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MISCELLANEOUS

Investigation of the prognostic role of neutrophil-to-lymphocyte ratio in Idiopathic Sudden Sensorineural Hearing Loss based on propensity score matching: a retrospective observational study

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Abstract

Introduction The aetiology, management and prognosis of idiopathic Sdden Sensorineural Hearing Loss (ISSNHL) are still uncertain despite adequate investigation.

Objective We conducted the present study to investigate the possible relationship between the neutrophil-to-lymphocyte ratio (NLR) and the prognosis of ISSNHL based on PSM.

Methods This was a retrospective observational study. Data and statistical analyses were performed using the SPSS statistical program (SPSS 19.0). PSM was performed using STATA (15.0).

Results NLR = 3.42 was the cut-off value. After PSM, 84 pairs of patients were successfully matched. The number of patients in the effective group with the NLR < 3.42 and NLR < 3.42 were significantly different ($P < 0.001$).

Conclusion The NLR is an inexpensive and reliable index to predict the ISSNHL. We hold the view that the NLR can be a reliable factor for clinical doctors to predict the prognosis in ISSNHL. To further prove that the NLR is a powerful prognostic factor in ISSNHL, larger prospective studies are required in the future.

Keywords Neutrophil-to-lymphocyte ratio · Idiopathic Sudden Sensorineural Hearing Loss · Propensity score matching · Prognosis role

Introduction

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is a common medical emergency, that is defined as a hearing loss of more than 30 dB and no less than 3 consecutive frequencies in one or both ears [1, 2]. The aetiology of ISSNHL is thought to be multifactorial [3]. Viral infections, chronic inflammation, immunological diseases and impairment of the vascular microcirculation have been suggested as possible reasons [4]. In addition, factors such as mental tension, stress, emotional fluctuation, irregular life and sleep obstacles are also considered being associated with the prevalence of ISSNHL. Many studies have been were designed to investigate the prognostic factors of ISSNHL, and factors such as the type of audiogram, duration and severity of hearing loss, age, accompanying symptoms, and gene polymorphism are considered to affect recovery from ISSNHL [5–10]. It still has no identifiable aetiology despite adequate investigation. To help doctors diagnose and manage patients with ISSNHL, the guideline has been updated [2]. However, the aetiology, management and prognosis of ISSNHL is still uncertain. A meta-analysis published earlier by our team showed that four indices of blood routine examination (NLR, PLR, neutrophil count and lymphocyte count) can be recommended to predict the management outcomes in patients with ISSNHL [11]. The routine blood examination is an important blood test in clinical practice. Some haematological indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and red cell distribution width (RDW) have been considered as inexpensive markers to predict the prognosis of ISSHL in some recent studies [12–14]. However,

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we found that the studies included in the meta-analysis had relatively poor quality, and almost all had the obvious limitation of non-matched subjects that led to selection bias and affected the accuracy of the research results. Propensity score matching (PSM) is a popular method that can help us avoid selection bias in retrospective studies and strengthen the credibility of the research. Therefore, we conducted the present study to investigate the possible relationship between the neutrophil-to-lymphocyte ratio (NLR) and the prognosis of ISSNHL based on PSM.

Materials and methods

This research is a retrospective observational study. The flow diagram for study subject screening and grouping is shown in Fig. 1. To be included in the study, we selected patients without any type of otitis media, a history of otologic surgery, recent use of ototoxic medications, recent trauma or barotraumas, cerebellopontine angle pathology or congenital cochlear malformations on MRI, neurologic disorders predisposing to hearing loss, or neoplasm within the previous 2 years; patients lost to follow-up were not included. The data were collected from The Second Affiliated Hospital Yuying Children Hospital of Wenzhou Medical University from 2016 to 2019. Based on this inclusion and exclusion criteria, 245 patients diagnosed with ISSNHL were included. All patients were treated with corticosteroid intervention (methylprednisolone 80 mg/day for three days and 40 mg/day for another three days), and neurotrophic drugs. Some patients with vertigo were given anti-vertigo drugs. If there is contraindication, prednisone cannot be used. The contraindications include medical conditions affected by prednisone such as tuberculosis and peptic ulcer disease; prednisone is also contraindicated in insulin-dependent or poorly controlled diabetes [2]. The patients underwent a series of physical examinations, assessments of laboratory blood parameters and a cranial MRI before treatment; pure tone audiometry (PTA) evaluations were conducted pre and post treatment. According to the two PTA evaluations, we obtained the hearing changes after the treatment. Based on the Siegel's criteria of hearing improvement [15] (Table 1), the patients were grouped into either the effective group (complete recovery, partial recovery improvement and slight improvement) or ineffective group (no improvement) based on the outcomes. The group defined in this way was based on the earlier studies [13, 16].

