A were served for biomarkers of T1, T2, and T3 inflammation as previously reported [17]. Like cellular endotype, no sex-based differences were observed in cytokine endotypes. Since male and female patients with CRSwNP were comparable in count numbers of IFN-γ-, IgE-, IL-5-, and IL-17A-positive cells (Figure 1C). In summary, these results suggest that T1, T2 and T3 inflammatory profiles are similar in male and female patients.

Male-specific predominance of BMI-aggravated inflammatory response

We previously reported that increased BMI contributes to augmented mixed eosinophilic-neutrophilic and coexisting T2/T3 inflammation in CRSwNP [17]. However, whether this BMI-associated inflammatory exacerbation differs by sex remains unclear. Based on BMI, both male and female groups were further stratified into overweight/obese and underweight/normal weight subgroups. ECP-positive eosinophils were elevated in overweight/obese compared to underweight/normal weight male patients with CRSwNP (Figure 2A, Figure S1A). However, this sex-specific pattern was absent in females. Consistently, results from H&E staining demonstrated that male CRSwNP patients with elevated BMI showed significant increases in eosinophil

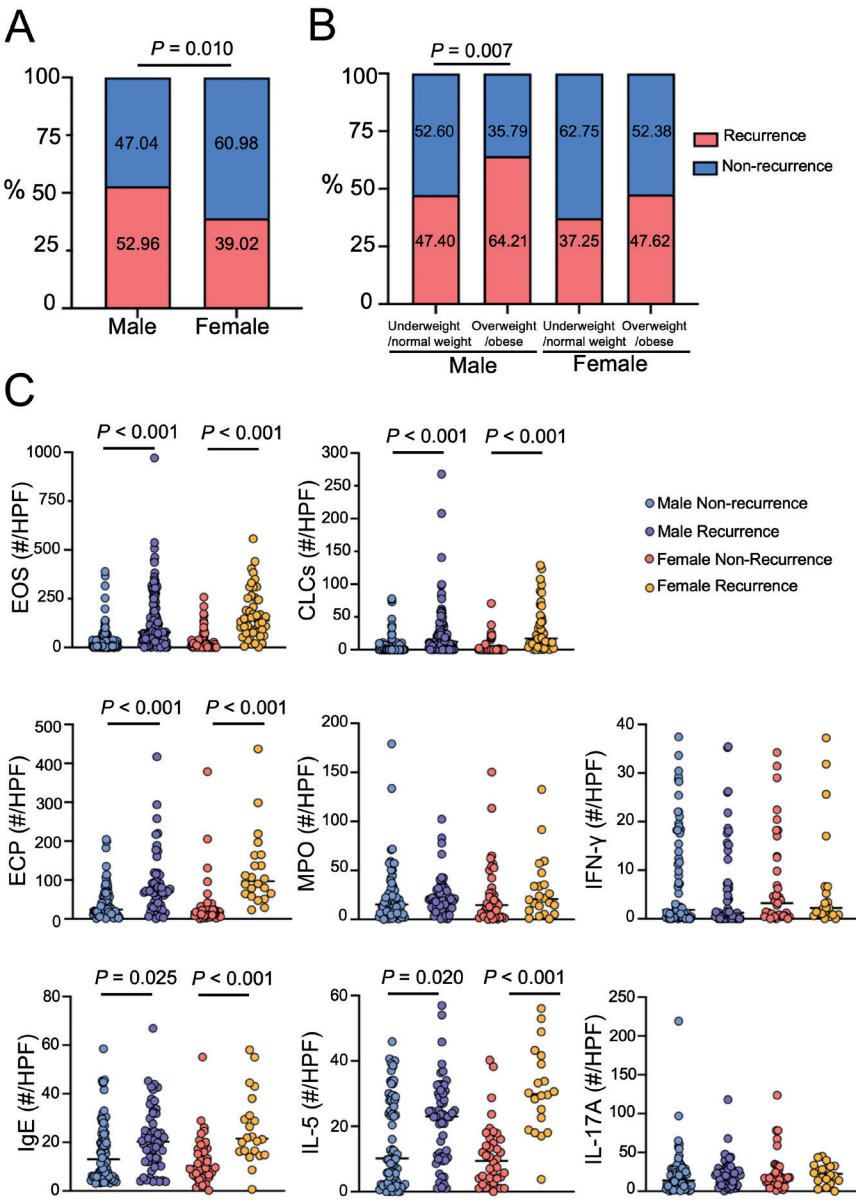

Figure 3. Male CRSwNP patients have a higher recurrence rate than females. (A) The recurrent rate in patients with CRSwNP by sex category. (B) The recurrence of CRSwNP subjects grouped by BMI across both sexes. (C) Quantitative analysis of EOS (H&E), CLCs, IgE^{+}, IL-5^{+}, ECP^{+}(IHC), MPO^{+}, IL-17A^{+} and IFN-γ^{+} cells in CRSwNP individuals grouped by BMI across both sexes. BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; MPO, myeloperoxidase; CLCs, Charcot-Leyden crystals; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL-5, interleukin-5; IL-17A, interleukin-17A; T1, type 1 inflammation; T2, type 2 inflammation; T3, type 3 inflammation (specific definition provided in the Methods section).

