A Model for Predicting the Future Risk of Incident Erosive Esophagitis in an Asymptomatic Population Undergoing Regular Check-ups

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Abstract: Erosive esophagitis is a major risk factor for Barrett esophagus and esophageal adenocarcinoma. Information regarding the putative risk factors for developing erosive esophagitis is considerably heterogeneous; thus, a risk model is required to clinically predict the incidence of erosive esophagitis. This study was to derive and validate a predictive model for the incidence of developing erosive esophagitis after negative index endoscopy in a population subjected to routine health check-ups. This retrospective cohort study of health check-ups included 11,535 patients who underwent repeated screening endoscopy after >3 years from a negative index endoscopy. We used logistic regression analysis to predict the incidence of erosive esophagitis, and a Simple Prediction of Erosive Esophagitis Development score for risk assessment was developed and internally validated using the split-sample approach. The development and validation cohorts included 5765 patients (675 with erosive esophagitis [11.7%]) and 5770 patients (670 with erosive esophagitis [11.6%]), respectively. The final model included sex, smoking behavior, body mass index, hypertension, and the triglyceride level as variables. This model predicted 667 cases of erosive esophagitis, yielding an expected-to-observed ratio of 1.00 (95% confidence interval [CI], 0.92–1.07). A simplified 5-item risk scoring system based on coefficients was developed, with a risk of erosive esophagitis of 6.2% (95% CI, 5.2–7.1) for the low-risk group (score ≤2), 15.1% (95% CI, 13.5–16.6) for the intermediate-risk group (score ≤3, 4), and 18.2% (95% CI, 15.2–21.3) for the high-risk group (score ≥5). The discriminative performance of the risk-prediction score was consistent in the derivation cohort and validation cohort (c-statistics 0.68 and 0.64, respectively) the calibration was good (Brier score 0.099 and 0.1, respectively). In conclusion, a simple risk-scoring model using putative risk factors can predict the future incidence of developing erosive esophagitis in asymptomatic populations.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common gastrointestinal (GI) disorder that frequently occurs in the primary care setting, with a high direct and indirect economic burden on society.1,2 Endoscopic erosive esophagitis is a major risk factor for Barrett esophagus, and the risk of esophageal adenocarcinoma substantially increases in patients with previously diagnosed erosive esophagitis.3–5 From the viewpoint of long-term complications of erosive esophagitis, treatment and prevention of esophagitis is necessary, whether it is symptomatic or silent esophagitis, although the natural history for silent GERD remains unclear.6

Massive endoscopic screening of the entire population to detect erosive esophagitis would not be feasible because of physical risks and cost effectiveness.7 Furthermore, a symptom-based approach has limits in terms of heterogeneity of symptoms, low correlation with the degree of endoscopic esophagitis, and a relatively high prevalence of silent esophagitis.8,9 Therefore, the comprehensive elucidation of risk factors for developing erosive esophagitis in the future would be helpful for determining a high-risk group and for subsequent individualized decision for screening. A large number of observational studies showed varying putative risk factors for erosive esophagitis, including demographic and metabolic parameters, even if they were somewhat heterogeneous.10–13 As these analyses were limited by significant temporal bias, the interpretation of parameters, including lifestyle changes, may be suboptimal, considering the positive benefit of only long-term intervention. Currently, there is no available risk predictive model for the incidence of erosive esophagitis after negative index endoscopy, especially one that uses accessible clinical primary care parameters.
To determine the comprehensive risk factors for the incidence of developing erosive esophagitis after negative index endoscopy, we have analyzed a large-scale health check-up cohort. We performed data analysis to derive and validate a risk-prediction model for new-onset erosive esophagitis. The results of the model were used to develop a simple scoring system that estimates the likelihood of developing erosive esophagitis. In addition, this scoring system was internally validated using split-sample method.

MATERIALS AND METHODS

Design Overview
We performed a retrospective cohort analysis of database records for patients who entered the health check-up program for upper GI cancer at the Center for Health Promotion, Samsung Medical Center, in Korea. This comprehensive health-screening program included anthropometric measurements, annual or biennial endoscopy, various laboratory studies, and an epidemiological questionnaire on lifestyle factors, medication, and chronic disease. Patients paid voluntarily for their health check-ups, or were partly supported by an affiliated company. The study was approved by the institutional review board of Samsung Medical Center, and due to the retrospective nature of the study, the requirement for informed consent was waived.

