Original Research

Optimal Fasting Insulin Cutoff Value to Predict Clinical and/or Biochemical Hyperandrogenism in Korean Women with Polycystic Ovary Syndrome

Seula Lee[1], Hyeonjun An[2], Soojin Rhee[1], Sungwook Chun[1,2,]*

[1]Department of Obstetrics and Gynecology, Inje University College of Medicine, Haeundae Paik Hospital, 48108 Busan, Republic of Korea
[2]Inje University College of Medicine, 47392 Busan, Republic of Korea
*Correspondence: wooki1974@empal.com (Sungwook Chun)

Abstract

Background: Insulin resistance and compensatory hyperinsulinemia play a critical role in the development of hyperandrogenism (HA) in polycystic ovary syndrome (PCOS) patients. To the best of our knowledge, however, few studies have determined the optimal fasting insulin cutoff value to predict HA in PCOS patients. Through this study, we aimed to investigate the optimal cutoff values for insulin and homeostatic model assessment for insulin resistance (HOMA-IR) to predict HA in women with PCOS. **Methods**: One hundred forty-eight women whose menarche occurred over eight years ago and were newly diagnosed with PCOS with irregular menstrual cycles (IM) and polycystic ovaries (PCO) using ultrasound after ruling out other etiologies were enrolled in this study. In this study, participants were categorized into two groups: those with clinical or biochemical HA (the IM/PCO/HA group) and those without HA (the IM/PCO group). To assess the relationship between androgen levels, including total testosterone (TT) and free testosterone (FT), and fasting glucose and insulin levels and HOMA-IR values, we performed correlation analysis using Spearman's rank correlation coefficient. We used receiver operating characteristic (ROC) analysis to identify the optimal cutoff values for fasting insulin and HOMA-IR to predict HA in PCOS patients. **Results**: Fasting glucose and insulin levels and HOMA-IR values were significantly different between the IM/PCO/HA and IM/PCO groups. TT and FT levels exhibited significant correlations with fasting glucose and insulin levels and HOMA-IR values. The ROC analysis identified the most suitable fasting insulin cutoff value of 9.85 µU/mL with an area under the ROC curve (AUC) of 0.817 (60.7% sensitivity and 91.3% specificity) for predicting HA in women with PCOS. The ROC analysis also showed a HOMA-IR value of 2.22 as the optimal cutoff value for predicting HA (AUC, 0.820; 60.7% sensitivity, and 92.4% specificity). **Conclusions**: Our results support the classical concept that hyperinsulinemia contributes to HA in PCOS patients. Women with PCOS with fasting insulin levels of 9.85 µU/mL or higher (approximately ≥ 10 µU/mL) are strongly suspected to have HA.

Keywords: insulin resistance; hyperinsulinemia; hyperandrogenism; polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is a prevalent metabolic and endocrine disorder that predominantly affects women of reproductive age [1]. It is characterized by hyperandrogenism (HA), chronic anovulation, and/or polycystic ovary (PCO), as shown by ultrasound [2].

Although no single etiological factor fully explains the range of abnormalities associated with PCOS, insulin sensitivity has been identified as an important factor in the pathophysiology of PCOS [3–6]. There are numerous factors that influence fasting insulin levels: medical conditions (diabetes mellitus (DM), insulinoma, pancreatic disease, Cushing's syndrome, acromegaly, etc.), obesity, and medication use (corticosteroids, sulfonylurea, oral contraceptives, etc.). According to a systemic review, insulin sensitivity was lower in women with PCOS than in controls [7]. It is widely acknowledged that obesity contributes to insulin sensitivity, and it is known that the prevalence of obesity and overweight is relatively high in women with PCOS [8].

Insulin resistance (IR) is the opposite of insulin sensitivity, meaning that decreased insulin sensitivity corresponds to increased IR, which means that IR can be confirmed by evaluating insulin sensitivity [9]. Although the hyperinsulinemic-euglycemic clamp (HEC) is considered the gold standard for evaluating insulin sensitivity/resistance, its application in clinical settings is often hindered by practical challenges related to cost and technical requirements. Therefore, several insulin sensitivity assessment indices (ISAIs) have been employed as surrogate indicators for evaluating insulin sensitivity and resistance [9,10]. Among these ISAIs, homeostatic model assessment for insulin resistance (HOMA-IR) stands as the predominant surrogate marker used in clinical research, offering the advantage of decreased time and cost while maintaining a reasonable level of accuracy [10].

