



# BMJ Open Correlation between neutrophil to lymphocyte ratio and overactive bladder in South Korean women: a community-based, cross-sectional study

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## ABSTRACT

**Objective** Many women with overactive bladder (OAB) do not seek medical care despite urinary symptoms. As the diagnosis and treatment of OAB are often late, there is a need to identify undiagnosed OAB patients and start effective treatment. Furthermore, an objective and appropriate screening biomarker for OAB is needed. This study aimed to investigate the relationship between serum neutrophil-to-lymphocyte ratio (NLR) and OAB in South Korean women.

**Design** Cross-sectional, retrospective study.

**Setting** Jeju National University Hospital.

**Participants** This study included a total of 4394 women (mean age=48.6 years) who underwent self-referred health screenings.

**Interventions** Blood tests were conducted and the NLR was calculated by dividing the number of neutrophils by the number of lymphocytes.

**Outcome measures** The severity of OAB was evaluated using the OAB Symptom Score (OABSS).

**Results** Approximately 9.8% of participants (n=432) were diagnosed with OAB. The association pattern between the NLR and urinary tract symptoms was variable; however, NLR was associated with OAB, by the OABSS and OAB severity ( $p<0.001$ ). The NLR had a significant relationship with OAB after age, body mass index, homeostatic model assessment for insulin resistance, 25-hydroxyvitamin D, stress status, and medication for hypertension (OR 1.19, 95% CI 1.06 to 1.32) were adjusted.

**Conclusions** Elevated NLR is associated with OAB; hence, NLR may be a cost-effective and readily available biomarker of OAB in women.

## INTRODUCTION

Overactive bladder (OAB) is a chronic disease with an overall prevalence in the adult population of above 10% and increases with age.<sup>1</sup> According to a study involving adults aged over 40 years in South Korea, 8%, 11%, 12% and 29% of women with only storage, storage plus voiding, storage plus postmicturition, and all three lower urinary tract symptoms (LUTS), respectively, consult healthcare professionals regarding urinary symptoms. In

## Strengths and limitations of this study

- This is the first study that examined the relationship between NLR and overactive bladder (OAB).
- In this study, we used OAB Symptom Score, which is validated and widely used to assess the OAB status.
- As this was a cross-sectional study, caution should be exercised in implying any causal associations.

contrast, 73%–83% of women with LUTS, including storage symptoms, seek healthcare for any other reason.<sup>2</sup> This indirectly shows that OAB healthcare is not being delivered properly in South Korea.

Symptoms of OAB significantly affect self-esteem, family relations, sexual relations and perceived health status.<sup>3</sup> In addition, increased severity of OAB is associated with impaired quality of life, reduced workplace productivity and increased anxiety and depression.<sup>4</sup> In South Korea, the estimated total economic cost of treating OAB including medical expenditures, pharmacological costs, traffic expenses and labour productivity loss was ₩145 billion in 2007.<sup>5</sup> Considering the increasing burden on individuals and society resulting from the late diagnosis and treatment of OAB, there is a need to actively seek out undiagnosed OAB patients and start effective treatment.

According to a survey, most women who had discussed OAB symptoms with a healthcare provider in the USA had waited for 3.1 years (mean) after symptoms occur. Moreover, it took over a year for the majority of those women who discussed OAB symptoms with a healthcare provider to seek treatment.<sup>3</sup> Among patients with OAB symptoms who had never discussed their problems with a healthcare provider, 71% said that the reason was that the doctor did not ask about OAB symptoms.<sup>3</sup> Hence, it is important to find an

objective and appropriate screening biomarker to identify OAB high-risk groups, even for healthy women who do not complain of any particular symptom. Thus, OAB high-risk groups can be identified and treated properly at an early stage by additional questions, following the use of biomarkers.

