# Blood eosinophils to direct oral corticosteroid treatment for patients with nasal polyps – an open label, non-inferiority, randomized control trial*

Jie Deng[1,#], Zaixing Wang[2,#], Zhaofeng Xu[1,#], Yinyan Lai[1], Rui Zheng[1], Wenxiang Gao[1], Jianbo Shi[1,†], Yueqi Sun[3,†]

[1] Otorhinolaryngology Hospital, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[2] Institute of Otorhinolaryngology and Shenzhen Key of Otorhinolaryngology, Longgang Otorhinolaryngology Hospital, Shenzhen, China

[3] Department of Otolaryngology, the Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, China

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[#,†] contributed equally to this work.

## Abstract

**Background**: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous disorder. We aimed to evaluate the value of blood eosinophil count (BEC) for guiding oral corticosteroid therapy for CRSwNP.

**Methods**: Subjects with CRSwNP were entered into a 2:1 randomized biomarker-directed corticosteroid versus standard therapy study base on the principle of potential benefits to patients. Subjects in the standard arm received oral prednisone (30mg/day) alone for 7 days, whereas in the biomarker-directed arm, prednisone (30mg/day), or nasal steroid spray (budesonide 256ug/day) was given according to the BEC which was measured to define eosinophil-high and -low CRSwNP (BEC ≥ and < 0.37×109/L, respectively). The primary outcome was the total nasal symptom scores (TNSS) of the two arms with the non-inferiority margin of 1.8. Secondary outcomes included nasal polyp size scores (NPSS) and SNOT-22. Patients were followed up the day after last dose of treatment.

**Results**: A total of 105 subjects with CRSwNP were randomized into the biomarker-directed therapy group or the standard care group. The biomarker therapy demonstrated non-inferiority compared to standard care. There were no between-group differences for TNSS, NPSS and SNOT-22 improvements after treatment. Comparisons of TNSS, SNOT-22 and NPSS revealed no significant difference in terms of the effectiveness ratios of the biomarker-directed therapy and the standard care.

**Conclusion**: A biomarker-directed strategy using the BEC can be used to direct corticosteroid therapy without increasing treatment failure or worsening of symptoms in patients with CRSwNP.

**Key words**: steroid treatment, CRSwNP

## Introduction

Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the sinonasal mucosa for more than 12 weeks [(1)]. It affects more than 10% of the general population in the United States [(2)] and 8% in China [(3)]. Studies typically categorize CRS patients into two subgroups, those with nasal polyps (CRSwNP) and those without nasal polyps (CRSsNP). However, emerging evidence reveals a considerable variation of inflammatory endotypes in patients with CRS, particularly those with nasal polyps [(4)]. CRSwNP is characterized by a T helper (Th) 2-skewed response and tissue eosinophilia in the western world, whereas a more distinct pathogenic phenotype that involves neutrophilic accumulations and mixed Th1/Th2/Th17 response in China [(5,6)] suggests a more heterogeneous nature of CRSwNP in China. Current international guidelines advocate a short course of oral corticosteroid treatment for CRSwNP [(1, 7)]. However, we and others revealed that roughly half (46%) of CRSwNP responded poorly to oral corticosteroid treatment, which suggests that the

therapeutic response varies markedly among individuals [8-11]. In addition, although previous studies showed that 2-3 moderate courses of oral corticosteroid annually is less likely to cause significant adverse effects such as osteoporosis [12], emerging evidence has suggested that cumulative doses of systemic corticosteroid are associated with a clear dose-dependent increase in the risk of developing adverse events. Exposure to 4 or more systemic corticosteroid prescriptions each year resulted in higher adverse effects in the current year [13-16]. Therefore, developing biomarkers to guide oral corticosteroid treatment may help patients avoid unnecessary corticosteroid exposure that may lead to adverse effects in the long run.

As part of a routine blood test, blood eosinophil number has been shown to be a well predictor for corticosteroid sensitivity in eosinophilic asthma [17]. Previous studies suggested that CRSwNP with the eosinophilic endotype is likely to be corticosteroid-sensitive [18]. In addition, studies in our and other institutes have indicated that blood eosinophil number could be used as a surrogate marker for the diagnosis of eosinophilic nasal polyps and it could predict recurrences of CRSwNP [19, 20]. Therefore, we hypothesized that the peripheral blood eosinophil count (BEC) can be used to guide oral corticosteroid treatment in patients with CRSwNP, which would result in reduced exposure to systemic corticosteroid without compromising the treatment outcome. To test this hypothesis, we undertook a non-inferiority study of patients with CRSwNP, randomized to BEC-directed oral corticosteroid therapy versus standard care.

## Materials and methods

### Study design and participants

This is a two-center randomized non-inferiority trial of biomarker-directed corticosteroid therapy versus standard care for the treatment of CRSwNP. Subjects with CRSwNP as per the European position paper [1] of CRS were recruited from the First Affiliated Hospital of Sun Yat-sen University and the Shenzhen Longgang Hospital between October 2018 and December 2020. All patients fulfilled the inclusion criteria of age >18 years and each side of nasal polyp score ≥ 2 as per the nasal polyp scoring system [8, 21]. Exclusion criteria included the following: 1) hypersensitivity to corticosteroids, 2) contraction of one of the following diseases: cystic fibrosis based on positive sweat test or DNA alleles, gross immunodeficiency (congenital or acquired), congenital mucociliary problems e.g. primary ciliary dyskinesia (PCD), non-invasive fungal balls and invasive fungal disease, systemic vasculitis and granulomatous diseases, cocaine abuse, neoplasia, 3) prescription with systemic or intranasal corticosteroids within one month before a routine blood test, 4) comorbidity with gross immunodeficiency, with systemic use of steroid, 5) upper respiratory tract infection 2 weeks before inclusion, 6) severe systemic diseases affecting the cardiovascular, metabolic, immunology, neurology, hematology, cerebrovascular or respiratory systems or history of psychic disease, or mental problems, (7) participation in other clinical research within the previous 30 days, 8) pregnancy or breast-feeding. All subjects gave written informed consent, and the study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University. The trial is registered with the Chinese Clinical Trial Registry (ChiCTR1800014933).