and CLC counts relative to underweight/normal weight males, whereas no such BMI-associated differences were detected in female cohorts (Figure 2B, Figure S1B). Of note, MPO-positive neutrophil counts showed no sex-based differences between overweight/obese and underweight/normal weight groups (Figure 2A, Figure S1A). Interestingly, the increased percentage of EOS^{high}NEU^{high}-dominated inflammation was observed in overweight/obese patients compared to underweight/normal weight counterparts in both sexes, with the difference being more pronounced in male subjects (Figure 2C). These findings indicate that BMI-associated mixed eosinophilic-neutrophilic inflammation predominantly augmented in males compared to females.

Beyond cellular endotypes, cytokine-defined inflammatory profiles were compared across BMI-based subgroups in both sexes. No significant differences in counts of IFN-γ-positive cells were detected between overweight/obese and underweight/normal weight groups, consistent across both sexes (Figure 2D,

Table 3. Predicting recurrence of nasal polyps by sex category using conventional predictors.

Variables	OR value	95% CI	P value
Multivariate analysis*			
Overall			
Sex (male)	1.924	1.142-3.244	**0.014**
EOS (#) in NPs	1.014	1.010-1.018	**< 0.001**
CLCs (#) in NPs	1.061	1.040-1.082	**< 0.001**
EOS (%) in PB	1.138	1.063-1.219	**< 0.001**
Male			
EOS (#) in NPs	1.012	1.008-1.017	**< 0.001**
CLCs (#) in NPs	1.057	1.033-1.081	**< 0.001**
EOS (%) in PB	1.100	1.016-1.191	**0.019**
Female			
EOS (#) in NPs	1.019	1.011-1.027	**< 0.001**
CLCs (#) in NPs	1.080	1.036-1.126	**< 0.001**
EOS (%) in PB	1.242	1.076-1.434	**0.003**

* Each logistic regression model is adjusted for BMI, age, AR, asthma. EOS, eosinophil; CLCs, Charcot-Leyden crystals; NPs, nasal polyps; PB, peripheral blood.