Chronic inflammation is one of the major causes of OAB. Biopsies of the bladder of OAB patients, revealed inflammatory cells in the lamina propria and the urothelium of the bladder.<sup>6</sup> Inflammation-associated proteins including monocyte chemotactic protein-1 and the soluble fraction of the CD40 ligand in urine of OAB patients was also higher than those of asymptomatic controls.<sup>7</sup> In addition, the concentrations of C reactive protein (CRP), nerve growth factor (NGF), interleukin-1b (IL-1b), IL-6, IL-8 and tumour necrosis factor- $\alpha$  in the serum of OAB patients refractory to antimuscarinic therapy were higher than those of asymptomatic controls.<sup>8</sup>

After systemic inflammation, the number of circulating lymphocytes decreases. Lymphocytopenia occurs because lymphocytes attach to the inner walls of blood vessels, are redistributed to the lymphatic system, and apoptosis is accelerated. On the contrary, the number of circulating neutrophils increases. Neutrophilia, the opposite phenomenon, occurs because neutrophils separate from the inner walls of blood vessels, apoptosis is delayed and growth factors (such as granulocyte colony stimulating factor) continue to stimulate stem cells.<sup>9</sup> The neutrophil-to-lymphocyte ratio (NLR) is given by the number of neutrophils divided by the number of lymphocytes. Neutrophils and lymphocytes are components of routine blood count analyses commonly practiced in clinics. Systemic inflammation measured by NLR has a significant association with prevalent chronic conditions and the use of the NLR as an inflammatory marker has been reported in previous articles.<sup>10</sup> The NLR was higher in a group of individuals with high metabolic syndrome scores than in a control group.<sup>11</sup> The elevated NLR has also been associated with poor prognosis in a variety of diseases including atherosclerosis, coronary artery disease,<sup>12</sup> chronic obstructive pulmonary disease,<sup>13</sup> non-metastatic clear renal cell carcinoma,<sup>14</sup> melanoma,<sup>15</sup> breast cancer<sup>16</sup> and gastrointestinal cancer.<sup>17</sup>

Therefore, this study aimed to investigate the relationship between serum NLR and OAB in South Korean women.

## METHODS

### Participants and study design

This cross-sectional study retrospectively reviewed medical records of adult women over the age of 19 years who underwent a self-referred health screening at the Jeju National University Hospital from April 2015 to January 2019. The participants underwent blood tests including complete blood cell (CBC) test and completed the Korean version of the OAB Symptom Score (OABSS) questionnaire. Women who were being treated for cancer,

and acute urinary tract infection checked by urinalysis were excluded. Finally, a total of 4390 women participated in this study.

### Korean version of the OABSS

The Korean version of the OABSS is a self-administered questionnaire about OAB symptoms (online supplemental table S1). Its translation and linguistic validation were done by Jeong *et al.*<sup>18</sup> This questionnaire consists of four questions including daytime frequency, nocturia, urgency and urgency incontinence. Urgency is a key symptom of OAB, such that OAB is diagnosed when the urgency score  $\geq 2$  and OABSS  $\geq 3$ .<sup>19</sup> The symptoms of OAB are categorised as mild (OABSS  $\leq 5$ ), moderate ( $6 \geq$  OABSS  $\leq 11$ ) and severe (OABSS  $\geq 12$ ).

### Demographics, anthropometric measurement and biochemical data

A self-administered questionnaire was used to collect information on participants' age, health, medical history, current medication, and social history (smoking, drinking, exercise). The Korean-translated Brief Encounter Psychosocial Instrument (BEPsi-K)<sup>20</sup> was used to measure participants' mental stress.

Body mass index (BMI) was calculated by dividing body weight (kg) by height in metres squared ( $m^2$ ). Waist circumference was measured by a trained nurse with a measuring tape. Body fat percentage was assessed by a bioelectrical impedance analysis machine (InBody 720; InBody, Seoul, Korea). Hand grip strength was measured by a hand dynamometer (Jamar 5030J1; Sammons Preston, Bolingbrook, Illinois, USA).