Patients enrolled were randomized to enter a biomarker-directed treatment group or a standard care treatment group. The peripheral blood eosinophil count was used to guide corticosteroid treatment in the biomarker-directed arm. Subjects in the biomarker-directed treatment group received a dose of 30mg of prednisone once daily or budesonide nasal spray 128mg twice daily for 7 days when BEC was ≥ and < the cut-off value of $0.37\times10^9$/L, respectively. This cut-off value was selected based on a retrospective study conducted in the First Affiliated Hospital of Sun Yat-sen University (supplemental materials), in which we found that this cut-off value of BEC was optimal, with a Youden index of 0.57, sensitivity of 71.3% and specificity of 84.4%, to discriminate between corticosteroid-sensitive and corticosteroid-insensitive subjects with CRSwNP. This was defined as in our prior study [9], namely patients who are able and unable to reduce more than 1 point by the nasal polyp size score (NPSS) after a 7-day course of oral prednisone (30 mg once daily) treatment. Subjects in the standard care group received 30 mg of prednisone once daily for 7 days irrespective of the blood eosinophil biomarker results. Blood eosinophils were measured at enrollment to define eosinophil-high and -low patients in both groups (peripheral BEC≥ $0.37\times10^9$/L termed eosinophil-high; peripheral BEC < $0.37\times10^9$/L termed eosinophil-low). The study personnel involved in data collection were blind to the randomization, biomarker results, and treatment assignments. Unblinding and analysis were performed at the end of the study.

### Measurements

At enrollment, we recorded patient demographics and comorbidities. Allergic rhinitis was diagnosed based on the Allergic Rhinitis and its Impact on Asthma guideline [22]. The diagnosis of asthma was performed by a specialist and was established according to the Global Initiative for Asthma 2006 guideline [23]. Baseline disease burden of CRSwNP was measured by the total nasal symptom score (TNSS), endoscopic NPSS, and 22-item sinonasal outcome test (SNOT-22). After a 7-day treatment (on day 8), subjects were re-evaluated with TNSS, NPSS and SNOT-22. In addition, an itemized questionnaire was completed by patients to assess symptoms potentially associated with the side effects of systemic corticosteroid therapy.

TNSS is a 4-item questionnaire widely used to evaluate the severity of sinonasal symptoms (nasal obstruction, rhinorrhea, olfactory dysfunction, and head and facial pain) on a 5-point scale from 0 (none) to 4 (severe), with a total range of 0 to 16 [1,

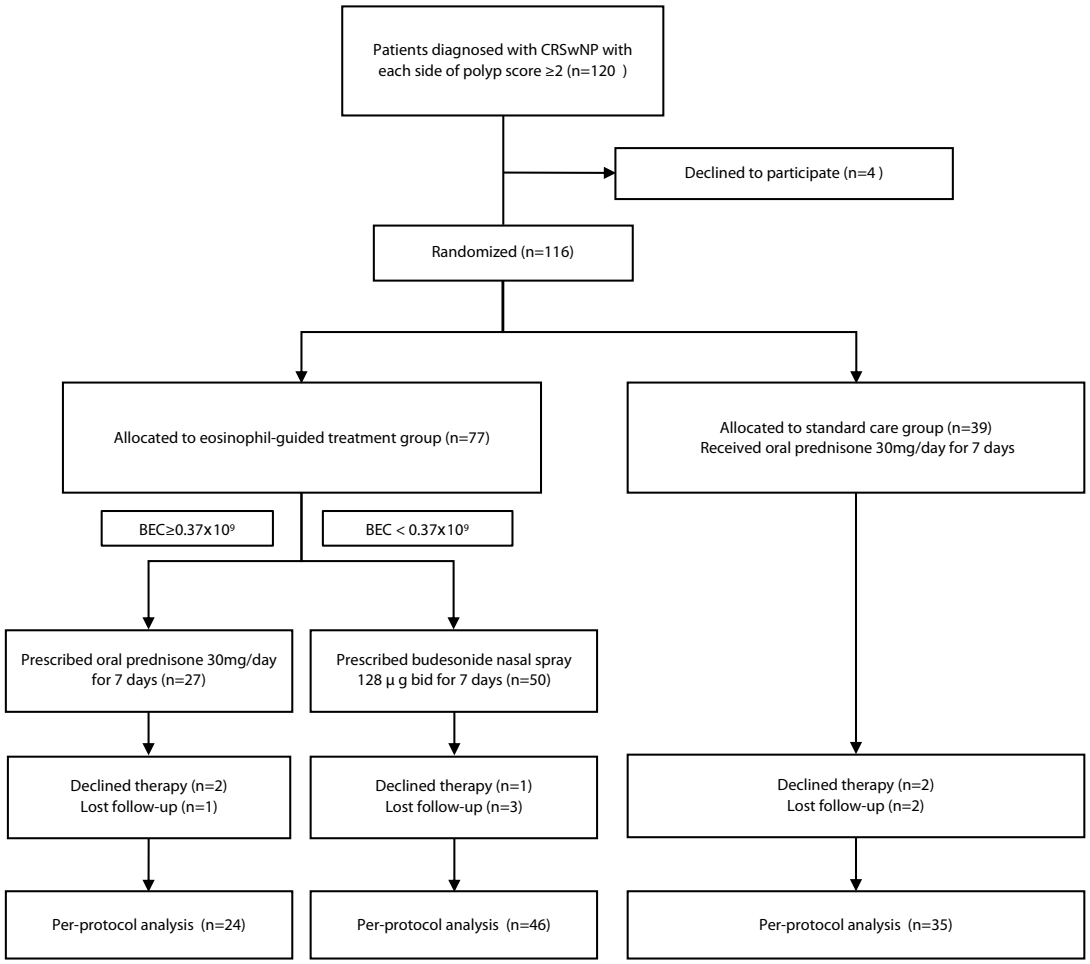


Figure 1. CONSORT flow diagram for patient enrollment and randomization. CRSwNP, chronic rhinosinusitis with nasal polyps; BEC, blood eosinophil count.

[18]. SNOT-22 is a 22-item questionnaire commonly used to measure sinus-specific patient-reported outcomes on a 6-point scale from 0 (no problem) to 5 (problem as bad as it can be), with a range of 0 to 110 [24]. NPSS was graded by nasal endoscopy using the Meltzer clinical scoring system [25], which consists of a 0 to 4 polyp grading system (0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps extending beyond middle meatus, 4 = polyps completely obstructing the nasal cavity).

We used TNSS as the primary outcome. NPSS and SNOT-22 were studied as secondary outcome measures. All subjective and objective evaluations were made by otolaryngologists blinded to the treatment arms. And the NPSS were evaluated by two senior otolaryngologists (J.D and Z.F.X) also blinded to the treatment arms.