Figure S2A). These results suggest that increased BMI did not contribute to the amplification of T1 inflammation in CRSwNP patients with both sexes. Consistent with increased eosinophil counts, elevated BMI showed upregulation in IgE-positive cells relative to underweight/normal weight males, whereas no such BMI-associated differences were detected in females. Despite no statistical difference, IL-5 positive cells showed an increase in overweight/obese males compared to underweight/normal weight counterparts. Furthermore, a significant elevation in IL-17A-positive cells were detected only in overweight/obese males compared to underweight/normal weight males, whereas this altered trend was not observed in female patients (Figure 2D, Figure S2A). As shown in Figure 2E, compared with underweight/normal weight males, overweight/obese male counterparts exhibited elevated proportions of IL-5^{high}IL-17A^{high} (27.27% vs. 13.10%) and IFN-γ^{high}IL-17A^{high} (20.45% vs. 11.90%) mixed inflammatory pattern, but decreased frequencies of single IFN-γ^{high} (4.55% vs. 10.72%), IL-5^{high} (6.82% vs. 11.90%), and IL-17A^{high} (6.82% vs. 11.90%) inflammatory profile. Conversely, compared with underweight/normal weight females, overweight/obese female subjects showed increased proportions of IFN-γ^{high} (25.00% vs. 13.04%) endotype, while frequencies of single IL-5^{high} (0.00% vs. 10.87%), IL-5^{high}IL-17A^{high} (8.33% vs. 13.04%), and IL-5highIFN-γhighIL-17A^{high} (8.33% vs. 15.22%) patterns decreased. Taken together, these data demonstrate a male-specific predominance of BMI-exacerbated eosinophilic/neutrophilic and T2/T3 mixed inflammation, with no significant association observed in females.

Male CRSwNP patients have a higher recurrence rate

Next, NP recurrence was compared between sex. In the follow-up cohort of 410 patients, males exhibited a higher recurrent rate (52.96%) than their female counterparts (39.02%) (Figure 3A). Interestingly, the increased recurrence was mainly observed in male CRSwNP patients with elevated BMI (Figure 3B), which is consistent with more severe inflammatory profiles in male overweight/obese patients with CRSwNP. Eosinophils [13], CLC [16, 26], IL-5 [13] and IgE [27] have been reported to be related with NP recurrence. As expected, elevated percentages and counts of tissue eosinophils and increased numbers of CLCs, IgE-positive and IL-5-positive cells were observed in recurrent patients compared to non-recurrent individuals in both sexes (Figure 3C). However, in both sexes, MPO-positive, IL-17A-positive, and IFN-γ-positive cells were not upregulated in patients with recurrence (Figure 3C). These data suggest that recurrence is associated with more severe T2-dominated inflammation.

Based on sex, both recurrent and non-recurrent groups were further stratified into male and female subgroups. Within the recurrent group, compared with male CRSwNP subjects, females exhibited higher percentages (49.25% [22.23, 66.30] vs. 35.10% [12.33, 55.98]) and counts (139.00 [76.13, 250.28] vs. 77.55 [37.93, 155.98]) of tissue eosinophils, elevated counts of CLCs (17.05 [4.28, 47.20] vs. 12.10 [2.30, 26.80]), ECP-positive cells (96.70 [62.55, 163.70] vs. 68.80 [29.20, 97.60]), and IL-5-positive cells (29.90 [19.83, 40.95] vs. 23.05 [10.65, 30.00]), as well as increased frequency of Eos CRSwNP (93.75% vs. 81.58%) (Table 2). In contrast, within the non-recurrent group, only ECP-positive

eosinophils were significantly higher in males, while other biomarkers demonstrated comparable levels between males and females (Table 2). These findings indicate that while the overall recurrence rate is higher in males, female patients experiencing recurrence demonstrate an aggravated T2 inflammatory profile compared to their male counterparts.

Predicting NP recurrence overall and within different sex groups

Since male patients with CRSwNP demonstrated increased recurrence, we ask whether male sex contribute to NP recurrence. A multivariable logistic regression model incorporating eosinophil count (EOS#) and CLCs count (CLCs#) in NPs, as well as peripheral blood eosinophil percentage (PB EOS%), was employed. This model was adjusted for BMI, age, and comorbid AR and asthma to predict NP recurrence across all subjects and within distinct sex categories. Overall analysis revealed that like conventional biomarkers such as EOS and CLCs, being male is a risk factor for recurrence (OR 1.924, P=0.014) (Table 3). Furthermore, we found that the predictive efficacy of the conventional predictive biomarkers was similar in male and female patients with CRSwNP, suggesting that sex does not affect the predictive efficacy of NP predictive parameters.