Blood sampling was done after the participants fasted for a minimum of 10 hours. Blood tests included CBC, serum albumin, uric acid, high-sensitivity CRP (hs-CRP), thyroid-stimulating hormone, and 25-hydroxyvitamin D (25-OH-vitamin D). Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using the formula: insulin ( $\mu$ IU/mL)  $\times$  fasting plasma glucose (mg/dL)  $\times 0.05551 / 22.5$ .<sup>21</sup> NLR was calculated by dividing the number of neutrophils by the number of lymphocytes.

### Statistical analysis

Baseline characteristics were analysed by dividing the participants into two groups. One group included participants not diagnosed with OAB and the other group included participants diagnosed with OAB. Baseline characteristics values were calculated using a two tailed t-test and  $\chi^2$  test. Baseline characteristics were reported for all participants as mean with SD or numbers (percentage). One-way analysis of variance and the Jonckheere-Terpstra test were used to analyse the correlation between NLR and urinary tract symptoms. All statistical analyses were performed using SPSS software (V.22.0; SPSS) and STATA software V.15.0 (StataCorp).

### Patient and public involvement

No patients were involved in the design, recruitment or conduct of the study.

**Table 1** Baseline characteristics according to OAB status

	No OAB (median $\pm$ SD)	OAB (median $\pm$ SD)	P value
Age, year	47.0 $\pm$ 10.7	53.0 $\pm$ 13.2	<0.001
Height, cm	157.8 $\pm$ 5.5	156.4 $\pm$ 5.8	<0.001
Weight, kg	57.7 $\pm$ 8.5	58.9 $\pm$ 8.7	0.0822
Body mass index, kg/m <sup>2</sup>	23.2 $\pm$ 3.3	23.8 $\pm$ 3.6	<0.001
Waist circumference, cm	79.0 $\pm$ 8.4	81.5 $\pm$ 9.2	<0.001
Body fat, %	33.2 $\pm$ 6.0	34.2 $\pm$ 7.0	<0.001
Grip strength, kg	24.3 $\pm$ 4.7	22.9 $\pm$ 5.0	<0.001
White cell count, 10 <sup>9</sup> /L	4.9 $\pm$ 1.4	4.9 $\pm$ 1.6	0.1481
Neutrophil, 10 <sup>3</sup> / $\mu$ L	2.6 $\pm$ 1.1	2.7 $\pm$ 1.2	0.0085
Lymphocyte, 10 <sup>3</sup> / $\mu$ L	1.7 $\pm$ 0.5	1.6 $\pm$ 0.5	0.0829
NLR	1.6 $\pm$ 0.8	1.6 $\pm$ 0.9	0.0009
Albumin, g/dL	4.2 $\pm$ 0.2	4.1 $\pm$ 0.2	0.0012
Uric acid, mg/dL	4.6 $\pm$ 1.0	4.6 $\pm$ 1.1	0.7522
hs-CRP, mg/L	0.05 $\pm$ 0.29	0.06 $\pm$ 0.22	0.2339
HOMA-IR	1.3 $\pm$ 1.3	1.3 $\pm$ 1.5	0.0179
TSH, $\mu$ IU/mL	1.9 $\pm$ 1.7	1.8 $\pm$ 1.9	0.5985
25-OH-vitamin D, ng/mL	17.2 $\pm$ 10.5	18.4 $\pm$ 10.2	0.0271
OABSS	1.0 $\pm$ 1.1	5.0 $\pm$ 2.3	<0.001
Hypertension	384 (9.7%)	91 (21.1%)	<0.001
Diabetes mellitus, n (%)	119 (3.0%)	37 (8.6%)	<0.001
Angina or MI, n (%)	46 (1.2%)	7 (1.6%)	0.4078
Chronic liver disease or LC, n (%)	22 (0.6%)	4 (0.9%)	0.3413
Chronic kidney disease, n (%)	7 (0.2%)	0 (0.0%)	0.3818
Current smoking	156 (3.9%)	22 (5.1%)	0.2553
Alcohol consumption	513 (13.0%)	45 (10.4%)	0.1337
Regular exercise	878 (22.2%)	86 (19.9%)	0.2781
BEPSI-K			<0.001
Low stress	2108 (53.3%)	165 (38.2%)	
Moderate stress	1541 (38.9%)	200 (46.3%)	
High stress	309 (7.8%)	67 (15.5%)	