Study Sample
In total, 19,217 patients who underwent upper endoscopic examination for screening from January 2006 through December 2008 were enrolled. All patients were asymptomatic at the time of index endoscopy. Patients were included if they underwent repeated screening endoscopy after at least 3 years until July 2014, considering previous data from the kinetic curve showing the progression to erosive esophagitis.14 Patients were excluded when they were diagnosed with erosive esophagitis, Barrett esophagus, malignant disease of the upper GI tract, and active or healing peptic ulcer disease on index baseline endoscopy; when they had prior gastroesophageal surgery; when they had not fully completed the epidemiological questionnaire; or when their records were missing. The final cohort included 11,535 patients (Figure 1), and none of them needed additional medical treatment, as they did not have clinically noticeable GI symptoms at the time of index endoscopy.

Endpoint, Definitions, and Covariates
The primary endpoint was the development of erosive esophagitis after negative index endoscopy during screening. Erosive esophagitis was defined if definite erosions (mucosal breaks) were present, and were classified according to the Los Angeles classification system.15 All participants had their body mass index (BMI), body fat, and waist circumference measured by previously described techniques.16 Weight and height were measured in the morning with participants wearing light clothing, but no shoes, and BMI was calculated as weight in kilograms divided by the square of the height in meters. According to the World Health Organization’s classification for BMI, participants were stratified into underweight (BMI < 18.5 kg/m²), normal (BMI 18.5–23.0 kg/m²), overweight (BMI 23.0–25.0 kg/m²), and obesity (BMI ≥ 25.0 kg/m²).17 The waist circumference was measured midway between the lower border of the rib cage and iliac crest when participants were standing at the end of normal expiration. Percentage of body fat was measured by bioelectrical impedance analysis (In Body 3.0; Biospace, Seoul, Korea). We measured blood pressure and blood markers such as levels of fasting glucose, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, apolipoprotein (Apo)-A1, and ApoB. Blood samples were collected from the antecubital vein after overnight nothing per oral. Total cholesterol, LDL, HDL, triglyceride, and fasting glucose were measured using enzymatic or colorimetric methods. HbA1c levels were measured using a high-performance liquid chromatography method with a Tosoh Glycohemoglobin Analyzer (Tosoh Bioscience Inc, Tokyo, Japan). Serum glucose levels were measured using the hexokinase/glucose-6-phosphate dehydrogenase method with a Hitachi 7600 Modular Dp-110 autoanalyzer (Hitachi, Tokyo, Japan). The average interassay and intraassay coefficients of variation for quality control were 6.5% and 2.1% for fasting glucose, and 2.5% and 2.5% for HbA1c levels, respectively. Systolic blood pressure and diastolic blood pressure were measured after a patient had rested for 5 min in a sitting position. Structured questionnaires included self-reported comorbidities of diabetes, hypertension, or dyslipidemia. Regarding alcohol intake, patients were classified into current drinker, former drinker, or never drinker. Patients were also classified as current smoker, former smoker, or never smoker. Regular exercise was defined as doing physical exercise of at least moderate intensity >3 times per week, for at least 30 minutes each time. Medication history of antihypertensive agents, aspirin, and nonsteroidal anti-inflammatory drug use was also collected.
Power Calculations and Statistical Analysis

Power estimates focused on identifying independent predictors in a multivariate logistic regression model for erosive esophagitis. Assuming an overall prevalence of erosive esophagitis of 8.0% for a Korean population, a sample of 5765 patients would provide 98% power of detecting an adjusted odds ratio (OR) of 1.5 for a predictor with a prevalence of 25%.