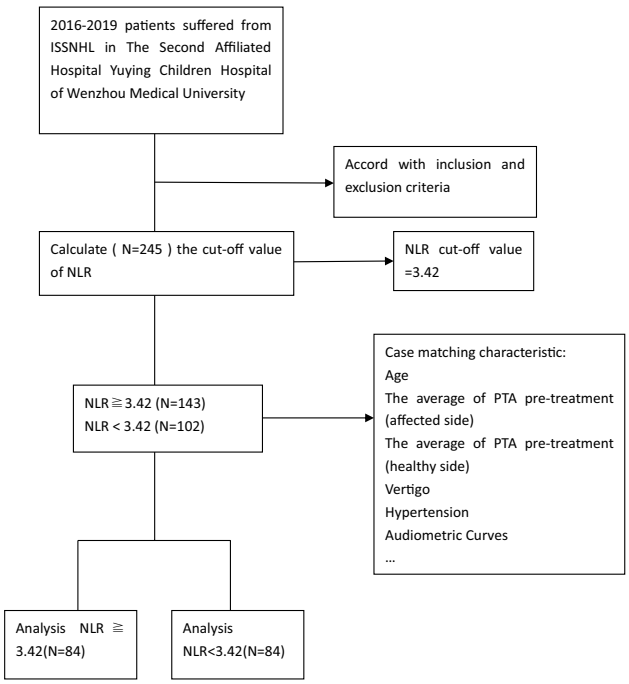

Fig. 1 Flow chart of the study

We collected standard demographic and clinicopathological data, including sex; age; affected side; body mass index (BMI); concomitant symptoms such as vertigo and tinnitus, lifestyle factors such as drinking and smoking, systemic disease such as hypertension and diabetes, audiometric curves; the average of the pure tone audiometry evaluations conducted pre and post treatment, time to treatment initiation, and haematological parameters collected before treatment (conclude neutrophil, lymphocyte, monocyte, platelet, red cell distribution width, platelet distribution width, mean platelet volume, NLR; LMR and PLR).

Statistical analyses

Data and statistical analyses were performed using the SPSS statistical program (SPSS 19.0). Measurement data that conformed to the normal distribution were expressed as $\bar{x}\pm S$ and

Table 1 Siegel's criteria of hearing improvement

Hearing recovery	Definition
Complete recovery	Patients having a final hearing level better than 25 dB regardless of the size of the gain
Partial recovery	Patients having a gain of more than 15 dB and having a final hearing level between 25 and 45 dB
Slight recovery	Patients having a gain of more than 15 dB and having a final hearing level poorer than 45 dB
No improvement	Patients having a gain less of than 15 dB

the differences between clinicopathological characteristics grouped by NLR were examined by independent sample *T* test. The count data were expressed by rate or constituent ratio, and the difference was examined by the x^2 test. *P* values lower than 0.05 were defined as statistically significant. PSM was performed using STATA (15.0).

Propensity score matching

To overcome selection biases in this research, we performed a 1:1 match for each patient by using propensity score matching (PSM). Eighty-four pairs of patients were successfully matched using 14 covariates: sex, age, affected side, body mass index (BMI), concomitant symptoms such as vertigo and tinnitus, lifestyle factors such as drinking and smoking, systemic disease such as hypertension and diabetes, audiometric curves, the average of pure tone audiometry evaluations pre and post treatment, and time to treatment initiation.