Several studies have investigated the relationship between IR and HA in PCOS patients, providing evidence that hyperinsulinemia contributes to the development of HA [3,6,11–13]. Compensatory hyperinsulinemia fol-

lowing IR stimulates ovarian theca cells to produce and secrete higher amounts of androgens, and in addition, IR/hyperinsulinemia also promotes androgen synthesis in the adrenal gland and inhibits follicular maturation, which induces anovulation and HA, both of which are characteristic features of PCOS. Furthermore, insulin increases the concentration of free testosterone (FT) in the blood by inhibiting the production of sex hormone binding globulin (SHBG) in the liver [3,6,11–13]. HA is one of the key diagnostic criteria for PCOS, and it acts as both a cause and effect of the various major clinical features of PCOS. Various markers to assess androgen status, such as SHBG, total testosterone (TT), and the free androgen index (FAI), have been used to reveal the association between IR and HA in PCOS patients, and it is suggested that these markers can predict IR in women with PCOS [14–18]. However, since hyperinsulinemia contributes to HA, it seems more reasonable to identify an insulin cutoff value to predict HA than to determine an androgen cutoff value to indicate IR. To the best of our knowledge, studies on the optimal fasting insulin cutoff value for predicting HA in PCOS patients are still lacking.

In this research, we aimed to identify optimal cutoff values for IR, particularly for fasting insulin and HOMA-IR, as a means of predicting HA in women with PCOS.

2. Materials and Methods

2.1 Subjects

This study, which was conducted at Inje University Haeundae Paik Hospital, recruited Korean women aged 21 to 35 years who were newly diagnosed with PCOS based on ultrasound examination showing PCO and irregular menstrual cycles (IM). The research was carried out from January 2010 to December 2013. It had been 8 or more years since menarche for the participants. PCOS was diagnosed according to the international guidelines for PCOS, excluding other etiologies [2,19]. Clinical HA was diagnosed when hirsutism with a modified Ferriman–Gallwey score of 6 or higher, which is a standard examination, was present [19]. Biochemical HA was defined when serum androgen levels were beyond the upper level of the 95% confidence interval of the normal population using the results of previous studies conducted in Korean women (FT level >1.72 pg/mL and/or TT level >0.68 ng/mL) [20].

Patients were excluded from this research for the following reasons: a current or previous diagnosis of diabetes or treatment with antidiabetic medications; current or past diagnoses of hyperprolactinemia or thyroid disease; underwent ovarian surgery; and using medications known to impact gonadotropin levels or sex hormones within 6 months before enrollment, such as glucocorticoids, oral contraceptives, antiandrogens, or ovulation induction agents [21–25]. According to the above criteria, a total of one hundred forty-eight PCOS patients were included in this research. The participants were categorized into two groups: the group

with clinical or biochemical HA (IM/PCO/HA group) and the group without HA (IM/PCO group). This retrospective cohort study was approved by the institutional review board of the university hospital, which waived the need to obtain patient informed consent for the present research.

2.2 Ultrasound Examinations and Measurement of Anthropometric Parameters

All study participants underwent pelvic ultrasound imaging in accordance with international guideline [26], and the definition of PCOS in this study was 20 or more follicles measuring 2–9 mm per ovary and/or an ovarian volume $\geq$10 cm^3 [19]. Clinical characteristics of all participants were recorded, including age, parity, weight, height, hip circumference, and waist circumference, during their initial visit to the outpatient department.

2.3 Biochemical Measurements and Calculation of Homeostatic Model Assessment for Insulin Resistance

Blood samples from all participants were collected in the early follicular phase after overnight fasting, following the guidelines of the Helsinki Declaration. Serum total testosterone (TT) levels were measured using the Elecsys Testosterone II assay (Roche, Indianapolis, IN, USA), while free testosterone (FT) levels were measured using the Free Testo-RIA-CT test (DIA Source, Louvain, Belgium). Serum glucose was evaluated using the L-Type GluI device (Wako, Osaka, Japan), and insulin levels were measured using the Elecsys Insulin assay (Roche, Basel, Switzerland) [23–25]. The intra- and interassay coefficients of variation for all analyses were less than 8%.

