

Is nucleate cell count and neutrophil to lymphocyte ratio related to patients with audiographically distinct sudden sensorineural hearing loss?

Yuanyuan Sun, MD, Liang Xia, MD, Hui Wang, PhD, Zhengnong Chen, PhD, Yaqin Wu, MD, Bin Chen, PhD, Haibo Shi, PhD*, Yanmei Feng, PhD*, Shankai Yin, PhD

Abstract

The aim of this study was to investigate the possible relationships between sudden sensorineural hearing loss (SSNHL) patients with distinct audiographic data and nucleate cell count and neutrophil to lymphocyte ratio (NLR).

SSNHL patients differed in audiographic curves were included, 40 with low-frequency SSNHL (LF-SSNHL), 33 with high-frequency SSNHL (HF-SSNHL), 36 with all-frequency SSNHL (AF-SSNHL), 34 with total-deafness SSNHL (TD-SSNHL), and 31 age- and sex-matched healthy controls. Peripheral venous blood samples were collected and nucleate cell such as white blood cell (WBC), neutrophil and lymphocyte, and NLR were measured. Each group was divided into recovery and unrecovery subgroup according to hearing levels after 1-month therapy, and then compared the difference of the count of WBC, neutrophil and lymphocyte, and NLR between the 2 subgroups.

The WBC count of the HF-SSNHL, AF-SSNHL, and TD-SSNHL group was significantly higher than that of the control group ($P=.024$, $P=.003$, $P=.008$, respectively), not for LF-SSNHL group ($P=.248$). WBC count between LF-SSNHL and AF-SSNHL group was significantly different ($P=.045$). The neutrophil count of the HF-SSNHL, AF-SSNHL, and TD-SSNHL group was significantly higher than that of the control group ($P=.002$, $P=.000$, $P=.000$, respectively), not for LF-SSNHL group ($P=.069$). Neutrophil count of LF-SSNHL was significantly lower than that of AF-SSNHL and TD-SSNHL groups ($P=.014$, $P=.013$). The lymphocyte count of AF-SSNHL and TD-SSNHL group was significantly lower than that of the control group ($P=.027$, $P=.003$), not for LF-SSNHL and HF-SSNHL group ($P=.119$, $P=.054$). NLR of HF-SSNHL, AF-SSNHL, and TD-SSNHL group was significantly higher than that of the control group ($P=.001$, $P=.000$, $P=.000$, respectively), not for LF-SSNHL group ($P=.070$). NLR of LF-SSNHL was significantly lower than that of AF-SSNHL and TD-SSNHL group ($P=.041$, $P=.005$). In HF-SSNHL patients, lymphocyte count of unrecovery subgroup was significantly lower, while NLR of the unrecovery subgroup were significantly higher than those of recovery subgroup ($P=.017$, $P=.015$).

The count of WBC, neutrophil, lymphocyte, and NLR may be related to SSNHL, but they were unreliable at predicting SSNHL characterized by differences in audiometric curves. Higher NLR and lower lymphocyte count maybe used to evaluate prognosis of HF-SSNHL patients.

Abbreviations: AF-SSNHL = all-frequency SSNHL, HF-SSNHL = high-frequency SSNHL, LF-SSNHL = low-frequency SSNHL, NLR = neutrophil to lymphocyte ratio, SSNHL = sudden sensorineural hearing loss, TD-SSNHL = total deafness SSNHL, WBC = white blood cell.

Keywords: neutrophil to lymphocyte ratio, nucleate cell count, sudden sensorineural hearing loss

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Department of Otolaryngology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.

* Correspondence: Yanmei Feng, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, No. 600, Yishan Road, Xuhui District, Shanghai 200233, China (e-mail: feng.yanmei@126.com); Haibo Shi, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, No. 600, Yishan Road, Xuhui District, Shanghai 200233, China (e-mail: haibo99@hotmail.com).