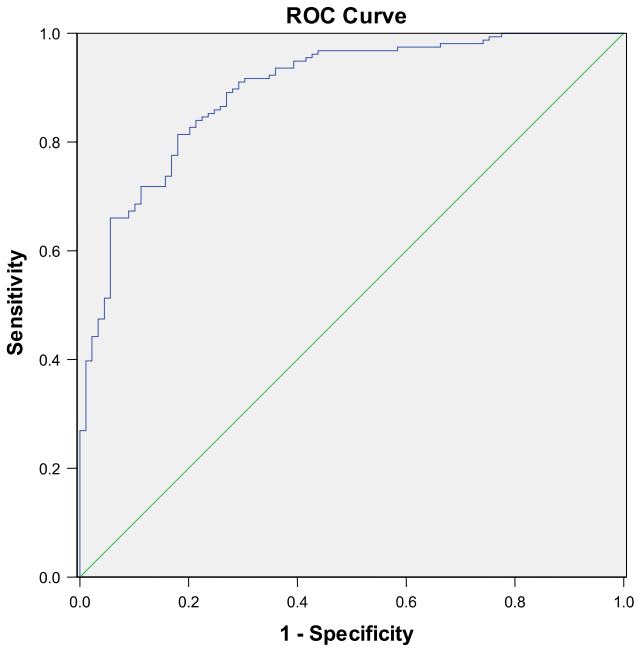

Fig. 2 ROC curve. ROC receiver operating characteristic

Results

Receiver operating curve characteristic analysis (Fig. 2)

The continuous variable NLR was defined as the test variable, and the outcomes were used as the state variable. The area under the ROC curve for NLR was 0.895 (95% confidence interval [CI], 0.856–0.935; $P < 0.001$;). For all the patients, the NLR = 3.42 had the highest Youden index (0.634). The sensitivity was 81.4% and the specificity was 82.0%. Accordingly, NLR = 3.42 was the cut-off value selected.

Characteristics of low and high NLR for ISSHL before PSM (Table 2)

The data of 245 patients (143 patients with NLR > 3.42, and 102 patients with NLR < 3.43) were analyzed by using SPSS19.0.Comparing the low NLR group with the high NLR group, age ($P = 0.021$), the average pre-treatment PTA on the affected side ($P = 0.007$), the average pre-treatment PTA on the health side ($P = 0.021$), concomitant symptoms such as vertigo ($P = 0.017$), systemic disease such as hypertension ($P = 0.029$), and the audiometric curve ($P < 0.001$) were with significantly different ($P < 0.05$).

Characteristics of low and high NLR for ISSHL after PSM (Table 3)

After PSM, 84 pairs of patients were successfully matched. Characteristics such as sex, age, affected side, body mass index (BMI), concomitant symptoms such as vertigo and tinnitus, lifestyle factors such as drinking and smoking, systemic disease such as hypertension and diabetes, the audiometric curves, the average of the pure tone audiometry evaluations pre and post treatment, and time to treatment initiation were all without significant differences. The number of patients in the effective group with an NLR < 3.42 and NLR ≥ 3.42 were significantly different ($P < 0.001$).

Discussion

Some studies indicate that 32–65% of cases of ISSNHL may recover spontaneously [1, 17, 18]. However, in some clinical studies, this rate of spontaneous recovery may be overestimated [2]. Due to the unknown prognosis of hearing loss and tinnitus, many patients have a strong desire for treatment. However, not all patients can recover from ISSNHL. The unknown aetiology makes the treatment and prognosis uncertain. Many studies have examined the treatment and prognosis of ISSNHL [7, 14, 19]. In the updated guideline, the treatments for ISSNHL include systemic and topical steroids, herbal and other complementary and alternative treatments, hyperbaric oxygen therapy (HBOT) and other medications [2, 10]. Systemic steroid therapy is currently the most widely accepted treatment [2, 7, 20, 21]. The prognosis for recovery from ISSNHL can be influenced by a number of factors, such as age, accompanying symptoms such as vertigo, degree of hearing loss, audiometric configuration, and time to treatment initiation [1, 10, 19, 22, 23]. The