The original dataset was randomly partitioned to generate derivation and validation cohorts. To split the data randomly, we generated the random numbers and used the seed of the number to split the data. The model was built with the derivation cohort using logistic regression analysis. Univariate logistic regression analysis was conducted to identify risk factors associated with erosive esophagitis, and corresponding unadjusted relative risks were computed. In multivariate logistic regression analysis, we included risk factors with P values <0.05 from univariate analysis. Multivariate logistic regression analysis was used to verify the relationship between erosive esophagitis and variables shown as significant risk factors in univariate analysis. Additionally, stepwise selection analysis was performed to elucidate the most influential risk factors without multicollinearity between the independent variables for erosive esophagitis; a risk factor was entered into the model if the P value was <0.05, and it stayed in the model if the P value was <0.05. The model was internally validated using the validation cohort. The ability to discriminate the development of erosive esophagitis was evaluated by the area under the receiver-operating characteristic curve. Model calibration, in the sense of directly comparing a model’s predicted probabilities to observed probabilities, was assessed graphically and was tested using the Hosmer–Lemeshow goodness-of-fit test of the model’s predictions. As the Hosmer–Lemeshow goodness-of-fit test is sensitive to sample size, we chose smaller subsets chosen at random (n = 500) to avoid escalation of power estimates focused on identifying independent predictors in a multivariate logistic regression model for erosive esophagitis. Assuming an overall prevalence of erosive esophagitis of 8.0% for a Korean population, a sample of 5765 patients would provide 98% power of detecting an adjusted odds ratio (OR) of 1.5 for a predictor with a prevalence of 25%.

RESULTS

Patient Characteristics

The study population (11,535 participants) was divided into the derivation cohort (5765 participants) and validation cohort (5770 participants). Overall, there were 1345 cases of erosive esophagitis. General characteristics of the cohorts are presented in Table 1. Characteristics of each cohort were well balanced. The incidence of erosive esophagitis was not different between cohorts (11.7% in derivation cohort and 11.6% in validation cohort; P = 0.871, testing equality of rate).

Development of a Prediction Model

Univariate associations between potential risk factors and the development of erosive esophagitis after negative index endoscopy are presented in Table 2. Sex; BMI; waist circumference; body fat; systolic blood pressure; diastolic blood pressure; levels of triglyceride, HDL, fasting glucose, and HbA1c; current history of hypertension, dyslipidemia, and...
diabetes mellitus; use of antihypertensive agents; alcohol intake; smoking behavior; and physical exercise had P values <0.05 and were included as covariates in the multivariate logistic regression models. Those with a prognostic significance in univariate analysis were entered into the multivariate model, and stepwise regression was performed to eliminate multicollinearity. Five variables maintained their prognostic significance after multivariate analysis (Table 3): sex, hypertension, smoking behavior, BMI, and triglyceride level.

Model Discrimination and Calibration

The model was applied to derivation cohort patients resulting in a concordance statistic of 0.68 (95% confidence interval [CI], 0.66–0.70) and a Hosmer–Lemeshow goodness-of-fit statistics of 4.362 (P = 0.823). The model was then applied to patients from the validation cohort, resulting in a concordance statistic of 0.64 (95% CI, 0.62–0.66), indicating moderate discrimination (Figure 2A). Based on the derivation model, the probability for developing erosive esophagitis in the validation cohort was used to divide patients into deciles. In each of the deciles, the number of expected cases of erosive esophagitis was compared to the observed number of erosive esophagitis cases (Figure 3). Although Figure 3B indicates that the probability of the incidence of erosive esophagitis was slightly underestimated for low and intermediate-risk patients in the validation cohort, the Hosmer–Lemeshow goodness-of-

### Table 2. Estimated Relative Risk of Developing Erosive Esophagitis by Univariate Analysis in the Derivation Cohort (n = 5765)