HOMA-IR was calculated as follows: insulin value (μU/mL) $\times$ glucose value (mg/dL)/405.

2.4 Statistical Analyses

The values of variables are presented as the mean $\pm$ standard deviation (SD). To compare continuous variables between the IM/PCO/HA and IM/PCO groups, unpaired *t*-tests were used. Spearman's rank correlation coefficients were calculated to evaluate the relationships among androgen levels (including TT and FT), insulin levels, fasting blood glucose levels, and HOMA-IR values. Partial correlation analysis was conducted to account for the potential influences of other anthropometric measurements. Using data from all participants, ROC (receiver operating characteristic) analysis was performed to determine the optimal cutoff values for both fasting insulin and HOMA-IR in predicting HA in PCOS. The ideal threshold was defined as the cutoff value that maximized the sum of sensitivity and specificity. IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses in this study, and a significance level of $p < 0.05$ was considered to indicate statistical significance.

Table 1. Baseline laboratory and clinical characteristics of participants with clinical or biochemical hyperandrogenism and those without hyperandrogenism among women with polycystic ovary syndrome.

	Group 1 (n = 92)	Group 2 (n = 56)	p value
Age (years)	26.79 ± 3.79	26.00 ± 4.31	0.243
Parity	0.14 ± 0.43	0.14 ± 0.44	0.983
Height (cm)	162.98 ± 5.67	161.40 ± 5.80	0.106
Body weight (kg)	57.34 ± 14.14	62.92 ± 16.34	0.037*
Body mass index (kg/m^2)	21.56 ± 5.10	24.02 ± 5.41	0.007**
Waist to hip ratio	0.77 ± 0.06	0.82 ± 0.09	0.001**
Fasting glucose (mg/dL)	88.53 ± 6.39	95.07 ± 14.47	0.002**
Fasting insulin (μU/mL)	6.13 ± 3.33	20.33 ± 21.94	<0.001**
HOMA-IR (fasting)	1.35 ± 0.77	5.08 ± 6.42	<0.001**
Total testosterone (ng/mL)	0.33 ± 0.18	0.55 ± 0.18	<0.001**
Free testosterone (pg/mL)	0.61 ± 0.58	2.40 ± 0.66	<0.001**

Values are presented as mean ± standard deviation. p-value was obtained by unpaired t test. *, $0.01 < p < 0.05$; **, $p < 0.01$. HOMA-IR, homeostasis model assessment of insulin resistance.

3. Results

Table 1 compares the baseline laboratory and clinical parameters between the IM/PCO/HA and IM/PCO groups. The comparative analysis utilizing unpaired t tests revealed significant differences between the two groups in terms of fasting glucose levels, insulin levels, and HOMA-IR values.

All clinical parameters, i.e., HOMA-IR values, fasting glucose levels, and insulin levels, except for age were significantly correlated with TT and FT levels (Table 2 and Fig. 1). Even after considering adjustments for other anthropometric covariates, such as waist-to-hip ratio (WHR) and body mass index (BMI), these findings remained consistent (data not shown).

The ROC analysis identified the optimal fasting insulin cutoff point to be 9.85 μU/mL with an area under the ROC curve (AUC) of 0.817 (60.7% sensitivity and 91.3% specificity) for predicting HA in women with PCOS (Fig. 2). The ROC analysis revealed that a HOMA-IR value of 2.22 was identified as the optimal threshold for predicting HA (AUC, 0.820; 60.7% sensitivity and 92.4% specificity).

Group 1 included patients who were diagnosed with polycystic ovary syndrome (PCOS) with irregular menstrual cycles and polycystic ovaries on ultrasound but without hyperandrogenism, and Group 2 included patients who were diagnosed with PCOS with irregular menstrual cycles and polycystic ovaries on ultrasound and hyperandrogenism.

4. Discussion

In patients with PCOS, HA is not only the cause of clinical symptoms such as hirsutism, acne, and alopecia but

Table 2. Correlations of total testosterone and free testosterone with insulin resistance-related parameters.