Data are presented as mean $\pm$ SD or n (%). Values were calculated using a t-test and  $\chi^2$  test.

BEPSI-K, Brief Encounter Psychosocial Instrument - Korean version; HOMA-IR, homoeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C reactive protein; LC, Liver cirrhosis; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; OAB, overactive bladder; OABSS, OAB Symptom Score; 25-OH-vitamin D, 25-hydroxy vitamin D; TSH, thyroid-stimulating hormone.

## RESULTS

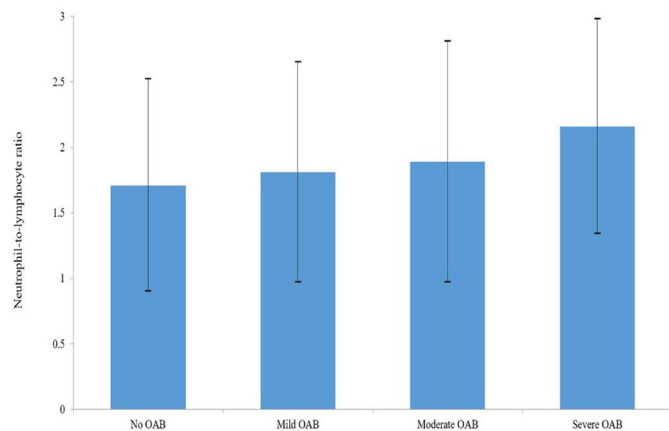
### Baseline characteristics

Approximately 9.8% of participants (n=432) were diagnosed with OAB. The mean $\pm$ SD OABSS of participants not diagnosed and diagnosed with OAB was 1.1 $\pm$ 1.1 and 5.9 $\pm$ 2.3, respectively. The participants with OAB had a higher mean age, BMI, waist circumference, body fat ratio, and lower grip strength than the other group. The prevalence of hypertension, diabetes and the stress on BEPSI-K were higher in the participants with OAB than those in the other group. There was no statistically

significant difference between whole white cell count and hs-CRP (table 1).

### NLR and OAB symptoms and severity

The pattern of association between the NLR and the OAB symptoms was variable (online supplemental table S2). Daytime frequency, night-time frequency, frequency of urinary urgency and frequency of urge incontinence were not statistically significantly when associated with NLR. In the case of daytime frequency, NLR increased as frequency increased, but there was no statistical significance (p=0.290). The NLR was 1.81 when night-time



**Figure 1** Neutrophil-to-lymphocyte ratio (NLR) and overactive bladder (OAB) severity calculated using one-way analysis of variance and the Jonckheere-Terpstra test. Relationship between NLR and OAB severity.

frequency was  $\geq 3$  times, higher than when the frequency was  $\leq 2$  times ( $p=0.403$ ). For urinary urgency, NLR (2.01) was highest when the frequency was  $\geq 2$  times per day ( $p=0.071$ ). The NLR of urge incontinence was highest when the frequency was one or more times per week or once daily. The NLR was relatively low when there was no urinary incontinence (1.72), or when it occurred less than once per week (1.73). The NLR was lowest when urinary incontinence occurred  $>5$  times a day (1.69) ( $p=0.101$ ). The severity of OAB was classified as no OAB, mild OAB, moderate OAB and severe OAB according to the OABSS. Mean $\pm$ SD NLR for participants without OAB and with severe OAB symptoms were  $1.71\pm 0.81$  and  $2.16\pm 0.82$ , respectively. There was a significant relationship between NLR and OAB severity ( $p<0.001$ ) (figure 1).