Table 2 Characteristics of low and high NLR for ISSHL before PSM

Characteristic	Total ($n=245$)	NLR ≥ 3.42 ($n=143$)	NLR < 3.42 ($n=102$)	P
Age	45.66 ± 18.51	47.87 ± 20.27	42.57 ± 15.30	0.021
Time to treatment initiation	5.22 ± 3.26	5.52 ± 3.43	4.78 ± 2.96	0.79
BMI	22.55 ± 3.38	22.34 ± 3.57	22.86 ± 3.08	0.229
The average of PTA pre-treatment (affected side)	59.46 ± 16.51	61.84 ± 15.36	56.14 ± 17.53	0.007
The average of PTA pre-treatment (healthy side)	27.35 ± 21.17	29.87 ± 23.15	23.82 ± 17.55	0.021
Affected side				
Left	127	77	50	
Right	118	66	52	0.517
Sex				
Male	117	65	52	
Female	128	78	50	0.437
Tinnitus				
Yes	225	130	95	0.693
No	20	13	7	
Vertigo				
Yes	76	53	23	
No	169	90	79	0.017
Drink				
Yes	22	10	12	0.257
No	223	133	90	
Smoke				
Yes	28	20	8	0.157
No	217	123	94	
Hypertension				
Yes	37	28	9	0.029
No	208	115	93	
Diabetes				
Yes	13	11	2	0.079
No	232	132	100	
Audiometric curves				
Low frequencies affected	25	8	17	< 0.001
High frequencies affected	36	28	8	
Flat descending	105	53	52	
Total deafness	79	54	25	

meta-analysis published earlier by our team showed that the NLR is recommended for predicting the management outcomes of ISSNHL [11]. However, we found that the studies included in the meta-analysis had relatively poor quality, and almost all had the obvious limitation of non-matched subjects that led to selection bias and affected the accuracy of the research results.

PSM is developing into an increasingly popular method for controlling the effects of characteristics in retrospective studies. Our study used PSM to control the effects of confounding variables to determine the relationship between prognosis in ISSNHL and NLR. Characteristics including age, vertigo, degree of hearing loss, the audiometric curves, and time to treatment initiation are thought to influence prognosis. A study showed that lifestyle factors such as smoking and drinking, a history of diabetes and hypertension and body mass index, may influence ISSNHL [24]. Sex is an important demographic characteristic. Tinnitus is a common symptom in ISSNHL. Affected side is also a major characteristic in diseases. These factors are all included in the selection of covariates. Few studies clearly specify the standard process of the variable selection [25, 26]. The selection of variables for inclusion in PSM is still a challenge to us [27, 28]. The bias in the remaining variable will have a great influence on the final analysis results.

Before PSM, we found that characteristics such as age ($P=0.021$), average PTA pre-treatment (affected side) ($P=0.007$), average PTA pre-treatment (healthy