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1. Introduction

Sudden sensorineural hearing loss (SSNHL) represents a common disease, with the most common diagnostic criteria of acute idiopathic hearing loss more than 20 dB at 2 continuous frequencies at least within 72 hours.^[1] Several epidemiological studies reported SSNHL incidence rates of 5 to 30 cases per 100,000 people per year in industrialized countries.^[2,3] SSNHL is generally unilateral, isolated and with variable clinical features in terms of hearing loss degree, accompanying symptoms, and post-treatment outcomes. Although the etiologies of most cases of SSNHL remain unknown, the Chinese guidelines for the diagnosis and treatment of sudden deafness (2015) and the German guidelines for the diagnosis of sudden idiopathic hearing loss (2004) stress that membranous labyrinthine edema may lead to low-frequency SSNHL (LF-SSNHL); hair cell damage may be relative to high-frequency SSNHL (HF-SSNHL); endothelial dysfunction or vasospasm can trigger all-frequency SSNHL (AF-SSNHL); and inner ear embolism or thrombosis may play an important role in the pathophysiology of total-deafness SSNHL (TD-SSNHL).^[1,4] Therefore, audiographic data are important when planning the treatment of SSNHL.

Nucleated cell count is an important part of blood examinations, which are simple and inexpensive, yielding information on not only red and white blood cell and platelet counts but also the cell subgroups present,^[5] blood coagulation, inflammation, thrombosis, and atherosclerosis.^[6] Several authors evaluated the role of nucleated cell count and NLR as risk and prognostic factors for SSNHL^[7–11]; however, few of them focused on the possible influence on the audiometric profile. Thus, we would like to explore that by using count of WBC, neutrophil and lymphocyte and NLR in terms of SSNHL pathogen and prognosis in such patients. Higher count of WBC and neutrophil and lower lymphocyte count are associated with inflammation; NLR is a marker of inflammation. We thus evaluated the roles played by inflammation in SSNHL patients who differed audiographically.

2. Materials and methods

This retrospective study enrolled 143 patients with SSNHL diagnosed at Shanghai Jiaotong University Affiliated Sixth People's Hospital. All work with humans adhered to the ethical standards of Shanghai Jiaotong University Affiliated Sixth People's Hospital. The study included 4 groups in terms of the pre-treatment audiographic features defined in the Chinese guidelines for the diagnosis and treatment of sudden deafness (2015)^[1]: 40 patients in LF-SSNHL group with hearing loss at 0.125 to 1 kHz or at both 0.25 and 0.5 kHz hearing loss ≥ 20 dB; 33 patients in HF-SSNHL group with high-frequency hearing loss at 2 to 8 kHz or at both 4 and 8 kHz ≥ 20 dB; 36 patients in AF-SSNHL group with overall hearing loss at all frequencies and mean pure-tone thresholds ≤ 80 dB; 34 patients in TD-SSNHL group with totally deaf (hearing loss at all frequencies and a mean pure tone threshold ≥ 81 dB). The control group contained 31 age- and sex-matched healthy individuals without hearing loss on regular check-ups. The subjects underwent a general physical examination; assessment of laboratory blood parameters. None of these individuals had an acute inflammation or otologic disease.

Patients were excluded from the study if they had any history of following: otitis media, otological surgery, acute or chronic inflammation, trauma, diabetes mellitus, hypertension, metabolic

syndrome, cancer, hepatitis, nephritis, heart failure, myocardial infarction, a cerebral embolism, Meniere disease, an autoimmune disease, chronic obstructive pulmonary disease, pregnancy, cor pulmonale, or for whom data were incomplete. All enrolled SSNHL patients were treated within 7 days from disease onset, without receiving previous therapy, and underwent both hematological assessment and pure-tone hearing testing during the first visit.

Pure tone audiometry was carried out in soundproof rooms to obtain the air and bone conduction thresholds at 125, 250, 500, 1, 2, 4, and 8 kHz. Fasting blood samples for all patients were obtained at the first visit to prevent adverse effects of steroids for high-risk patients with metabolic and/or cardio-cerebrovascular disease; all samples were drawn from the antecubital vein in the morning. And fasting blood samples of the controls were also taken in the morning.