	Total testosterone		Free testosterone	
	r	p	r	p
Age	–0.011	0.893	–0.147	0.074
Body mass index	0.245	0.003**	0.254	0.002**
Waist-to-hip ratio	0.258	0.004**	0.221	0.015*
Fasting glucose (mg/dL)	0.290	<0.001**	0.355	<0.001**
Fasting insulin (μU/mL)	0.360	<0.001**	0.541	<0.001**
HOMA-IR (fasting)	0.366	<0.001**	0.547	<0.001**

r, Spearman's rank correlation coefficient. *, $0.01 < p < 0.05$; **, $p < 0.01$. HOMA-IR, homeostasis model assessment of insulin resistance.

also a key etiological cause of characteristic symptoms of PCOS such as anovulation and metabolic disorders. In addition, IR is a common metabolic characteristic in PCOS patients and can directly or indirectly contribute to HA [3,6]. IR has been identified as a major contributor to the pathophysiology of PCOS, and IR plays a pivotal role in the development of HA in PCOS patients. However, studies on the optimal insulin cutoff value to predict HA in PCOS patients are still insufficient. We aimed to confirm the positive correlation between HA and IR and to investigate the optimal cutoff values of insulin and HOMA-IR, a representative ISAI, to predict HA in women with PCOS. We determined that the optimal cutoff values for predicting hyperandrogenism in women with PCOS were 9.85 μU/mL (approximately 10 μU/mL) for fasting insulin and 2.22 for HOMA-IR.

A single fasting insulin level test is a commonly used method for discriminating IR. However, fasting insulin levels may not reflect the severity of IR [27]. In the diabetic state with fasting hyperglycemia, an inappropriately low level of fasting insulin is not sufficient to maintain euglycemia, and it has been suggested that more useful surrogate indices, rather than fasting insulin only, should be taken into account [27]. In the present study, we made efforts to mitigate the impact of other medical conditions and the use of medications on fasting insulin levels, and specifically, we excluded patients with diabetes who were taking antidiabetic medications.

As mentioned above, IR and HA are the key pathophysiological factors that can elucidate the various clinical manifestations of PCOS [3–6]. Several studies have suggested that insulin exerts both direct and indirect effects on the development of HA in PCOS patients [3,6]. Women with PCOS face an elevated risk of developing glucose intolerance and type 2 diabetes mellitus and IR is a common feature in these patients, leading to compensatory hyperinsulinemia [5,6]. Hyperinsulinemia stimulates the production of androgens in the ovaries, increases androgen bioavailability, and hinders the synthesis of SHBG, leading to elevated levels of FT, thus contributing to the develop-
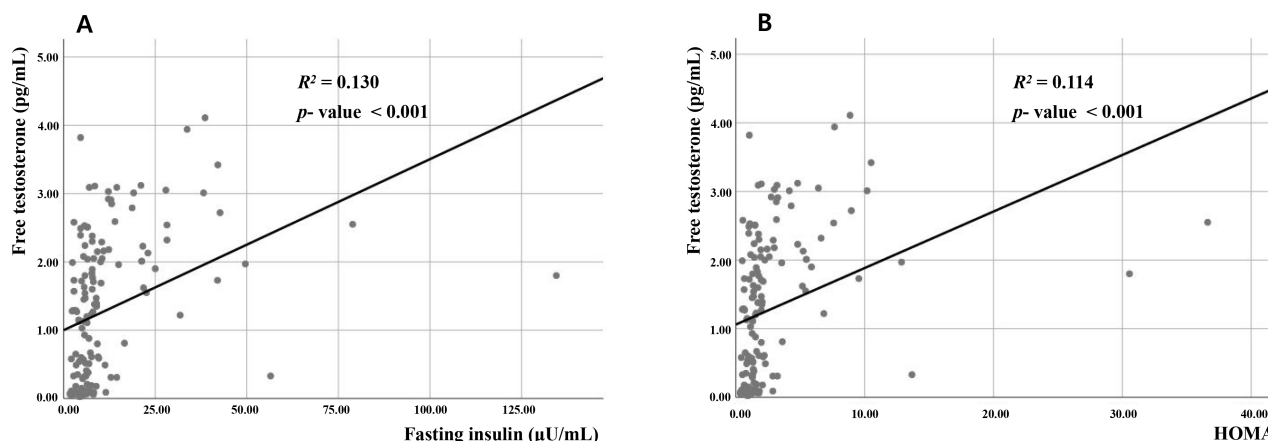
Fig. 1. Correlations between free testosterone and (A) fasting insulin level and (B) homeostatic model assessment for insulin resistance in women with polycystic ovary syndrome. R^2 by linear regression analysis. HOMA, homeostatic model assessment for insulin resistance.
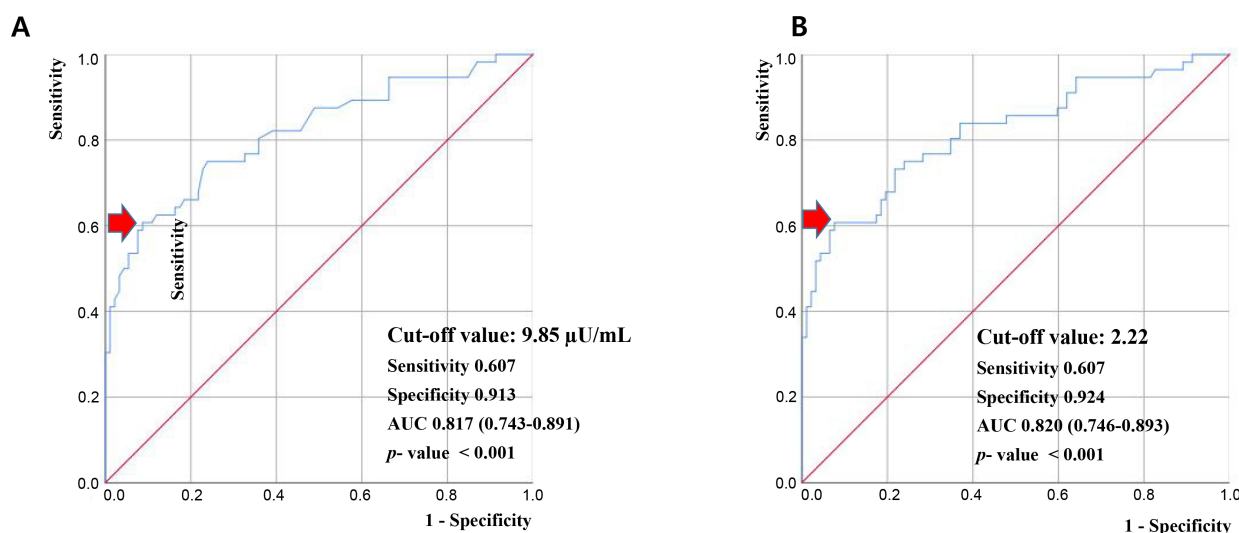