### Sample size calculation

The primary non-inferiority hypothesis in TNSS was evaluated through a statistical model for a continuous outcome in a parallel group noninferiority trial [26]. According to a previous study [27, 28], a non-inferiority margin of 1.8 for the differences of TNSS was calculated. To calculate the sample size, we use a non-inferiority test for the difference of two means. 35 subjects were required in each group to have 90% power at an alpha level of 5%. Base on the principle of potential benefits to patients and the distribution of BEC skewed to the higher level, more patients were allocated to the experimental arm, which resulted in a ratio of 2:1 of subjects for the biomarker-directed treatment arm compared to the standard care arm. In view of a typical loss of 10% participants in the follow-up examinations, 40 subjects for standard care treatment and 80 subjects for biomarker-directed treatment were recruited.

### Statistical analysis

Statistical analysis was performed with PRISM version 4 (GraphPad Software, San Diego, CA), SPSS version 16 (SPSS, Inc., Chicago, IL, USA) and MedCalc for comparison of different ROC curves, after consultation with a medical statistician. Pearson's chi-square tests were used for categorical data for sex, age, smoking status, and skin prick test. Multiple logistic regression mo-

Table 1. Baseline characteristics of participants who completed the study.

| | Biomarker-directed group (n=70) | Standard care group (n=35) | p |
|---|---|---|---|
| Male, n (%) | 46 (65.7) | 22 (62.9) | 0.773 |
| Age, year (SD) | 43.1 (14.1) | 41.9 (12.6) | 0.683 |
| Smoker, n (%) | 11(15.7%) | 6(17.1%) | 0.898 |
| Allergic rhinitis, n (%) | 8(11.4) | 3(8.6) | 0.748 |
| Asthma, (%) | 17(24.3) | 6(17.1) | 0.404 |
| Previous surgery, N (%) | 15(21.4) | 13(37.1) | 0.120 |
| Blood eosinophil count before treatment, mean (SD) ($\times 10^9$/L) | 0.30 (0.026) | 0.27 (0.041) | 0.369 |
| Blood eosinophil count after treatment, mean (SD) ($\times 10^9$/L) | 0.015 (0.005) | 0.008 (0.001) | 0.898 |
| TNSS, mean (SD) | 8.59 (2.511) | 8.72(2.993) | 0.813 |
| NPSS, mean (SD) | 7.47 (2.153) | 6.86 (1.751) | 0.152 |
| SNOT-22, mean (SD) | 39.51 (18.135) | 41.71 (22.327) | 0.616 |
| ΔTNSS, mean (SD) | 2.73 (2.562) | 3.25 (2.946) | 0.283 |
| ΔNPSS, mean (SD) | 1.54 (1.939) | 1.60 (2.001) | 0.888 |
| ΔSNOT-22, mean (SD) | 10.91 (15.122) | 10.91 (17.794) | 0.999 |

Δ: the differences between before and after treatments. Abbreviations: SD, standard deviation; TNSS, total nasal symptoms score; NPSS, nasal polyp size score; SNOT-22, sino-nasal outcome test-22.

del was used for the variables of BEC or neutrophil count, blood eosinophil or neutrophil percentage, pre-treatment TNSS, and pre-treatment NPSS to estimate the likelihood of these events in relation to CS response. Parametric and nonparametric data are presented as mean (SD, 95% confident interval) and median (IQR). Differences between groups were tested with $\chi^2$ or Fisher's exact test for categorical variables and with t-test for continuous variables and Mann-Whitney U test for nonparametric variables unless otherwise stated. Nonparametric Z tests (2-tailed) were used for ROC curve area comparisons. Minimum clinically important differences (MCID) for TNSS, SNOT-22 and NPSS were used to evaluate the effectiveness for each treatment arm, which was 1.7, 8.9 and 1 point, respectively, according to previous studies (9, 24, 27, 28). Statistical significance was defined as a p value $<0.05$.

## Results

### Patient characteristics and primary outcome analysis

Between October 8, 2018 and December 30, 2020, a total of 120 subjects were diagnosed with CRSwNP according to the European position paper and recruited into the non-inferior randomized control trial, with 4 of them declining to participate in the study. One hundred and sixteen subjects were randomized into the biomarker-directed therapy group (n=77) or the standard care group (n=39), as shown in Figure 1. After randomization, 2 subjects in the standard care group and 3 in the biomarker-directed therapy group (2 BEC-high and 1 BEC-low) declined to receive therapy. At the end of the study, 4 in the biomarker-directed therapy group and 2 in the standard care group could not be contacted for the follow-up. As a result, a total of 105 subjects were included in the per-protocol analysis, with 70 in the biomarker-directed therapy arm (mean [SD] age, 43.1 [14.1] years; 46 men, 24 women) and 35 in the standard care arm (mean [SD] age, 41.9 [12.6] years; 22 men, 13 women). Baseline characteristics of participants who completed the study are shown in Table 1. An adequate randomization was achieved, since there were no differences between the biomarker-directed therapy and standard care arms in terms of age, sex, medical comorbidities, or previous sinus surgery history. In addition, there was a similar preoperative disease burden as measured by the baseline TNSS, SNOT-22 score and NPSS. No asthma exacerbation occurred during the study and the follow-up.

The primary outcome of noninferiority of TNSS in the biomarker-directed therapy versus the standard care groups after one week of treatment was achieved (mean change, 2.73 vs 3.25; 95%CI, -0.58 to 1.63; p=0.353) (Figure 2A, Table 1). There were similar reductions in the NPSS (mean change, 1.54 vs. 1.60; p=0.88) and the SNOT-22 scores (mean change, 10.91 vs. 10.92; p=0.99)

Table 2. Before and after treatment for the biomarker-directed group.