Since PB EOS% is comparable in recurrent males and females (5.80% vs. 5.15%, P=0.362), the effect of sex on cutoff values of tissue predictive parameters was analyzed across all subjects and within each sex category (Table S2). Compared to male (28.70/HPF) and overall (29.00/HPF) patients, the cutoff for EOS in NPs to predict recurrence is notably higher in females (48.95/HPF). In addition to higher threshold, females exhibited superior predictive capability with sensitivity 0.875, specificity 0.827, and Youden index 0.702. Similarly, the cutoff value of CLCs for predicting recurrence is also higher in females (1.80/HPF) than in males (1.55/HPF) and overall population (1.55/HPF). In summary, these results suggest that male sex is a risk factor for NP recurrence, but female patients require a higher predictive cutoff value of conventional tissue biomarkers than males.

Discussion

To our knowledge, this is the first study to investigate the effects of sex difference on pathological characteristics and recurrence for CRSwNP patients. In the current study, while no significant sex differences were observed in histopathological endotypes, elevated BMI was more strongly associated with increased eosinophil/neutrophil- and T2/T3- dominated inflammatory profiles in male patients. While male patients exhibited a higher recurrence rate, female patients who experienced recurrence demonstrated more severe inflammation and required elevated cutoff thresholds for predicting NP recurrence.

Despite similar Lund-Kennedy total scores, female patients in the present study reported higher subjective disease burden than males, evidenced by increased SNOT-22 scores, consistent with previous studies [8,28,29]. Similarly, results from sinus CT scans demonstrated that women with CRSwNP had higher SNOT-22 scores than men for similar or even lower CT scores [9,30]. These results suggest that the Lund-Mackay and Lund-Kennedy scores, used as objective measures of disease, are not well correlated with symptoms or surgical outcomes. Although the underlying reason remains unclear, potential explanations for the increased SNOT-22 scores observed in females include: 1) Female CRS patients may be more perceptive of their symptoms while exhibiting greater tolerance [31]. 2) Women are more likely to report symptoms, seek medical care, and rate their overall health status lower [32,33]. 3) The higher prevalence of migraine, primary headache, or psychiatric disorders among females may contribute to elevated SNOT-22 scores [8,34]. 4) Anatomical or hormonal factors may underlie these findings, although specific research investigating this mechanism is currently lacking [28].

The reduced levels of estradiol are associated with nasal polyposis [35]. In addition, previous studies have demonstrated that estrogen and progesterone exacerbate T2 inflammation and contribute to asthma pathogenesis [3,36], whereas testosterone decreases lung T2 inflammation in asthmatics patients [37]. These findings suggest that sex hormones may modulate inflammatory endotype. Unexpectedly, despite consistent reports from us and others indicating a higher prevalence of CRSwNP in males [5,19,38], comparative analysis revealed no significant differences in eosinophilic/neutrophilic inflammation profiles or T1/T2/T3-dominated inflammatory profiles between male and female patients. Consistently, dupilumab treatment improved subjective and objective outcomes of CRSwNP patients, irrespective of sex [29]. The sex discrepancy between upper and lower airway inflammatory diseases may reflect that sex hormones exhibit disease-specific regulatory patterns. Notably, prior research identified a predominance of T1 inflammation in female CRS patients without nasal polyps (CRSsNP) [39], implying that sex-based differential immune responses should be considered into therapeutic strategy across disease subtypes.

Our prior work demonstrated that overweight/obese CRSwNP patients exhibit amplified eosinophilic-neutrophilic and T2-T3 mixed inflammatory patterns [17]. In the current study, we further found that elevated BMI significantly aggravated inflammatory severity exclusively in males, with higher BMI linking to increased tissue eosinophil counts and activation status (CLCs), as well as mixed eosinophilic/neutrophilic and T2-T3 inflammatory profiles. Conversely, no such BMI-inflammatory associations were observed in female CRSwNP patients. This sexually dimorphic pattern suggests that male-specific susceptibility to metabolic-inflammatory crosstalk. In addition to CRSwNP, emerging evidence reveals that increased BMI-induced sexual dimorphism manifests in the pathophysiological progression of cardiovascular diseases [40], depressive illness [41] and insulin resistance in dia-