We prescribed patients dexamethasone 10 mg/day (5 mg/mL; Furuitang Drug Industry, China) through intravenous for the first 3 days, then a progressively reductive dose was maintained for at least 1 week; vasodilators (Breviscapine injection, 40 mg/day; Kunming Longjin Pharmaceutical Co., Ltd, China) was injected for 2 weeks; oral neurotrophic factor (Extract of Ginkgo Biloba Leaves Tablets, 80 mg, tid, Dr. Willmar Schwabe) was given for 1 month. The treatment outcomes were evaluated referring the Chinese guidelines for the diagnosis and treatment of sudden deafness (2015)^[1] after 1-month therapy: complete recovery: the mean pure-tone thresholds of the impaired frequencies within 20 dB or reached to the level of the normal unaffected ear; notable recovery: the mean pure-tone thresholds of the impaired frequencies rose by ≥ 30 dB; partial recovery: the mean pure-tone thresholds of the impaired frequencies rose by ≥ 15 dB but < 30 dB; and no improvement: the pure-tone thresholds of impaired frequencies improved by < 15 dB.

Data analyses were performed with the statistical package for the social sciences (SPSS for Mac, version 24.0) software. Student *t* test and analysis of variance (ANOVA) were used to evaluate the significant differences in continuous variables with normally distributing. The χ^2 test was used to compare categorical variables. LSD post hoc test was applied to explore relationships of hematological parameters among audiographically distinct SSNHL. A *P* value $< .05$ was considered significant. GraphPad Prism version 7.0 for Mac was used to draw the figures.

3. Results

Table 1 summarizes demographic characteristics, nucleate cell count, and NLR of all groups. Each SSNHL group and control group did not differ significantly in terms of age and sex ($P = .952$; $\chi^2 = 1.062$, $P = .926$).

3.1. The count of WBC, neutrophil and lymphocyte, and NLR

Figure 1 shows that WBC count was $7.34 \pm 3.97 \times 10^9/L$, $8.25 \pm 3.24 \times 10^9/L$, $8.79 \pm 3.15 \times 10^9/L$, $8.56 \pm 2.86 \times 10^9/L$, and $6.48 \pm 1.45 \times 10^9/L$ in the LF-SSNHL, HF-SSNHL, AF-SSNHL, TD-SSNHL, and control groups, respectively. WBC count was significantly elevated in HF-SSNHL, AF-SSNHL, and TD-SSNHL group compared with the control group ($P = .024$, $P = .003$, $P = .008$ for HF-, AF-, and TD-SSNHL group, respectively); however, the difference of WBC count between LF-SSNHL and control group was not significant ($P = .248$). WBC count of LF-SSNHL group was significantly lower than

Table 1
Demographic and laboratory data.

Parameter	LF-SSNHL group (n=40)	HF-SSNHL group (n=33)	AF-SSNHL group (n=36)	TD-SSNHL group (n=34)	Control group (n=31)
Age, y	44.60±9.29	43.18±15.54	45.25±13.77	44.58±19.19	51.06±10.01
Sex, F/M	18/22	15/18	20/16	16/18	15/16
Tinnitus (%)	27 (67.5)	26 (78.79)	27 (75%)	28 (82.35)	–
Vertigo (%)	6 (15)	4 (12.12)	6 (16.67)	13 (38.24)	–
Ear fullness (%)	18 (45)	13 (39.39)	17 (47.22)	15 (44.12)	–

Ages are shown as means ± standard deviations.

AF-SSNHL=all-frequency SSNHL, HF-SSNHL=high-frequency SSNHL, LF-SSNHL=low-frequency SSNHL, SSNHL=sudden sensorineural hearing loss, TD-SSNHL=total-deafness SSNHL.