Multivariate analysis models were used to evaluate OAB and NLR. Model 1 was unadjusted, model 2 was adjusted for age and BMI, and model 3 was adjusted for age, BMI, HOMA-IR, 25-OH vitamin D level, antihypertensive medications, diabetes and BEPSI-K score. NLR was

significantly correlated with OAB in model 1 (OR 1.18; 95% CI 1.03 to 1.05,  $p<0.001$ ), model 2 (OR 1.21; 95% CI 1.10 to 1.34;  $p<0.001$ ) and model 3 (OR 1.15; 95% CI 1.02 to 1.30;  $p=0.021$ ) (table 2).

## DISCUSSION

In our study, the NLR in women with OAB was significantly higher than the NLR in women without OAB. Furthermore, NLR was closely linked with the severity of OAB, assessed by the OABSS.

The previously studied OAB biomarkers include NGF and CRP. NGF is produced by the human urinary bladder, which has sensory fibres that express high-affinity tropomyosin receptor kinase A (TrkA). NGF binds to TrkA and is involved in neuronal differentiation and survival.<sup>22</sup> According to a study investigating NGF levels in women with OAB, urinary NGF/creatinine (Cr) was significantly elevated in OAB patients compared with healthy subjects. When a cut-off value of 0.12 for NGF/Cr was used as a diagnostic criterion, sensitivity was 85.2% and a specificity was 65.4%. NGF/Cr did not correlate with symptom severity assessed by OAB-Validated 8 (OAB-V8) questionnaire and Incontinence Questionnaire Short Form (ICIQ-SF). There was no significant difference in NGF/Cr after antimuscarinic treatment had been done for 4 weeks ( $p=0.063$ ), even though there was a statistically significant difference in both OAB-V8 and ICIQ-SF scores.<sup>23</sup> However, in another study conducted on OAB patients, urinary NGF/Cr levels significantly decreased ( $p=0.03$ ) after fesoterodine treatment had been administered for 16 weeks, as well as the OABSS and the Overactive Bladder Questionnaire.<sup>24</sup> Therefore, it is still unclear whether NGF can reflect the effect of treatment and the prognostic value of NGF seems to be limited since it does not represent symptom severity. Another drawback of NGF is that it requires a rather complex method, ELISA, for its measurement

**Table 2** Multivariate analysis of overactive bladder and NLR

	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (97% CI)	P value
NLR	1.18 (1.07 to 1.31)	<0.001	1.21 (1.10 to 1.34)	<0.001	1.15 (1.02 to 1.30)	0.021
Age			1.04 (1.03 to 1.05)	<0.001	1.04 (1.03 to 1.06)	<0.001
BMI			1.04 (1.01 to 1.07)	0.017	1.02 (0.98 to 1.06)	0.323
HOMA-IR					0.97 (0.88 to 1.06)	0.524
25-OH-vitamin D					1.00 (0.99 to 1.01)	0.675
Hypertension					1.42 (1.06 to 1.96)	0.037
Diabetes					1.80 (0.96 to 2.45)	0.072
BEPSI-K					1.81 (1.56 to 2.12)	<0.001

Model 1: unadjusted; model 2: adjusted for age, BMI; model 3: adjusted for age, BMI, HOMA-IR, 25-OH vitamin D, current medication for hypertension, diabetes, BEPSI-K score. Values were calculated using a multivariable logistic regression analysis.

.BEPSI-K, Brief Encounter Psychosocial Instrument; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; NLR, neutrophil-to-lymphocyte ratio; 25-OH-vitamin D, 25-hydroxy vitamin D.