betes [42]. The hypothesized mechanisms underlying BMI's effects on male-specific inflammation exacerbation may include: 1) Sex-specific fat pattern persists through adulthood, with males preferentially storing visceral fat (central obesity), contrasting with females' subcutaneous fat distribution (peripheral obesity) [43]. The subcutaneous deposition pattern can protect females from obesity-induced pathophysiological changes, thereby resulting in attenuated inflammatory responses [44]. In contrast, myeloid cells in the visceral adipose tissue of obese male mice exhibited elevated inflammasome activation [45]. 2) Obese men frequently develop hypogonadism with low levels of testosterone, a condition that diminishes the anti-inflammatory effects of androgens [46]. 3) Obesity impairs patients hypothalamic-pituitary-gonadal axis function [47], leading to decreased levels of testosterone that drives visceral fat accumulation and exacerbated inflammation [48]. Therefore, in addition to traditional therapeutic strategies, male CRSwNP patients with elevated BMI may need to consider weight control to mitigate inflammatory burden.

Recurrence rate was higher in males (52.96% vs 39.02%, P=0.010), with male sex being identified as an independent risk factor (OR 1.924, 95% CI 1.142-3.244). Consistent with our observations, previous studies have documented increased recurrence rates among male CRSwNP patients, though statistical significance was not achieved, potentially attributable to limited sample sizes [14].

The increased recurrence in male patients may be attributed to insufficient estrogen, as estrogen, prevalent in females, has well-documented anti-inflammatory properties that inhibit pro-inflammatory cytokines such as TNF-α and IFN-γ [49], thereby potentially reducing inflammation severity and recurrence risk. Additionally, a study demonstrated that low serum estradiol levels were associated with increased risk of NP formation in females [35]. Therefore, investigating whether hormonal substitution in CRSwNP patients with diminished estradiol levels could prevent recurrence may be significant.

Unlike the compromised predictive efficacy of parameters influenced by BMI [17,50], the predictive capability of traditional biomarkers such as eosinophils and CLCs was unaffected by sex. Of note, although female patients had a lower recurrence rate than males, those patients who experienced with recurrence exhibited more severe inflammation, particularly T2- and eosinophil-dominated inflammation. Previous research has reported that T1-orchestrated inflammation may be more common in female CRSsNP patients [39], suggesting distinct endotypes may vary among CRS subgroups. Further analysis reveals that the predictive cutoff values for tissue eosinophils and CLCs were substantially higher in females than in males. These findings indicate that female patients may require a higher threshold for disease recurrence. Notably, while females present with exacerbated preoperative subjective symptoms, their enhanced capacity to resist postoperative recurrence implies that disease relapse in this cohort may be contingent upon local inflammation surpassing a critical severity threshold. Consequently, females who experience recurrence may require higher drug dosages or more extensive ESS. Additionally, due to amplified T2- and eosinophilic inflammation, the recurrent female patients may represent ideal candidates for T2 biologics.

This study has several limitations. First, median cut-off values of selected biomarkers were used to classify cytokine-based endotypes. While median-based dichotomization is statistically straightforward, it may not reflect biologically meaningful thresholds. Future study should categorize cytokine-based endotypes using reference intervals based on healthy individuals or clinical decision limits based on patients. Second, due to the lower prevalence of CRSwNP in females, the number of overweigh/obese females used for recurrence is small. Our study may have been underpowered to detect associations between BMI and recurrence in females. The conclusion should be further validated through a large cohort of overweigh/obese females in a multi-center collaboration.