| | Eosinophil-high (n=24) | | P1 | Eosinophil-low (n=46) | | P2 | P3 | P4 | Differences between groups (95% CI)# |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Post-treatment | | Baseline | Post-treatment | | | | |
| TNSS, mean (SD) | 8.84(2.386) | 5.09 (2.417) | <0.001 | 8.46 (2.589) | 6.26 (2.927) | <0.001 | 0.546 | 0.100 | 0.31, 2.79 |
| NPSS, mean (SD) | 7.46 (2.146) | 5.21 (1.285) | <0.001 | 7.47 (2.180) | 6.27 (1.483) | <0.001 | 0.910 | 0.673 | 0.13, 2.02 |
| SNOT-22, mean (SD) | 42.79 (19.762) | 26.58 (18.297) | <0.001 | 37.67 (17.128) | 30.31 (16.944) | <0.001 | 0.271 | 0.289 | 0.820, 15.83 |
| Nasal symptom, mean (SD) | 18.79 (4.690) | 9.79 (6.022) | <0.001 | 16.37 (6.241) | 12.15 (6.077) | <0.001 | 0.230 | 0.126 | **2.23, 7.33** |
| Extra-nasal symptom, mean (SD) | 6.21 (3.730) | 3.58 (2.653) | 0.001 | 6.15 (3.026) | 4.83 (3.227) | <0.001 | 0.950 | 0.110 | 0.03, 2.57 |
| Ear/facial symptom, mean (SD) | 6.54 (4.818) | 4.54 (4.736) | 0.037 | 4.83 (4.149) | 3.48 (3.488) | 0.001 | 0.190 | 0.298 | -1.02, 2.32 |
| Psyco-physical symptom, mean (SD) | 10.50 (9.776) | 7.46 (6.928) | 0.095 | 8.28 (8.180) | 7.22 (2.090) | 0.165 | 0.318 | 0.892 | -1.28, 5,23 |
| Sleep dysfunction, mean (SD) | 9.25 (6.415) | 7.17 (4.860) | 0.109 | 6.50 (6.281) | 5.57 (5.239) | 0.139 | 0.159 | 0.218 | -1.33, 3.63 |

Numbers in bold type were p<0.05. The data was under per protocol analysis. # Differences were the changes before and after treatment between eosinophil-high and -low patients in biomarker directed group. P1: Difference between pre-treatment and post-treatment for Eosinophil-high subjects. P2: Difference between pre-treatment and post-treatment for Eosinophil-low subjects. P3: Difference between Eosinophil-high and -low subjects before treatment. Abbreviations: SD, standard deviation; TNSS, total nasal symptoms score; NPSS, nasal polyp size score; SNOT-22, sino-nasal outcome test-22.

Table 3. Before and after treatment for the oral prednisone group.

| | Eosinophil-high prednisone (n=32) | | p | Eosinophil-low given prednisone* (n=27) | | p | Differences between groups (95% CI)# |
|---|---|---|---|---|---|---|---|
| | Baseline | Post-treatment | | Baseline | Post-treatment | | |
| TNSS (mean, SD) | 9.01(2.349) | 5.22 (2.351) | <0.01 | 8.48 (3.166) | 5.43 (3.183) | <0.01 | -0.686, 2.170 |
| NPSS (mean, SD) | 7.19 (2.070) | 4.94 (1.318) | <0.01 | 7.00 (1.776) | 5.59 (1.866) | <0.01 | -0.16, 1.85 |
| SNOT-22 (mean, SD) | 43.16 (20.887) | 27.59 (17.176) | <0.01 | 40.00 (21.635) | 29.92 (19.162) | <0.01 | -4.09, 15.06 |
| Nasal symptom (mean, SD) | 18.84 (4.566) | 10.66 (5.976) | <0.01 | 16.11 (6.554) | 12.52 (5.944) | 0.016 | **1.23, 7.95** |
| Extra-nasal symptom mean, (SD) | 6.13 (3.679) | 3.56 (2.422) | <0.01 | 5.26 (3.323) | 3.96 (2.361) | 0.019 | -0.35, 2.88 |
| Ear/facial symptom mean, (SD) | 6.75 (4.873) | 4.47 (4.333) | 0.012 | 5.07 (3.689) | 3.78 (3.434) | 0.043 | -1.19, 3.15 |
| Psyco-physical symptom mean, (SD) | 11.16 (10.125) | 8.06 (6.862) | 0.071 | 11.63 (11.496) | 9.67 (9.503) | 0.154 | -3.24, 5.50 |
| Sleep dysfunction mean, (SD) | 8.94 (6.739) | 6.91 (4.489) | 0.103 | 7.63 (7.742) | 7.70 (6.521) | 0.949 | -1.28, 5.49 |

Numbers in bold type were p<0.05. *: data for the eosinophil-low patients in the standard care group. Data was analysis after pooling up two arms. #: Differences were the changes before and after treatment between eosinophil-high and -low patients in biomarker directed group. Abbreviations: SD, standard deviation; TNSS, total nasal symptoms score; NPSS, nasal polyp size score; SNOT-22, sino-nasal outcome test-22.

in the biomarker-directed therapy and the standard care arms. (Figure 2B and 2C, Table 1).

The number of each patient cohort achieving an MCID in TNSS total from baseline, was 53 out of 70 (75.7%) for the biomarker-directed therapy group vs 28 out of 35 (80.0%) for the standard care group. Moreover, for SNOT-22 and NPSS, the numbers of each patient cohort reaching an MCID from the baseline were 35 out of 70 (50.0%) and 37 out of 70 (52.9%) for the biomarker-directed therapy group vs 17 out of 35 (48.6%) and 20 out of 35 (57.1%) for the standard care group, respectively. Comparisons

Table 4. Treatment effects of oral and topical corticosteroids.

| | Oral steroid treatment (n=59) | Topical steroid treatment (n=46) | p |
|---|---|---|---|
| Male, n (%) | 32 (55.2) | 36 (78.2) | 0.5790 |
| Age, year (SD) | 41.63 (12.707) | 43.74 (14.316) | 0.4280 |
| AR, n (%) | 6 (11.8) | 5 (9.3) | 0.6990 |
| AS, (%) | 15 (29.4) | 8 (14.8) | 0.1000 |
| Previous surgery, n (%) | 19 (37.3) | 9 (16.7) | **0.02** |
| Blood eosinophil count (×109/L), mean (SD) | 0.44 (0.18) | 0.14 (0.11) | **0.000** |
| Pretreatment TNSS, mean (SD) | 8.77 (2.741) | 8.46 (2.589) | 0.4520 |
| SNOT-22, mean (SD) | 41.74 (21.097) | 37.67 (17.128) | 0.3030 |
| NPSS, mean (SD) | 7.46 (2.146) | 7.47 (2.180) | 0.9880 |
| ΔTNSS, mean (SD) | 3.45 (2.731) | 2.20 (2.499) | **0.01** |
| ΔTNSS, 95%CI | 0.22, 2.281 | | |
| ΔNPSS, mean (SD) | 1.86 (1.952) | 1.17 (1.901) | 0.07 |
| ΔNPSS, 95% CI | -0.062, 1.443 | | |
| ΔSNOT-22, mean (SD) | 13.10 (18.155) | 7.88 (11.956) | 0.107 |
| ΔSNOT-22, 95% CI | -1.154, 11.599 | | |

Numbers in bold type were p<0.05. Δ: the differences between before and after treatments. Abbreviations: SD, standard deviation; TNSS, total nasal symptoms score; NPSS, nasal polyp size score; SNOT-22, sino-nasal outcome test-22.

of TNSS, SNOT-22 and NPSS revealed no significant difference (p=0.14 ,0.89, and 0.28, respectively) according to the effectiveness ratios calculated for the biomarker-directed therapy and the standard care groups.