Table 3 Characteristics of low and high NLR for ISSHL after PSM

characteristic	Total ($n=168$)	NLR > =3.42 ($n=84$)	NLR < 3.42 ($n=84$)	P
Age	45.67 ± 17.23	45.10 ± 19.17	44.04 ± 15.14	0.691
Time to treatment initiation	5.20 ± 3.35	5.29 ± 3.69	5.11 ± 3.00	0.731
BMI	22.68 ± 3.22	22.53 ± 3.39	22.83 ± 3.04	0.545
The average of PTA pre-treatment (affected side)	58.57 ± 17.09	59.39 ± 16.40	57.75 ± 17.81	0.534
The average of PTA pre-treatment (healthy side)	25.95 ± 18.14	25.94 ± 17.94	25.95 ± 18.45	0.997
Affected side				
Left	76	38	38	1.000
Right	92	46	46	
Sex				
Male	96	48	48	1.000
Female	72	36	36	
Tinnitus				
Yes	154	77	77	1.000
No	14	7	7	
Vertigo				
Yes	47	25	22	0.731
No	121	59	62	
Drink				
Yes	9	4	5	1.000
No	159	80	79	
Smoke				
Yes	9	4	5	1.000
No	159	80	79	
Hypertension				
Yes	15	7	8	1.000
No	153	77	76	
Diabetes				
Yes	5	3	2	1.000
No	163	81	82	
Audiometric curves				
Low frequencies affected	14	4	10	0.145
High frequencies affected	25	20	5	
Flat descending	82	35	47	
Total deafness	47	25	22	
Outcome				
Yes	69	11	58	< 0.001
No	99	73	26	

side) ($P=0.021$), vertigo ($P=0.017$) and hypertension ($P=0.029$) were significantly different between patients with NLR ≥ 3.42 and patients with NLR < 3.42. After PSM, P values for the comparison of these factors between patients with NLR ≥ 3.42 and patients with NLR < 3.42 were all > 0.05. These factors all had no effect on the association between ISSNHL and NLR. The outcome was still significantly different between the two groups ($P<0.001$).

In this study, the pre-treatment NLR is considered to be a useful and powerful predictor of prognosis in ISSNHL. The outcome after PSM ($P<0.001$) was significantly different between the NLR ≥ 3.42 group and NLR < 3.42 group. A previous study considered viral infection as the cause of ISSNHL, but there was no strong evidence [29]. In recent years, chronic inflammation has been considered the cause of ISSNHL. Some studies have indicated that

ISSNHL is an immunological disease [30, 31]. The role of impairment of the vascular microcirculation has also been considered by some researchers [32].Additionally, other theories such as the cochlear membrane rupture theory, have also been suggested by some studies [33–35]. Viral infections, chronic inflammation, immunological diseases, impairment of the vascular microcirculation and cochlear membrane rupture theory have been suggested as possible reasons [4]. A study found that a high level of neutrophils was associated with poor prognosis in ISSNHL [36]. Other studies also indicated the relationship between cochlear damage and inflammatory factors [37]. Routine blood examination is an important blood test in clinical practice. The neutrophil and lymphocyte counts play essential roles in reflecting the inflammation. The ratio of neutrophil and lymphocyte is also important in detecting inflammation. A high level of NLR may indicate a high level of inflammation [16]. Many studies have reported that the NLR may be a prognostic parameter in cardiovascular diseases, cancers, renal disease, Alzheimer's disease and other inflammatory diseases [26, 38–40]. Some studies have been published to show the relationship between the NLR and prognosis in ISSNHL. A study published by Seo indicated the prognosis role of neutrophil and lymphocyte rate in ISSNHL [16]. A comment published by Sertogle suggested that Seo's research may have been affected by confounding factors. Additional statistical analyses that can take all factors into account may be performed [41]. Our study took almost all factors into account. Thus, our results may be credible.

The NLR is an inexpensive and reliable index to predict ISSNHL prognosis. We hold the view that the NLR can be a reliable factor for clinical doctors to predict the prognosis of ISSNHL. This study has several limitations. First, this was a retrospective study, and selection bias may have existed because of the small the sample size, despite attempting to use PSM to control the bias. Second, the consensus of the NLR thresholds in different populations remains disputed. We need to establish a definitive cut-off value for the NLR in further studies in this field. Finally, if the NLR was deemed a predictor of ISSNHL, the cut-off should be assessed more accurately in future research. To further prove that the NLR is a powerful prognostic factor in ISSNHL, larger prospective studies are required in the future.

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Compliance with ethical standards

Conflict of interest We do not have any conflict of Interest.

Ethical approval Our study is a retrospective observational study, the institutional of ethics committee did not require formal approval.

Informed consent Our study is a retrospective observational study, the informed consent did not require formal approval.

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