Conclusion

Male CRSwNP patients exhibited higher BMI and AR prevalence, while females had more asthma comorbidity and higher preoperative subjective symptoms. Elevated BMI is more likely to exacerbate eosinophilic/neutrophilic and T2/T3 inflammatory profiles in males. While male patients exhibited a higher recurrence rate, female patients who experienced recurrence demonstrated more severe inflammation and required elevated cutoff thresholds for predicting NP recurrence. These findings may underscore the necessity for sex-tailored therapeutic strategies, particularly emphasizing: 1) In addition to traditional therapeutic strategies, weight control needs to be highlighted in male individuals with elevated BMI to mitigate inflammatory burden. 2) Females who experience recurrence may require higher corticosteroid dosages or more extensive ESS, or prioritization of T2 biologics. 3) Potential benefits of estrogen supplementation in CRSwNP subjects with decreased levels of estrogen.

Conflict of interest

All authors agree with the presented findings, have contributed to the work, and declare no conflict of interest.

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Authors contributions

Study idea and design: YZ; Sample screening and collection: WC, HW, DW, WL, JC and QY; Experiment and data analysis: WC, HW and YL; Manuscript preparation: HW and WC; Critical review of the manuscript: YZ and QY; Follow up: YZ, QY and WC; Final approval: all authors.