| Parameters                  | Crude Model | Age-adjusted Model |
|-----------------------------|-------------|--------------------|
|                             | Coefficient | RR (95% CI)        | P     | Coefficient | RR (95% CI) | P     |
| Age                         | 0.0075      | 1.01 (0.99–1.02)   | 0.0611| 1.2647      | 3.54 (2.89–4.33) | <0.0001|
| Sex                         | 1.2693      | 3.56 (2.91–4.35)   | <0.0001| 0.972       | 1.10 (1.08–1.13) | <0.0001|
| Anthropometric profile      |             |                    |       |             |             |       |
| Body mass index             | 0.0979      | 1.10 (1.08–1.13)   | <0.0001| 0.425       | 1.04 (1.04–1.05) | <0.0001|
| Waist circumference         | 0.0425      | 1.04 (1.04–1.05)   | <0.0001| 0.151       | 1.02 (1.00–1.03) | 0.0282 |
| Body fat                    |             |                    |       |             |             |       |
| Blood pressure profile      |             |                    |       |             |             |       |
| SBP                         | 0.0045      | 1.00 (1.00–1.01)   | 0.0490| 0.0038      | 1.00 (1.00–1.01) | 0.1032|
| DBP                         | 0.0137      | 1.01 (1.01–1.02)   | <0.0001| 0.0133      | 1.01 (1.01–1.02) | <0.0001|
| Lipid profile               |             |                    |       |             |             |       |
| Total cholesterol           | −0.0007     | 0.99 (0.99–1.00)   | 0.5088| −0.0008     | 0.99 (0.99–1.00) | 0.4546|
| LDL                         | −0.0008     | 0.99 (0.99–1.00)   | 0.5001| 0.0001      | 1.00 (1.00–1.01) | 0.1032|
| Triglyceride                | 0.5413      | 1.71 (1.74–2.00)   | <0.0001| 0.1561      | 0.98 (0.98–0.99) | <0.0001|
| HDL                         | −0.0161     | 0.98 (0.98–0.99)   | <0.0001| 0.0160      | 0.98 (0.98–0.99) | <0.0001|
| ApoA1                       | −0.0026     | 0.99 (0.99–1.00)   | 0.2651| 0.0026      | 1.00 (0.99–1.00) | 0.2649|
| ApoB                        | 0.0029      | 1.02 (0.99–1.01)   | 0.2662| 0.0026      | 1.00 (0.99–1.01) | 0.2726|
| Insulin resistance profile  |             |                    |       |             |             |       |
| Fasting glucose             | 0.0065      | 1.01 (1.00–1.01)   | <0.0001| 0.0063      | 1.01 (1.00–1.01) | <0.0001|
| HbA1c                       | 0.1623      | 1.18 (1.09–1.27)   | <0.0001| 0.1533      | 1.17 (1.08–1.26) | 0.0001|
| Comorbidity                 |             |                    |       |             |             |       |
| Hypertension                | 0.3910      | 1.48 (1.27–1.72)   | <0.0001| 0.3785      | 1.46 (1.24–1.71) | <0.0001|
| Dyslipidemia                | 0.2222      | 1.25 (1.05–1.48)   | 0.0100| 0.2006      | 1.22 (1.03–1.45) | 0.0217|
| Diabetes mellitus           | 0.4166      | 1.52 (1.22–1.88)   | 0.0022| 0.3868      | 1.47 (1.18–1.84) | 0.0006|
| Medication                  |             |                    |       |             |             |       |
| Antihypertensive agent      | 0.3654      | 1.44 (1.23–1.68)   | <0.0001| 0.3528      | 1.42 (1.21–1.68) | <0.0001|
| Aspirin                     | 0.1497      | 1.16 (0.95–1.43)   | 0.1559| 0.1029      | 1.11 (0.89–1.37) | 0.3477|
| NSAID                       | −0.1082     | 0.90 (0.55–1.46)   | 0.6612| −0.1547     | 0.86 (0.53–1.39) | 0.5329|
| Lifestyle-related activities|             |                    |       |             |             |       |
| Alcohol drinking            |             |                    |       |             |             |       |
| Never                       | 1.00 (reference) | 1.00 (reference) |       | 1.00 (reference) | 1.00 (reference) |       |
| Former                      | 0.7808      | 2.21 (1.56–3.06)   | <0.0001| 0.9792      | 2.21 (1.58–3.09) | <0.0001|
| Current                     | 0.9613      | 2.62 (2.10–3.25)   | <0.0001| 0.9794      | 2.66 (2.14–3.31) | <0.0001|
| Smoking                      |             |                    |       |             |             |       |
| Never                       | 1.00 (reference) | 1.00 (reference) |       | 1.00 (reference) | 1.00 (reference) |       |
| Former                      | 0.6864      | 1.99 (1.68–2.35)   | <0.0001| 0.6670      | 1.95 (1.64–2.31) | <0.0001|
| Current                     | 0.9787      | 2.66 (2.23–3.18)   | <0.0001| 0.9949      | 2.70 (2.26–3.23) | <0.0001|
| Regular physical exercise   |             |                    |       |             |             |       |
| Yes                         | 1.00 (reference) | 1.00 (reference) |       | 1.00 (reference) | 1.00 (reference) |       |
| No                          | 0.2556      | 1.29 (1.02–1.64)   | 0.0350| 0.2158      | 1.24 (0.97–1.58) | 0.0816|