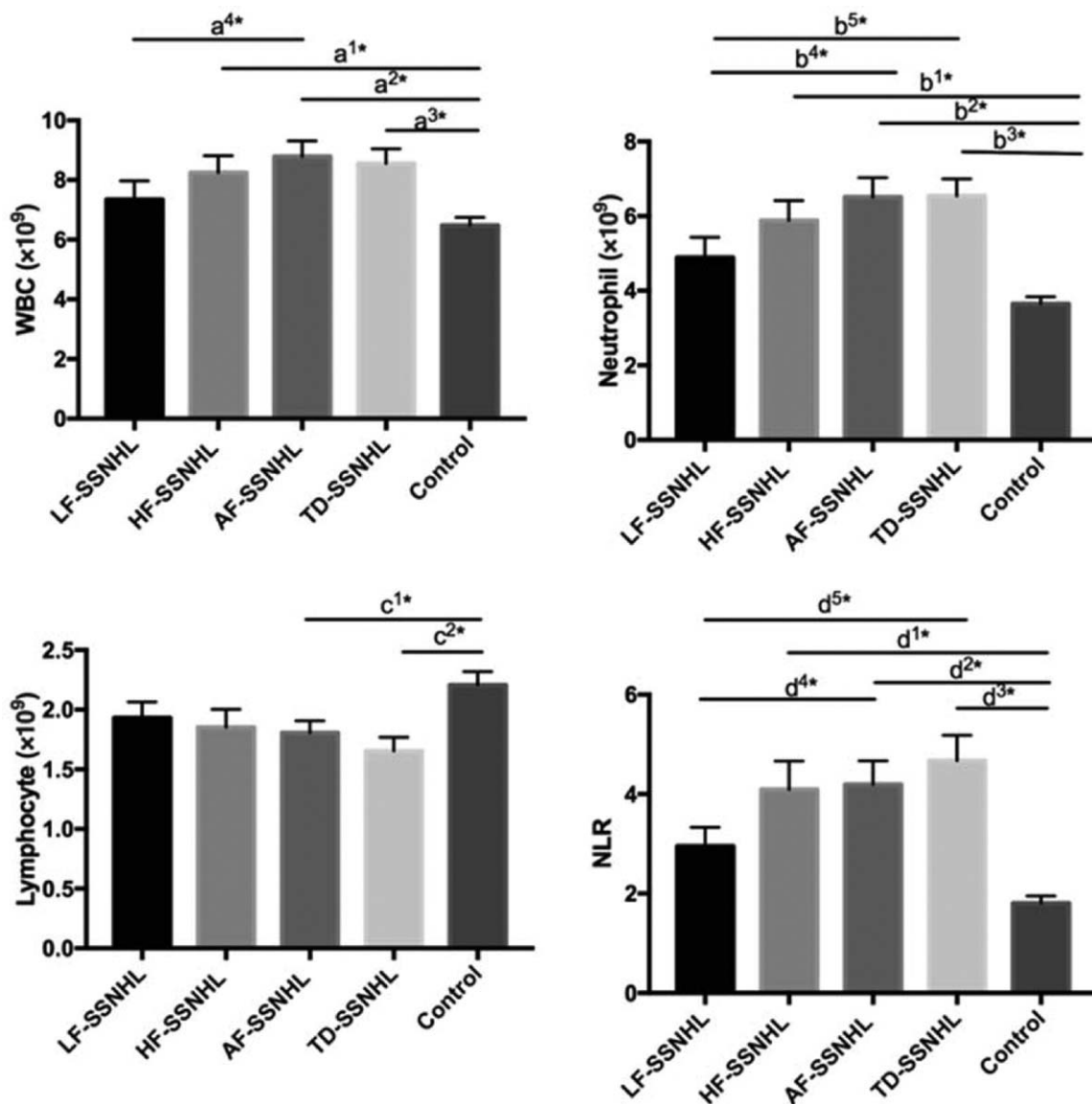


Figure 1. The difference of WBC, neutrophil, lymphocyte, and NLR between SSNHL groups and control group. The error bars indicate standard errors. AF-SSNHL=all frequencies SSNHL; HF-SSNHL=high frequencies SSNHL; LF-SSNHL=low frequencies SSNHL; NLR=neutrophil to lymphocyte ratio; SSNHL=sudden sensorineural hearing loss; TD-SSNHL=total deafness SSNHL; WBC=white blood cell. *Significant difference between 2 groups ($P < .05$). $a^1* = .024$, $a^2* = .003$, $a^3* = .008$, $a^4* = .045$; $b^1* = .002$, $b^2* = .000$, $b^3* = .000$, $b^4* = .014$, $b^5* = .013$; $c^1* = .027$, $c^2* = .003$; $d^1* = .001$, $d^2* = .000$, $d^3* = .000$, $d^4* = .041$, $d^5* = .005$.