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SUPPLEMENTARY MATERIAL

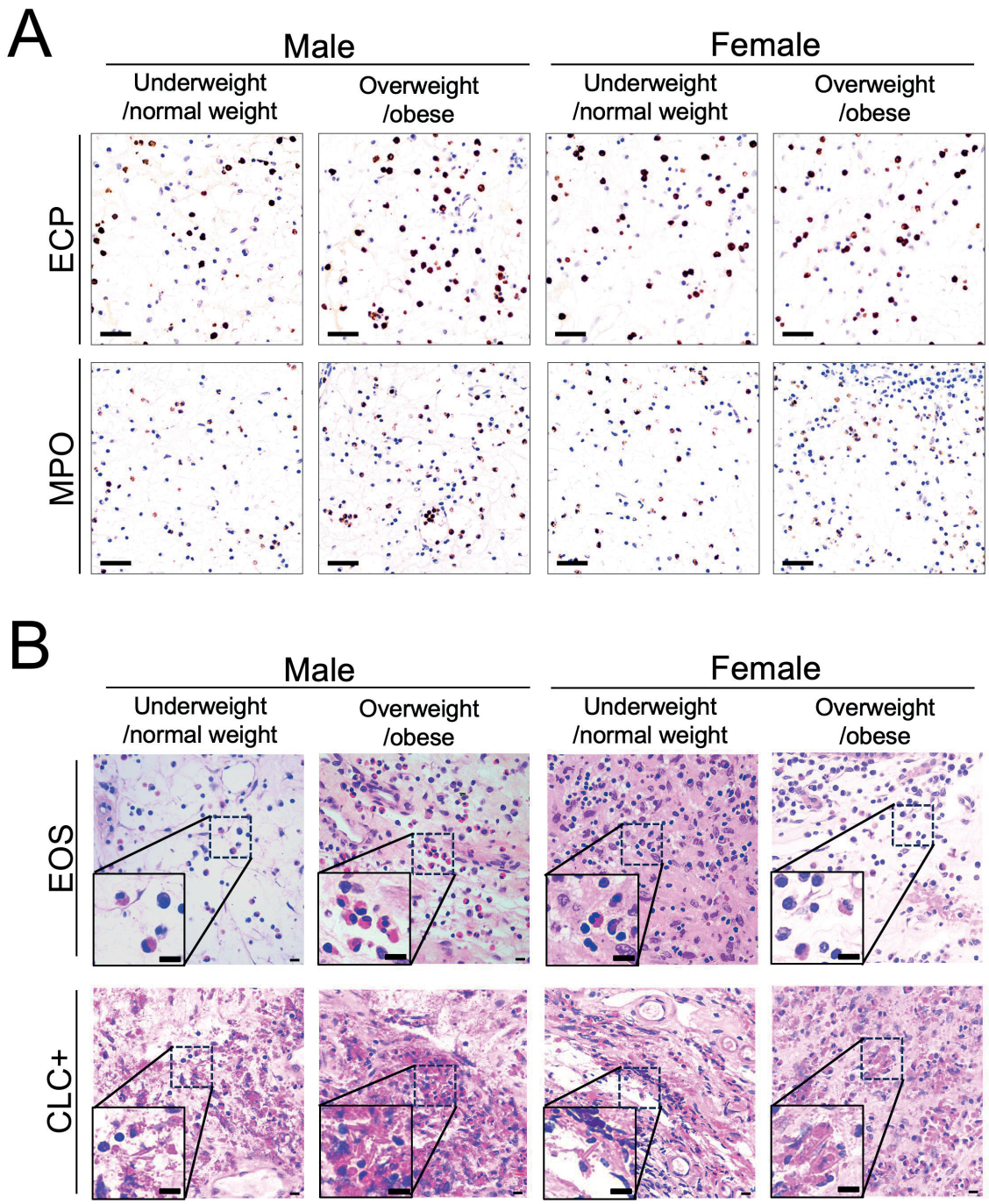

Figure S1. Inflammatory cell-based endotypes in CRSwNP patients grouped by BMI. (A) Representative photomicrographs of ECP+ eosinophils and MPO+ neutrophils in CRSwNP individuals grouped by BMI across both sexes. (B) Representative H&E photomicrographs of EOS and CLCs in CRSwNP subjects grouped by BMI across both sexes. Original magnification x400. Underweight/normal weight, BMI of 24.9 kg/m^2 or less; Overweight/obese, BMI of 25kg/m^2 or greater. BMI, body mass index; ECP, eosinophil cationic protein; MPO, myeloperoxidase; CLCs, Charcot-Leyden crystals; EOS, eosinophils; HPF, per high-power field.