### Treatment effects of eosinophil-high and-low subjects in the biomarker-directed therapy group

To further explore the effect of oral and topical steroid after grouping by eosinophil, we analysis the subjective effect in the biomarker-directed therapy group. The TNSS, SNOT-22 and NPSS in both eosinophil-high and -low subjects was significantly reduced after allocated treatments, but the change between groups were not significant. In addition, the domain analysis of nasal symptoms, extra-nasal symptoms and ear/facial symptoms were also significantly reduced after treatment in both eosinophil-high and -low subjects. However, the domain analysis of psycho-physical symptoms and sleep dysfunction were not significantly reduced (p>0.05) (Table 2).

### Treatment effects of oral steroid for eosinophil-high and -low subjects

To find out the differences of treatment effects for oral prednisone between eosinophil-high and -low patients, we pooled the patients prescribed oral prednisone together. 32 subjects who were eosinophil-high (BEC≥0.37×$10^9$/L) and 27 subjects who were eosinophil low (BEC<0.37×$10^9$/L) received oral prednisone treatment. TNSS, NPSS and SNOT-22 total scores were all significantly improved after oral prednisone treatment for both eosinophil-high and -low subjects (Table 3). With respect to the SNOT-22 subdomains, significant improvements in rhinologic, extra-nasal rhinologic, and ear/facial subdomains were observed after prednisone treatment both in eosinophil-high and -low subjects low, whereas the psycho-physical symptoms and the sleep function was similar before and after prednisone treatment (Table 3). The differences between eosinophil-high and -low subjects were only significant in nasal symptoms, but not in either TNSS, NPSS, SNOT-22 total scores or other subdomains of SNOT-22 (Table 3).

### Treatment effects between oral and topical corticosteroids

Finally, we also compare the effects between oral and topical corticosteroids for all the included patients. When groups were pooled together, there were 59 subjects who were prescribed oral prednisone (including 35 subjects in the standard

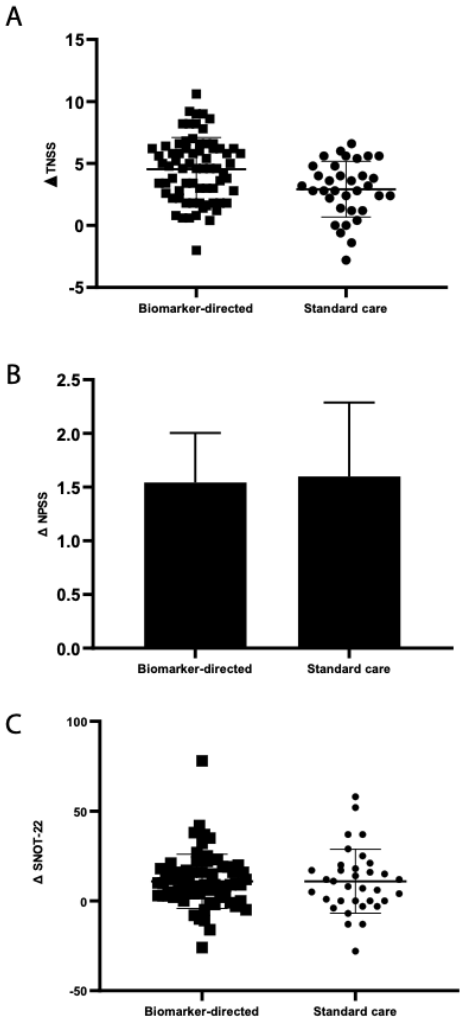


Figure 2. Improvements in TNSS, NPSS and SNOT-22 after treatment between the biomarker-directed therapy and standard care arm. TNSS, total nasal symptom score; NPSS, nasal polyp size score; SNOT-22, 22-item sinonasal outcome test.

care group and 24 subjects in the biomarker-directed group with BEC≥0.37×10$^9$/L), and 46 subjects prescribed topical steroid (subjects in the biomarker-directed group with BEC<0.37×10$^9$/L). No differences were observed in the baseline characteristics between those with oral prednisone and those with topical steroid therapy (Table 4). In addition, there was a significant TNSS improvement in the subjects with oral steroid therapy compared with those with topical steroid therapy (mean change, 8.42 vs. 5.13; 95%CI, 0.78-5.785; p=0.01) (Table 4). This was in line with our previous study24. However, there were no differences in NPSS reduction and SNOT-22 improvement between oral and topical steroid group after treatment allocation (mean change for polyp size score, 1.86 vs. 1.17; p=0.07, and mean change for SNOT-22, 13.1 vs. 7.88; p=0.10) (Table 4). Because of the nature of pooling up subjects, the effects of oral steroid might be better than previous study. These might be why the change of NPSS and SNOT-22 were not significantly different between two treatments.

### Long-term follow-up

To further evaluate the prognosis of the patients, we followed the participants up by phone since September 20th, 2022. There were 58 patients in the biomarker directed group and 29 patients in the standard care group who responded. The mean follow-up time was 33 months (range 23-48 months). Patients characteristics were shown in Table S4. The outcome measurements were not significantly different, including TNSS and SNOT-22 (Table S5).

### Side effect analysis

During the treatment period, one patient reported gaining weight for 1kg after one-week of prednisone medication. No major side effects were reported.

## Discussion

To our knowledge, this is the first randomized control trial for biomarker-directed systemic corticosteroid treatment in patients with CRSwNP. In this non-inferiority, randomized control trial to compare efficacy of oral corticosteroid determined by blood eosinophil levels with current guideline-proposed treatment in reducing the clinical symptoms and disease burdens in patients with CRSwNP, we found the biomarker-directed treatment was non-inferior to the standard care treatment. However, the effectiveness ratio for both groups were similar in TNSS, NPSS and SNOT-22, indicating that the use of this biomarker-directed strategy does not lead to an increase in treatment failure or worsening of symptoms compared with standard corticosteroid therapy. More importantly, we have shown that a biomarker-directed strategy using blood eosinophil levels can safely reduce systemic corticosteroid prescription in the treatment of CRSwNP. Together, these findings suggest that BEC alone can be used as an easy-to-measure biomarker for guiding oral corticosteroid therapy in patients with CRSwNP. We believe that these results have great practical advantages.