Table 2**Treatment outcomes of SSNHL patients with different audiograms.**

	Case number	Complete recovery (%)	Remarkable recovery (%)	Partial recovery (%)	No improvement (%)	Total improvement (%)
LF-SSNHL group	40	34 (85)	0	0	6 (15)	34 (85)
HF-SSNHL group	33	5 (15.15)	1 (3.03)	5 (15.15)	22 (66.67)	11 (33.33)
AF-SSNHL group	36	4 (11.11)	6 (16.67)	8 (22.22)	18 (50)	18 (50)
TD-SSNHL group	34	1 (2.94)	4 (11.76)	5 (14.71)	24 (70.59)	10 (29.41)
Total number	143	44 (30.77)	11 (7.69)	18 (12.59)	70 (48.95)	73 (51.05)

AF-SSNHL = all-frequency SSNHL, HF-SSNHL = high-frequency SSNHL, LF-SSNHL = low-frequency SSNHL, SSNHL = sudden sensorineural hearing loss, TD-SSNHL = total-deafness SSNHL.

that of AF-SSNHL group ($P=.045$). The neutrophil count was $4.89 \pm 3.38 \times 10^9/L$, $5.88 \pm 3.06 \times 10^9/L$, $6.51 \pm 3.13 \times 10^9/L$, $6.54 \pm 2.67 \times 10^9/L$, and $3.65 \pm 1.02 \times 10^9/L$ in the LF-SSNHL, HF-SSNHL, AF-SSNHL, TD-SSNHL, and control groups, respectively. Neutrophil count of HF-SSNHL, AF-SSNHL, and TD-SSNHL group was significantly higher than that of control group ($P=.002$, $P=.000$, $P=.000$ for HF-, AF-, and TD-SSNHL group, respectively), however, not for LF-SSNHL group ($P=.069$). Neutrophil count of LF-SSNHL was significantly lower than that of AF-SSNHL and TD-SSNHL groups ($P=.014$, $P=.013$). The lymphocyte count was $1.93 \pm 0.84 \times 10^9/L$, $1.85 \pm 0.86 \times 10^9/L$, $1.81 \pm 0.59 \times 10^9/L$, $1.66 \pm 0.67 \times 10^9/L$, and $2.21 \pm 0.64 \times 10^9/L$ in the LF-SSNHL, HF-SSNHL, AF-SSNHL, TD-SSNHL, and control groups, respectively. Lymphocyte count was significantly lower in AF-SSNHL and TD-SSNHL group than in the control group ($P=.027$, $P=.003$), not for LF-SSNHL and HF-SSNHL group ($P=.119$, $P=.054$). The NLR was 2.95 ± 2.40 , 4.09 ± 3.27 , 4.19 ± 2.84 , 4.67 ± 2.97 , and 1.81 ± 0.81 in the LF-SSNHL, HF-SSNHL, AF-SSNHL, TD-SSNHL, and control group, respectively. The NLR of HF-SSNHL, AF-SSNHL, and TD-SSNHL SSNHL groups was significantly higher than control group ($P=.001$, $P=.000$, $P=.000$ for HF-, AF-, and TD-SSNHL group, respectively); however, the difference of NLR between LF-SSNHL and control group was not significant ($P=.070$). NLR of LF-SSNHL was significantly lower than that of AF-SSNHL and TD-SSNHL groups ($P=.041$, $P=.005$).

3.2. Subgroup analysis

All patients were divided into subgroups based on whether or not they recovered (complete, notable, and partial recovery) after 1 months of treatment with steroids, batroxobin, vasodilators,

neurotrophic factors. The recovery rates were 85%, 33.33%, 50%, and 29.41% in the LF-SSNHL, HF-SSNHL, AF-SSNHL, and TD-SSNHL groups, respectively. Table 2 details the treatment outcomes. Table 3 lists the nucleate cell count and NLR of all SSNHL groups. Lower lymphocyte and higher NLR of the HF-SSNHL recovery subgroup was observed than that of unrecovery subgroup ($P=.017$, $P=.015$); no other parameter differed significantly among the subgroups ($P=.674$, $P=.433$, $P=.793$, $P=.764$ for LF-SSMHL group; $P=.763$, $P=.683$ for HF-SSNHL; $P=.801$, $P=.561$, $P=.555$, $P=.567$ for AF-SSNHL; $P=.693$, $P=.758$, $P=.991$, $P=.525$ for TD-SSNHL, respectively).