Fig. 2. Receiver operating characteristic curve analysis to evaluate the accuracy of fasting insulin levels and homeostatic model assessment for insulin resistance values for predicting hyperandrogenism in patients with polycystic ovary syndrome. (A) Fasting insulin level. (B) Homeostatic model assessment for insulin resistance. AUC, area under the receiver operating characteristic curve. Red arrow means cutoff values for predicting hyperandrogenism.

ment and exacerbation of HA in PCOS patients [3,6,11–13]. IR/hyperinsulinemia also promotes androgen synthesis in the adrenal gland and inhibits follicular maturation. Additionally, IR/hyperinsulinemia results in an increase in the serum luteinizing hormone to follicle-stimulating hormone (LH/FSH) ratio by increasing LH secretion from the pituitary gland [3,4,6]. Through the aforementioned mechanisms, IR/hyperinsulinemia induces anovulation and HA. At high concentrations, insulin can mimic the actions of insulin-like growth factor-1 (IGF-1) by binding to the IGF-I receptor, which has been suggested as another possible explanation for insulin's role in causing HA [13,28,29]. Furthermore, other studies have demonstrated that insulin ex-

erts distinct effects on steroidogenesis through its own receptor, even in states of insulin resistance [13,30,31]. These findings support the existing concept that there is a strong association between HA and IR in PCOS patients.

Recently, one study estimated the cutoff value for HOMA-IR to evaluate IR based on the SHBG level in PCOS patients [32]. In a study of 854 Caucasian women by Biernacka-Bartnik *et al.* [32], an empirical optimal cutoff value of 2.1 for HOMA-IR was suggested to predict circulating SHBG levels below the normal range (26.1 nmol/L) (AUC value of 0.73 with a sensitivity of 72.3% and a specificity of 63.1%), which is partially consistent with our results. However, the study of Biernacka-Bartnik *et al.* [32]

differs from ours in that it did not measure the insulin cutoff value for actual androgens such as TT or FT but rather the value of HOMA-IR for SHBG, an indirect indicator for evaluating androgens.