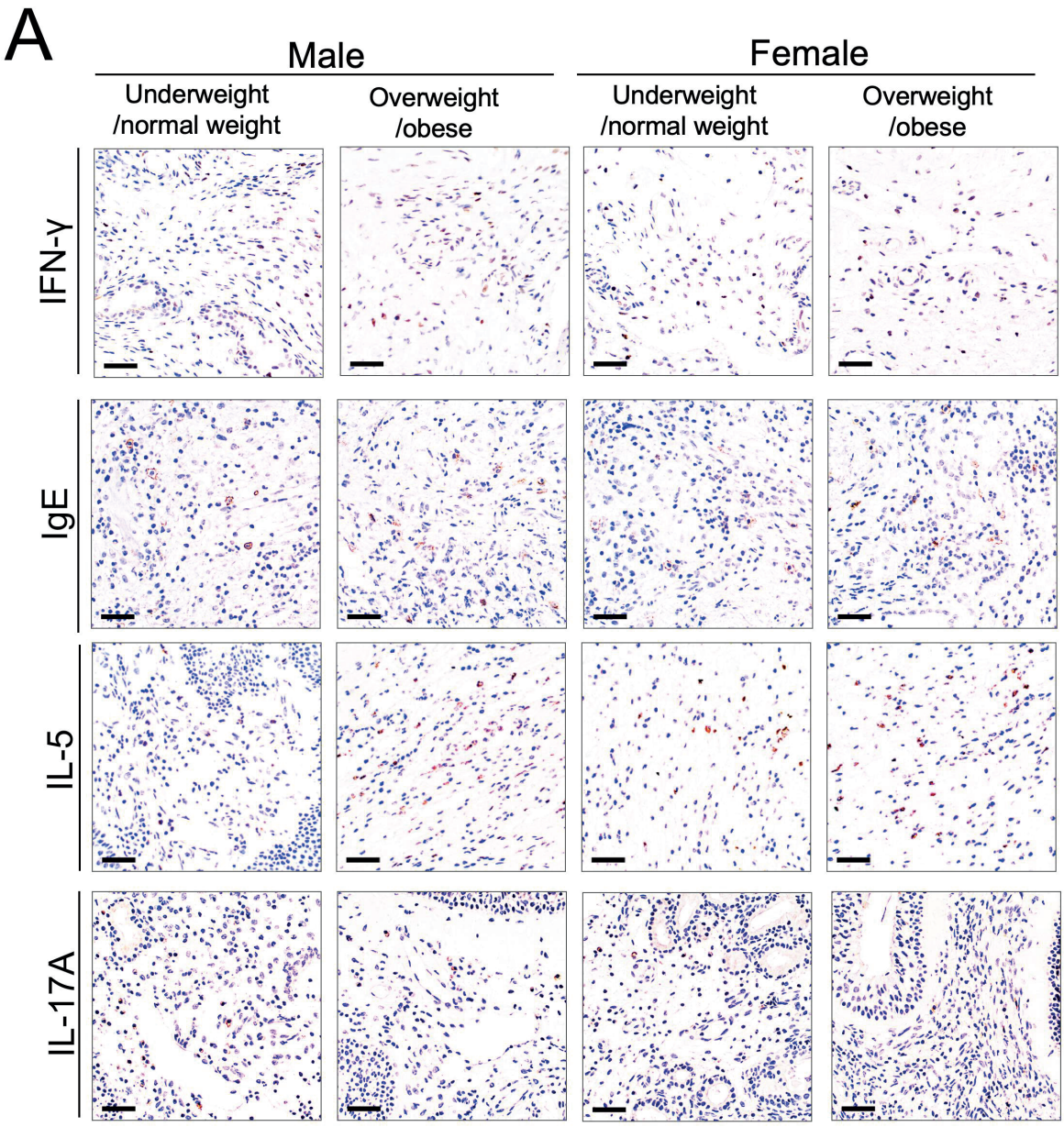

Figure S2. Inflammatory cytokine/mediator-based endotypes in CRSwNP patients grouped by BMI. (A) Representative photomicrographs of IFN-γ$^+$ cells, IgE$^+$ cells, IL-5$^+$ cells and IL-17A$^+$ cells in samples from patients with CRSwNP grouped by BMI across both sexes. Original magnification x400. Underweight/normal weight, BMI of 24.9 kg/m^2 or less; Overweight/obese, BMI of 25 kg/m^2 or greater. BMI, body mass index; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL-5, interleukin-5; IL-17A, interleukin-17A; T1, type 1 inflammation; T2, type 2 inflammation; T3, type 3 inflammation; HPF, per high-power field.

Table S1. Primary antibodies used in immunohistochemistry .

Antibody	Application	Host	Concentration	Clone ID	Reference	Source
ECP	IHC	Rabbit	1:400	Polyclonal	PA5-48595	Thermo Scientific (Rockford, IL, USA)
MPO	IHC	Mouse	1:400	Polyclonal	AF3667	R&D Systems (Minneapolis, MN, USA)
IFN-γ	IHC	Mouse	1:200	Polyclonal	MM700B	Thermo Scientific (Rockford, IL, USA)
IL-5	IHC	Rabbit	1:200	Polyclonal	26677-1-AP	Proteintech (Wuhan, China)
IgE	IHC	Rabbit	1:200	Polyclonal	ab75673	Abcam (Cambridge, UK)
IL-17A	IHC	Rabbit	1:400	Polyclonal	ab79056	Abcam (Cambridge, UK)

ECP, eosinophil cationic protein; MPO, myeloperoxidase; IFN-γ, interferon-gamma; IL-5, interleukin-5; IgE, immunoglobulin E; IL-17A, interleukin-17A; IHC, immunohistochemistry.

Table S2. The cutoff vale of tissue predictors in CRSwNP patients by sex category.

Biomarker	Sex category	Cut point	Sensitivity	Specificity	Youden
CLCs in NPs (#/HPF)	Overall	1.55	0.815	0.805	0.620
	Male	1.55	0.789	0.785	0.575
	Female	1.80	0.896	0.853	0.749
EOS in NPs (#/HPF)	Overall	29.00	0.855	0.719	0.574
	Male	28.70	0.842	0.696	0.538
	Female	48.95	0.875	0.827	0.702

CLCs, Charcot-Leyden crystals; EOS, eosinophil; NPs, nasal polyps.