4. Discussion

The opinion that SSNHL subgrouped by reference to different audiographic features may indicate different disease mechanisms and the optimal treatments should thus vary was stressed by both the Chinese and the German guidelines.^[1,4] Recently, many authors studied that nucleate cell count and NLR as risk factors and potential prognostic biomarkers for SSNHL, tried to understand the main pathogenetic mechanism of hearing loss onset, often with contradictory conclusions. However, only few studies have explored the relationships between SSNHL subgrouped by audiographic data and nucleate cell count. Therefore, we determined whether significant relationships were evident between various SSNHL audiographic patterns and nucleate cell count.

Our major findings were that the WBC and neutrophil count and NLR of the HF-SSNHL, AF-SSNHL, and TD-SSNHL group, and lymphocyte count of AF-SSNHL and TD-SSNHL group were significantly different from that of control group. WBC

Table 3**The blood routine parameters of the recovered and unrecovered group of 4 study groups.**

	LF-SSNHL group (n=34)		HF-SSNHL group (n=28)		AF-SSNHL group (n=32)		TD-SSNHL group (n=32)	
	Recovery subgroup (n=34)	Unrecovery subgroup (n=6)	Recovery subgroup (n=11)	Unrecovery subgroup (n=22)	Recovery subgroup (n=18)	Unrecovery subgroup (n=18)	Recovery subgroup (n=10)	Unrecovery subgroup (n=24)
WBC, $\times 10^9/L$	7.23 ± 4.12	7.98 ± 3.22	8.49 ± 3.78	8.13 ± 3.02	8.65 ± 3.00	8.92 ± 3.39	8.25 ± 2.46	8.68 ± 3.05
Neutrophil, $\times 10^9/L$	4.83 ± 3.48	5.23 ± 3.05	5.56 ± 3.20	6.05 ± 3.05	6.19 ± 2.97	6.82 ± 3.33	6.55 ± 2.69	6.54 ± 2.73
Lymphocyte, $\times 10^9/L$	1.89 ± 0.83	2.18 ± 0.93	2.35 ± 1.02	$1.47 \pm 0.60^{*,\dagger}$	1.87 ± 0.61	1.75 ± 0.58	1.60 ± 0.80	1.68 ± 0.62
NLR	2.90 ± 2.29	3.23 ± 1.32	2.58 ± 1.26	$4.85 \pm 3.71^{*,\ddagger}$	3.92 ± 2.96	4.47 ± 2.77	5.19 ± 3.24	4.46 ± 2.90

All data are means \pm standard deviations.

AF-SSNHL = all-frequency SSNHL, HF-SSNHL = high-frequency SSNHL, LF-SSNHL = low-frequency SSNHL, NLR = neutrophil-to-lymphocyte ratio, SSNHL = sudden sensorineural hearing loss, TD-SSNHL = total-deafness SSNHL.

* A significant difference was evident between those who recovered and those who did not.

\dagger .017.

\ddagger .015.

count of LF-SSNHL was significantly lower than that of AF-SSNHL group. Neutrophil count and NLR of LF-SSNHL was significantly lower than that of AF-SSNHL and TD-SSNHL group. These indicated that WBC, neutrophil, lymphocyte, and NLR maybe related to SSNHL, but they could not be used to classify the different types of SSNHL. Maybe we need further research with expanded number to find the possible biomarkers to distinguish different audiology features. Besides, the results are interesting that LF-SSNHL looks quite different from the rest of the groups in terms of the blood examination, which may be related to the membranous labyrinthine edema, consistent with mechanism we referred to.