An obvious strength and novelty of this trial was to prospectively compare objective biomarker-based treatment with current clinical care. Although several biomarkers, such as IL-25 [29], Charcot-Leyden crystal [10] and serum amyloid A [21], have been shown to be associated with corticosteroid sensitivity in patients with CRSwNP, most of these studies are limited by their retrospective nature, small sample sizes and lack of adequate control groups. For these reasons, their usefulness as biomarkers for predicting corticosteroid sensitivity is still difficult to estimate. In addition, we believe that other strengths of this trial include its randomized design as well as the participation of two centers. Moreover, this trial included a treatment period of 7 days, which meets current international guideline recommendations for patients with

CRSwNP [1, 24]. The study objectives addressed a patient population that is relatively difficult to treat in real-life practice (each side of NPSS ≥2), and for which more clinical evidence is needed to guide treatment strategies, especially in the Chinese population, where Th2/Th1/Th17 mixed reaction is more commonly present. Although corticosteroid therapies are recommended by current international guidelines for treatment of CRSwNP, the therapeutic response varies among different individuals [1, 7]. Identification of potential clinical parameters or biomarkers for prediction of the response to corticosteroid treatment would greatly improve the management of CRSwNP. Previous studies demonstrated positive changes in most of the subjective and objective evaluations after varying dose and lengths of oral corticosteroid treatment. The overall sensitivity rates of oral CS therapy in patients with CRSwNP range from 62% to 80% [1, 30]. Prior studies have attempted to clinically characterize the corticosteroid sensitive or insensitive CRSwNP. For example, Virat, et al. demonstrated that although a 14-day course of 50mg prednisone showed significantly greater improvements compare to placebo, patients with large polyps (greater than grade 3) or positive nasal endoscopy were more likely to have a poorer treatment outcome [31]. Won et al. found that a treatment with 20mg prednisolone daily for 14 days improves 62% of the CRSwNP patients' symptoms and quality of life, and comorbid allergic rhinitis favored responders [32]. Moreover, we recently reported that IL-25 in nasal polyp tissues would be a promising biomarker for corticosteroid sensitivity [29]. A tissue IL-25 cutoff value of 22.5pg/mL provided a sensitivity of 85.7% and a specificity of 95.8%. In another study, we showed that patients with neutrophil-negative nasal polyps (without tissue neutrophil infiltration) had significantly greater reductions in bilateral polyp size scores, TNSS and nasal resistance than those of neutrophil-positive nasal polyps after oral corticosteroid treatment [18]. While these studies point to the importance of clinical parameters or biomarkers in the prediction of corticosteroid response, there is still a lack of biomarker currently available in daily practice. Blood eosinophils have been shown to be associated with an increase in all-cause mortality in patients with airways disease [33] and simple to measure. In line with the previous study [19, 34], we showed that blood eosinophil level of $0.37\times10^9$/L displayed relatively high specificity and sensitivity in predicting oral corticosteroid response. A BEC higher than $0.37\times10^9$/L would be responsive to oral corticosteroid treatment, while a BEC lower than $0.37\times10^9$/L, prescribed nasal topical steroid, would not be worse than that prescribed oral corticosteroid. Although no severe reactions were reported in this trial, emerging evidence has suggested that even short-term oral corticosteroid treatment could be associated with more side effects. Sullivan et al. [35] performed a retrospective cohort study of asthmatic patients between 2000 and 2014 and found each oral corticosteroid prescription might result in a cumulative burden on current and future health regardless of dose and duration. The corticosteroid exposure of more than 4 times a year may increase the adverse effects of osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts. Our findings suggest that a biomarker-directed strategy for initiating corticosteroid therapy would result in the benefits of therapy with a simultaneous reduction in the patient number harmed by this treatment, and the need for oral corticosteroid in CRSwNP treatment. In addition, in the biomarker-directed arm, both oral corticosteroid treatment and topical steroid treatment significantly improve TNSS, SNOT-22 and NP scores after treatment, and the improvements of eosinophil-high subjects are significantly greater than eosinophil-those of eosinophil-low subjects. Lastly, subgroup analysis found that regardless of eosinophil-high and -low, the symptom scores, quality of life analysis and nasal polyp sizes were improved, which is like our previous report [28].

It should be noted that corticosteroid sensitivity is a relative definition. The prevalence of corticosteroid insensitivity varies depending on how it is defined. In the present study, we use NPSS to determine the corticosteroid sensitivity and TNSS as the primary outcome to evaluate the non-inferiority of the biomarker-directed treatment arms. The reasons are as follows: 1) based on the multivariate analysis and ROC curve, the NPSS showed a highest AUC, 2) TNSS was closer to the objective evaluation of the patients' disease burden compare to NPSS alone (data not shown). Additionally, there would be a dose-related and treatment duration-related effect on the response to corticosteroid treatment in CRSwNP. The most used dose of oral prednisone ranges from 25mg/day to 50mg/day in the literature. The treatment duration varies from 7 days to 3 weeks [27, 36, 37]. Although a higher dose and longer treatment duration may result in better disease control and thus lead to a higher corticosteroid response rate, it may increase the side effects and alter the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, smoking status might influence the effects of oral steroid. Patients with smoking burden tend to be neutrophil inflammation in COPD, thus maybe poorly responded to oral steroid.

There are several limitations in this study. Firstly, the cut-off value of BEC might be too high for this set of CRSwNP subjects. In either group, less than half of the subjects were eosinophil-high subjects, which may result in a skew to the eosinophil-low results. Secondly, a treatment duration and follow-up of one week might be too short to assess a fuller effect of the biomarker-directed treatment. Although the 7-day treatment already showed a non-inferiority to the biomarker-directed group compared to standard corticosteroid group, no significantly better effect was found in the biomarker-directed treatment group. What's more the patients in this study were all recruited from tertiary hospitals and may not be representative of the general patient population. Additionally, there were no assessments conducted of medication adherence prior to prescription of either drug.

Finally, due to the nature of the non-inferiority RCT design and the relatively small sample size of around 100 subjects, it was not possible to analyze data stratified by gender, age, asthma status, and other relevant factors.