CRP is an acute phase protein. It is actively produced as the concentration of serum IL-6 and other cytokines increases.<sup>25</sup> A study investigating the association between OAB and serum CRP in patients with benign prostatic hyperplasia demonstrated the correlation between the OABSS and the serum CRP levels. However, that study could not find the relationship between the serum CRP level and the degree of chronic prostatic inflammation evaluated by the MECA-79+/CD34 +vessel ratio, showing that serum CRP level is associated with storage dysfunction and not prostatic inflammation.<sup>26</sup> Furthermore, serum CRP is readily influenced by systemic inflammatory conditions and is not specific to OAB. Real-time PCR was used to quantify CRP expression in the bladder, and it was found that CRP synthesis was unlikely to occur in the bladder. This showed that urinary CRP is an unsuitable biomarker for bladder inflammation.<sup>27</sup>

The fundamental mechanism of neutrophilia is the activation of the stem cell growth factor, which stimulates neutrophil production.<sup>9</sup> At the beginning of the inflammatory reaction, the tumour necrosis factor family induces lymphocyte apoptosis, which is why lymphocytopenia is a diagnostic marker of infection.<sup>28</sup> Neutrophils may release reactive oxygen species and several peptides, such as antimicrobial peptides, forming neutrophil extracellular traps and adversely affecting the bladder.<sup>29</sup> These results are in line with a previous study suggesting that increased neutrophil-specific chemokines, such as GRO- $\alpha$  and MIP-1 $\beta$ , infiltrate the bladder tissue from urine in OAB patients.<sup>30</sup>

NLR is an objective index that can be derived easily from routinely performed blood tests. Moreover, compared with existing biomarkers, it is cost-effective, readily available and easily calculated. Accordingly, NLR can be readily adopted by clinical practices. NLR is helpful in deciphering whether symptomatic or asymptomatic outpatients have a disease, as well as predicting the prognosis of a disease.

This was a cross-sectional study and there was a limitation in proving causality between OAB and NLR elevation because it is not possible to determine the order of their incidence. Since NLR is influenced by various factors, such as race, gender, age, and underlying diseases, each study reports different reference values of NLR. A study of the mean NLR and racial differences in the USA reported that the mean NLR was lower in blacks and Hispanic patients than in non-Hispanic white patients.<sup>31</sup> Oestrogen and progesterone increase neutrophil count. Thus, a study involving healthy adults in South Korea showed a significant decrease in neutrophil count in women older than 40 years. Furthermore, NLR was shown to be higher in women than men aged <50 years, whereas this is reversed in age groups >51 years.<sup>32</sup> Similarly, the NLR differs depending on various factors including race and age. However, in this study, age was not considered in determining the NLR cut-off point. Moreover, this study included only South Koreans, thus, the results of this study are difficult to apply universally.

This study has several advantages. To our knowledge, this is the first study to reveal a correlation between NLR and OAB, and to suggest the possibility of using NLR as an OAB biomarker. Many studies have reported on the relationship between OAB and chronic inflammation, and OAB biomarkers.<sup>6-9</sup> However, research on the effectiveness of NLR as an OAB biomarker has been insufficient. Second, this study evaluated OAB using the validated OABSS. In 2011, the OABSS was translated into Korean,<sup>18</sup> and the Korean version was reported to be sensitive to symptomatic changes after treatment.<sup>33</sup> The OABSS short questionnaire is suitable for use even in the primary care setting due to its simplicity and practicality.

## CONCLUSION

The findings of our study demonstrate the relationship between elevated NLR and OAB in healthy women and suggests the possibility that NLR could be used as an OAB biomarker. If NLR elevation is observed, even in women who do not complain of any particular symptoms, additional consultation by a healthcare provider may be necessary because of the possibility of developing OAB. With further studies on proper NLR cut-off points, validity for the special attention will be increased.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** The study design and protocol were reviewed and approved by the institutional review board of Jeju National University Hospital (2020-03-041). The need for informed consent was waived due to the retrospective nature of the study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. The datasets used for analyses in this study are not publicly available as they are register based data, but are available from tropiajh@gmail.com on reasonable request.

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