On the basis of the therapy outcome, each SSNHL group was divided into recovery subgroup and unrecovery subgroup. Lower lymphocyte count and higher NLR of the HF-SSNHL unrecovery subgroup was observed than recovery subgroup. This indicated that lower lymphocyte count and higher NLR could be used to predict the prognosis of HF-SSNHL patients.

Higher WBC and neutrophil count and lower lymphocyte count are associated with inflammation response, and the NLR is used to evaluate the extent of systemic inflammation.^[5] NLR is recognized as an independent predictor of cardiovascular disease.^[11–14] SSNHL has been considered to be associated with inflammation, which can be explained by the perfect treatment outcome of dexamethasone.

Durmus et al^[7] found that NLR was significantly higher in SSNHL patients who did not recover than in those who did, emphasizing the predictive utilities of these parameters in terms of prognosis. Ozler^[15] described possible associations between high NLR levels and SSNHL, suggesting that inflammation might play a significant role in SSNHL pathogenesis; higher NLR values were indicative of a poorer prognosis.^[8] In addition, Seo et al^[10] and Ulu et al^[16] found that the NLR of SSNHL patients were significantly higher in those who remain unrecovered than in those who recovered; a higher NLR was thought to reflect high-level inflammation in the former group. Moreover, Yoo et al found that NLR was elevated in patients with both recurrent and nonrecurrent SSNHL, but were higher in the latter patients.

In our data, the difference of lymphocyte count was shown significantly different between AF-SSNHL and TD-SSNHL patients and controls, and lymphocyte count of the HF-SSNHL unrecovery subgroup was significantly higher than that of recovery subgroup. Both Seo et al^[10] and we found that the levels of lymphocytes were decreased to levels just below the normal value, but Seo et al^[10] emphasized that these findings could not be considered abnormal. Moreover, İkinçiogullari et al^[17] and Masuda et al^[18] found no correlation between the lymphocyte count and the recovery rate. Nonetheless, others have suggested that high white blood cell count and reduced lymphocyte count are associated with poorer recovery from hearing loss.^[8,18,19]

Recently, Salvago et al^[20] compared differences in routine blood parameters (fibrinogen level; activated partial thromboplastin time; prothrombin time; hemoglobin, white blood cell, neutrophil, lymphocyte levels, NLR, platelet count, and hematocrit) among SSNHL patients whose audiograms differed. They found that lymphocyte percentage was lower in those with HF-SSNHL hearing loss than in others; however, neither the white blood cell count nor the NLR differed significantly between patients varying in terms of audiographic data,^[20] which were similar to those of our present report.

There were other limitations in our study. The patients we included were all inpatients, which usually have higher stress levels than those healthy individuals, resulting in higher cortisol

levels. It is well known that the cortisol can cause the marginated neutrophils to enter the circulation. Also, cortisol may affect the lymphocyte count.^[21] These differences between the control and SSNHL patients may introduce bias favoring a higher NLR in the SSNHL patients. Besides, we need to analyze more inflammatory cytokines before we can explain the possible correlations between SSNHL audiographically distinct and inflammation markers.

5. Conclusion

The most important findings are that count of WBC, neutrophil and lymphocyte, and NLR maybe relate to SSNHL onset, but they were unreliable at predicting SSNHLs characterized by differences in audiometric curves. Higher NLR and lower lymphocyte count maybe used to evaluate prognosis of HF-SSNHL patients.

Author contributions

Conceptualization: Yuanyuan Sun, Liang Xia, yanmei feng.

Data curation: Yuanyuan Sun, Liang Xia, yanmei feng.

Formal analysis: Yuanyuan Sun, Liang Xia, yanmei feng.

Funding acquisition: yanmei feng, Shankai Yin.

Investigation: Yuanyuan Sun, Liang Xia, Hui Wang.

Methodology: Yuanyuan Sun.

Project administration: Hui Wang, Zhengnong Chen, Yaqin Wu.

Resources: Yaqin Wu, Haibo Shi, Shankai Yin.

Supervision: Hui Wang, Zhengnong Chen, Yaqin Wu, Bin Chen, Haibo Shi.

Validation: Bin Chen, Haibo Shi.

Writing – original draft: Yuanyuan Sun.

Writing – review & editing: yanmei feng.

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