## Conclusion

A biomarker-directed strategy using the peripheral BEC can be used to direct corticosteroid therapy of CRSwNP. This simple stratification may allow avoiding unnecessary exposure to systemic corticosteroids, thus most likely to reduce the burden of corticosteroid adverse effects substantially in a large and vulnerable patient group. Our data suggests that in the outpatient treatment of CRSwNP, oral corticosteroid should only be given to those who have a BEC greater than $0.37\times10^9$/L, but a larger confirmatory study is required.

## Authorship contribution

JS contributed to conception of the study. JD and YS contributed to the conception, data analysis, draft and approve the final version of the manuscript. ZW, WG, YL and ZX contributed to data collection. RZ contributed to statistical analysis of the data and prepared Tables 1-4. All authors reviewed the manuscript.

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## Conflict of interest

None.

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## Ethics approval and consent to participate

This is a multicenter interventional study. The ethic committee the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China approved the study. All the subjects included had signed informed consent.

## Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Yueqi Sun, MD, PhD
Department of Otolaryngology
the Seventh Affiliated Hospital of Sun Yat-sen University. No.628 Zhenyuan Road
Guangming (New) District
Shenzhen
Guangdong
518107, China

E-mail: aqi1733@163.com or sunyq7@mail.sysu.edu.cn

Jianbo Shi, MD, PhD
Otorhinolaryngology Hospital
The First Affiliated Hospital
Sun Yat-sen University
58 Zhongshan Road II
Guangzhou
Guangdong
510080, China

Tel.: 86-20-87333733
Fax: 86-20-87333733
E-mail: shijb@mail.sysu.edu.cn

**This manuscript contains online supplementary material**

**Additional files 1:**

Supplemental Methods and Results

The methods and results of a retrospective study where we define CS-sensitive and CS-insensitive for CRSwNP patients.

**Additional files 2:**

Supplemental Figures and Tables

Figures S1-2 and Tables S1-S5.

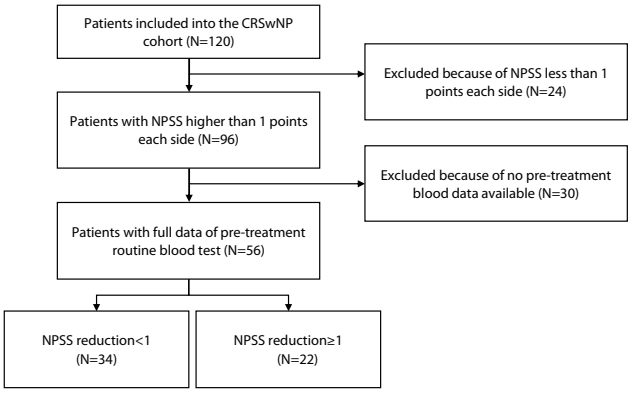
## SUPPLEMENTARY MATERIAL

### Methods

The diagnosis of CRSwNP was carried out according to the European position paper on rhinosinusitis and nasal polyps (EPOS 2012) [1]. The inclusion and exclusion criteria were as followed. Inclusion criteria: 1) Patients should be voluntary to take part in the cohort, understand and agree to take the drugs, accept follow-ups, and report the events properly, and the inform consent should be signed; 2) Aged between 18 and 70 years old. 3) With the diagnosis of CRSwNP according to EPOS 2012: Subjective symptoms: presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): ± facial pain/pressure; ± reduction or loss of smell; for > 12 weeks; Endoscopy: with polyps bilateral in middle meatus larger than the lower boarder of middle turbinate, purulent secretion the middle meatus, with/without middle meatus swelling or mucous block. Exclusion criteria: 1) Hypersensitive to CSs or budesonide; 2) With any one of the following diseases: cystic fibrosis based on positive sweat test or DNA alleles; gross immunodeficiency (congenital or acquired); congenital mucociliary problems eg. primary ciliary dyskinesia (PCD); non-invasive fungal balls and invasive fungal disease; systemic vasculitis and granulomatous diseases; Cocaine abuse; neoplasia; 3) Patients prescribed with systemic or intranasal corticosteroids within one month before blood routine test; 4) Comorbidity with gross immunodeficiency, using steroid systemically; 5) With upper respiratory tract infection 2 weeks before inclusion; 6) With severe systemic diseases affecting the cardiovascular, metabolic, immunology, neurology, hematology, cerebrovascular or respiratory system or history of psychic disease, or mental problems; 7) Participate in other clinical researches within latest 30 days. Pregnant or breast-feeding females.

### Results

A total number of 56 patients were included into the analysis (Figure S1). Demographic information and baseline characteristics were summarized in Table S1. Generally, after 7-day CS treatment, the mean TNSS and NP score were reduced significantly from 7.11 to 4.4 ($p<0.01$) and from 5.53 to 4.6 ($p=0.022$), respectively. Based on the criterion described in our and other studies, 39.3% (22/56) of patients were defined as CS-sensitive CRSwNP, while 60.7% (34/56) were CS-insensitive CRSwNP. Multivariate logistic regression revealed that, among the parameters analyzed, significant difference between CS-sensitive and CS-insensitive subgroup was found in BEC and blood eosinophil percentage, NP scores and TNSS after adjustment for age, sex, smoking habits, AR, Bronchial provocation test positive, asthma and prior surgery (Table S2). Further ROC comparison between these four markers showed that BEC had the highest area under curve (AUC) value for the prediction of CS sensitivity (AUC = 0.798, 95% CI: 0.666-0.896 $p<0.05$) (Figure S2). The optimal cutoff point for blood eosinophil level was $0.37\times10^9$/L, with a Youden index of 0.57, sensitivity of 71.3% and specificity of 84.4%. The positive and negative predictive values were 72.7% and 76.5%, respectively. According to this cut-off value, the prevalence of concomitant asthma and AR were significantly different, and the change of NP score after treatment was also different (Table S3).




Flow diagram of the retrospective study.