Apo = apolipoprotein, CI = confidence interval, DBP = diastolic blood pressure, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RR = relative risk, SBP = systolic blood pressure.
TABLE 3. Risk Factors Obtained From Multivariate Stepwise Regression Analysis for the Predictive Score Model For Developing Erosive Esophagitis in the Derivation Cohort (n = 5765)

| Parameters       | β Coefficient | RR (95% CI)     | P      | Risk Score |
|------------------|---------------|-----------------|--------|------------|
| Sex              |               |                 |        |            |
| Female           | Reference group | 0               |        |            |
| Male             | 1.1529        | 2.86 (2.28–3.58) | <0.0001 | 2          |
| Hypertension     |               |                 |        |            |
| No               | Reference group | 0               |        |            |
| Yes              | 0.2962        | 1.28 (1.08–1.51) | 0.0019 | 1          |
| Smoking          |               |                 |        |            |
| Never/former     | Reference group | 0               |        |            |
| Current          | 0.3637        | 1.34 (1.13–1.60) | 0.0002 | 1          |
| BMI              |               |                 |        |            |
| <18.5            | Reference group | 0               |        |            |
| 18.5 – <23.0     | 0.1792        | 1.18 (0.52–2.68) | 0.6804 | 0          |
| 23.0 – <25.0     | 0.3586        | 1.39 (0.61–3.16) | 0.4089 | 1          |
| ≥25.0            | 0.3259        | 1.34 (0.59–3.04) | 0.4527 | 1          |
| Triglyceride     |               |                 |        |            |
| <150 mg/dL       | Reference group | 0               |        |            |
| ≥150 mg/dL       | 0.3248        | 1.31 (1.12–1.54) | 0.0003 | 1          |

BMI = body mass index, CI = confidence interval, RR = relative risk.

FIGURE 2. Receiver-operating characteristic curve analysis for the discriminative ability of the prediction model (A) and the Simple Prediction of Erosive Esophagitis Development scoring system (B) for the incidence of developing erosive esophagitis after negative index endoscopy in the derivation and validation cohorts.

FIGURE 3. Expected versus observed incidence of developing erosive esophagitis by decile of the predicted risk. The derivation (A) and validation cohorts (B).
fit test showed no significant difference between the expected and observed number of erosive esophagitis ($\chi^2 = 12.949$, $P = 0.114$). The calibration curves (Figure 4A and B) show good agreement between the expected probability and observed incidence of erosive esophagitis risk across the observed range of risk.

Results of the model calibration performed in each category of risk factors of the validation dataset are shown in Table 4. Overall, this prediction model predicted that 667 participants would develop erosive esophagitis, compared with 670, who were observed for an expected-to-observed ratio of 1.00 (95% CI, 0.92–1.07). There was a significant overprediction in women, whereas an underestimation in men. Risk was also significantly underestimated in participant with current smoking, high BMI more than 25, and high level of triglyceride.