In contrast, some studies have been conducted to determine the cutoff values of androgen-related indicators to predict IR. Yetim Şahin et al. [17] conducted a study investigating the association between PCOS and obesity and IR with all factors that may impact IR. They found that the FAI can be used as a supporting IR marker in PCOS with an FAI cutoff value of 5.93 [17]. Banu et al. [14] suggested that the TT level significantly correlated with IR (defined fasting glucose level), whereby the cutoff value of TT that may predict IR was 46.25 ng/dL (sensitivity 43.6% and specificity 70.6%). Additionally, SHBG has also been shown to have a strong association with IR [15,16]. Kajaia et al. [15] suggested that SHBG can serve as a predictive marker of IR in women with HA. Chen et al. [16] showed that SHBG can be used as an independent predictive marker for IR in PCOS patients, especially obese/overweight patients. In the study, the optimal SHBG cutoff value to predict IR (defined as a HOMA-IR value $\geq$2.29) was 37 nmol/L (sensitivity 97.62% and specificity 80.85%) in the overweight group [16]. When IR was defined as a HOMA-IR value $\geq$2.5, the optimal SHBG cutoff value was 30.2 nmol/L (sensitivity 97.44% and specificity 82.69%) in the overweight/obese group [16]. According to these results, the association between IR and HA is not a one-way relationship; rather, they interact with each other in their occurrence and development. Therefore, these studies also have significant meaning in elucidating the relationship between IR and HA.

It is difficult to explain why there have been few studies on the cutoff value of insulin to predict HA to date. One possible explanation is that while insulin resistance is prevalent among women with PCOS, it does not seem to be universal across all cases [8,20], and hyperinsulinemia or IR is not included in the diagnostic criteria for PCOS. Hence, insulin tests are not routinely performed for all PCOS patients, and they are not regarded as essential to evaluate blood glycemic status in patients with PCOS [2,19]. Additionally, there may be limitations for insulin tests in terms of cost and setting, and some countries may not have the facilities or equipment necessary for such testing.

There are several limitations in our research. Because this study included only Korean women with PCOS, the possibility of different results in other ethnic groups cannot be ruled out. As mentioned, we were unable to use the HEC, which is considered the gold standard for assessing insulin sensitivity/resistance, due to practical limitations in clinical settings [9]. However, it would have been more comprehensive to incorporate postprandial ISAIs, such as the Matsuda index derived from insulin levels and postprandial glucose, for evaluating insulin sensitivity/resistance in our research [2,9,10]. In addition, SHBG is an emerging biomarker for predicting HA and IR. However, we were unable to evaluate the FAI using SHBG because there was no commercial test kit to evaluate SHBG at the university hospital where this study was conducted, which could be another drawback of this research.

The relatively small sample size of the number of participants also seems to be a limitation of our research. However, when the sample size was calculated using RStudio 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria) with reference to a previous study [32], the sample size was calculated as 46 participants with a significance level $\alpha = 0.05$ and a power of $(1 - \beta) = 0.80$. According to these calculations, the number of participants in our study seems to be sufficient to support our results.

5. Conclusions

In conclusion, our results support the classical concept that hyperinsulinemia contributes to HA in PCOS patients. Women with PCOS with fasting insulin levels of 9.85 µU/mL or higher (approximately $\geq$10 µU/mL) are strongly suspected to have HA. By utilizing these cutoff values in clinical practice, clinicians can identify PCOS patients at risk of HA development early and provide timely interventions, ultimately improving their quality of life. Further prospective large-scale trials involving diverse racial and ethnic groups are necessary to elucidate and validate these initial findings.

Availability of Data and Materials

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

Author Contributions

These should be presented as follows; Conceptualization: SL, HA, SC. Data curation: HA, SC. Formal analysis: SC. Methodology: SL, HA, SR, SC. Project administration: SC. Visualization: SC. Writing—original draft: SL. Writing—review & editing: SC. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital (IRB No. 129792-2014-035), which waived the requirement for written consent for subjects in the present study.

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Not applicable.

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Conflict of Interest

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