Table S1. Baseline characteristics of patients in the retrospective cohort.

| | Study entry |
|---|---|
| Male, n (%) | 36 (64.3) |
| Age, mean (SD) | 39.0 (13.93) |
| Smokers, n (%) | 10 (17.8) |
| Pack-year history, mean (SD) | 18.4 (14.12) |
| Asthma, n (%) | 16 (28.6) |
| Allergic rhinitis, n (%) | 26 (46.4) |
| TNSS, mean (SD) | 7.1 (2.98) |
| Blood neutrophil count ($\times10^9$ /L), mean (SD) | 4.75 (1.63) |
| Blood eosinophil count ($\times10^9$ /L), mean (SD) | 0.32 (0.278) |
| Lund-Mackay score, mean (SD) | 19.1 (8.83) |
| Lund-Kennedy endoscopic score, mean (SD) | 2.2 (3.83) |
| Nasal polyp size score, mean (SD) | 5.5 (1.61) |
| Bronchial provocation test positive, n (%) | 15 (26.8) |

Table S2. Multivariate logistic regression analysis of the predictive factors for CS sensitivity, unadjusted or adjusted for age, sex, smoking habits, allergic rhinitis, bronchial provocation test positive, asthma and prior surgery.

| | Unadjusted OR (95% CI) | p | Adjusted OR (95% CI) | p |
|---|---|---|---|---|
| Blood eosinophil count ($\times10^9$ cells/L) | 37.85 (2.718, 52.172) | **0.007** | 27.75 (1.143, 61.279) | **0.043** |
| Blood eosinophil percentage (%) | 25.28 (1.788, 55.98) | **0.013** | 29.89 (0.712, 35.342) | 0.312 |
| Blood neutrophil count ($\times10^9$ cells/L) | 0.89 (0.667, 1.192) | 0.437 | 1.21 (0.804, 1.819) | 0.361 |
| Blood neutrophil percentage (%) | 0.14 (0.004, 5.244) | 0.290 | 4.33 (0.032, 59.191) | 0.555 |
| Pre-operative TNSS | 1.13 (0.937, 1.372) | 0.198 | 1.47 (1.072, 2.001) | **0.017** |
| Pre- operative Lund-Mackay score | 1.03 (0.961, 1.1) | 0.416 | 1.05 (0.924, 1.196) | 0.449 |
| Pre- operative nasal polyp size score | 1.54 (1.032, 2.289) | **0.034** | 1.31 (0.762, 2.258) | 0.327 |

Numbers in bold type were p<0.05.

Table S3. Blood eosinophil count and corticosteroid sensitive polyps.

| | EOS≥0.37×10⁹ /L (n=22) | EOS<0.37×10⁹ /L (n=34) | p |
|---|---|---|---|
| Pre-treatment NP score, mean (SD) | 5.95 (1.81) | 5.21 (1.41) | 0.11 |
| Bronchial provocation test positive, n (%) | 10(45) | 5 (14.7) | **0.024** |
| Asthma, n (%) | 11(50) | 5 (14.7) | **<0.01** |
| Allergic rhinitis, n(%) | 17(77.3) | 9 (26.5) | **<0.01** |
| ΔPolyps score, mean (SD) | 1.61 (2.35) | 0.057 (1.91) | **0.01** |
| Pre-treatment TNSS, mean (SD) | 7.76 (2.76) | 6.88 (2.92) | 0.28 |
| ΔTNSS, mean (SD) | 2.95 (4.11) | 2.24 (3.96) | 0.89 |
| Lund-Mackay score, mean (SD) | 21.6 (7.52) | 17.36 (9.14) | 0.10 |

Numbers in bold type were p<0.05.

Table S4. Characteristics of patients before treatment according to oral steroid and topical steroid.

| | Oral steroid treatment (n=58) | Topical steroid treatment (n=47) | p |
|---|---|---|---|
| male, n (%) | 32 (55.2) | 36 (78.2) | 0.5790 |
| age, year (SD) | 41.63 (12.707) | 43.74 (14.316) | 0.4280 |
| AR, n (%) | 6 (11.8) | 5 (9.3) | 0.6990 |
| AS, (%) | 15 (29.4) | 8 (14.8) | 0.1000 |
| Previous surgery, n (%) | 19 (37.3) | 9 (16.7) | **0.02** |
| Blood eosinophil count (×109/L), mean (SE) | 0.44 (0.23,0.56) | 0.14 (0.08,0.28) | **0.000** |
| eosinophil%, mean (SE) | 6.30 (2.80,7.80) | 2.00 (1.18,3.63) | **0.000** |
| TNSS, mean (SD) | 21.79 (6.986) | 20.82 (6.172) | 0.4520 |
| SNOT-22, mean (SD) | 41.74 (21.097) | 37.67 (17.128) | 0.3030 |
| NPSS, mean (SD) | 7.46 (2.146) | 7.47 (2.180) | 0.9880 |
| ΔTNSS, mean (SD) | 8.42 (6.757) | 5.13 (5.932) | **0.01** |
| ΔTNSS, 95%CI | .78, 5.785 | | |
| ΔNPSS, mean (SD) | 1.86 (1.952) | 1.17 (1.901) | 0.07 |
| ΔNPSS, 95% CI | -.062, 1.443 | | |
| ΔSNOT-22, mean (SD) | 13.10 (18.155) | 7.88 (11.956) | 0.107 |
| ΔSNOT-22, 95% CI | -1.154, 11.599 | | |

Numbers in bold type were p<0.05.

Table S5. Characteristics of patents in the long-term follow-up.

| | Biomarker-directed group (n=58) | Standard care group (n=29) | p |
|---|---|---|---|
| Follow-up time, mean (SD) month | 32(25,48) | 35(24,46) | 0.795 |
| Male, n (%) | 35 (51.7) | 17 (58.6) | 0.863 |
| Age, year (SD) | 40.2 (15.1) | 39.8 (14.6) | 0.783 |
| TNSS, mean (SD) | 2.19 (1.52) | 1.99 (1.31) | 0.431 |
| SNOT-22, mean (SD) | 12.21 (5. 35) | 11.73 (4.32) | 0.530 |

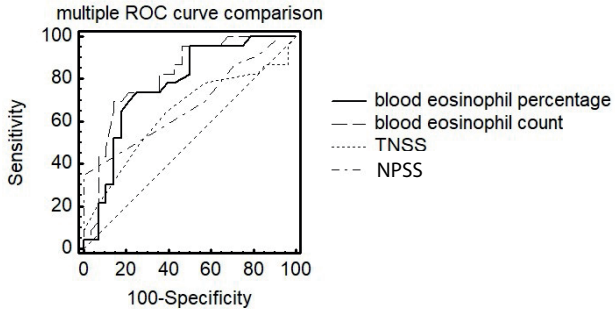



Figure S2. Multiple ROC curve comparison and optimal cut-off points for CS-sensitive NP in the retrospective study.