Simplified Risk Scoring Model

To calculate a risk score, we assigned each of the 6 prognostic variables a number of points proportional to its regression coefficient (Table 3). Summing the points yielded total risk scores ranging from 0 to 6, with higher scores indicating a greater predicted risk for the incidence of erosive esophagitis. This Simple Prediction of Erosive Esophagitis Development (SPEED) score predicted the incidence of erosive esophagitis well in the derivation and validation cohorts across all risk classes. As shown in Figure 2B, when applied to the derivation and validation cohorts, the risk-prediction score yielded a concordance statistic of 0.68 (95% CI, 0.66–0.70) and 0.64 (95% CI, 0.62–0.66), respectively, indicating moderate discrimination. For the cut-off point of 2.5, which maximizes the sum of sensitivity and specificity, the sensitivity, specificity, accuracy, negative predictive value, and positive predictive value were 0.81, 0.46, 0.51, 0.95, and 0.17 in the derivation cohort, and 0.77, 0.46, 0.50, 0.94, and 0.16 in the validation cohort, respectively. This scoring model also showed good calibration for predicting erosive esophagitis according to the Brier score (0.099 and 0.1 in the derivation and validation cohorts, respectively) (Figure 4C and D).

Figure 5 depicts the ratio of the expected-to-observed risk for developing erosive esophagitis in the validation cohort using the simplified score. The score calculated for each person from
TABLE 4. Comparison of the Number of Erosive Esophagitis Cases Predicted by the Model With the Number Observed in the Validation Cohort (n = 5770)

| Parameters       | Expected Number of Erosive Esophagitis | Observed Number of Erosive Esophagitis | E/O Ratio | 95% CI |
|------------------|----------------------------------------|----------------------------------------|-----------|-------|
| Overall          | 666.86                                 | 670                                    | 1.00      | 0.92–1.07 |
| Sex              |                                        |                                        |           |       |
| Female           | 262.87                                 | 127                                    | 2.00      | 1.74–2.46 |
| Male             | 403.98                                 | 543                                    | 0.74      | 0.68–0.81 |
| Hypertension     |                                        |                                        |           |       |
| No               | 516.32                                 | 495                                    | 1.04      | 0.96–1.14 |
| Yes              | 150.54                                 | 175                                    | 0.86      | 0.74–1.00 |
| Smoking          |                                        |                                        |           |       |
| Never/former    | 543.95                                 | 473                                    | 1.15      | 1.05–1.26 |
| Current         | 122.91                                 | 197                                    | 0.62      | 0.54–0.72 |
| BMI              |                                        |                                        |           |       |
| <18.5           | 12.37                                  | 10                                     | 1.24      | 0.67–2.30 |
| 18.5 < ≤ 22.9   | 198.25                                 | 126                                    | 1.57      | 1.32–1.87 |
| 22.9 < ≤ 24.9   | 191.03                                 | 196                                    | 0.97      | 0.85–1.12 |
| 24.9 <          | 265.22                                 | 338                                    | 0.78      | 0.71–0.87 |
| Triglyceride     |                                        |                                        |           |       |
| <150 mg/dL      | 488.42                                 | 448                                    | 1.09      | 0.99–1.20 |
| ≥150 mg/dL      | 178.43                                 | 222                                    | 0.80      | 0.70–0.92 |

BMI = body mass index, CI = confidence interval, E = expected, O = observed.

the validation set estimated the likelihood of detecting erosive esophagitis as 3.9% for patients with a score of 0, and 23.8% for patients with a score of 6 in the complete dataset. Patients were then divided into 3 categories based on the score distribution. Scores were collapsed into 3 categories: ≤2, 3 or 4, and ≥5 to identify potential low, intermediate, and high-risk individuals, respectively. Classification of the derivation cohort according to the risk score resulted in the assignment of 43.1% of patients to the low-risk group, 24.9% to the intermediate-risk group, and 12.2% to the high-risk group (Table 5). Results were similar for the validation cohort: 43.3% of patients were in the low-risk group, 12.2% to the high-risk group (Table 5). Results were similar for the validation set estimated the likelihood of detecting erosive esophagitis among asymptomatic patients.

In this study that involved a large-scale population that underwent regular health check-ups in the form of repeated screening endoscopy, we developed and validated a simple risk-prediction score (SPEED) to estimate the risk of developing the incidence of erosive esophagitis among symptomatic patients. The final model includes male sex, current smoker, BMI, hypertension, and serum triglyceride levels as predictive variables. In internal validation, the model was well calibrated in that it predicted 667 cases of erosive esophagitis of 670 that occurred (E/O ratio 1.0). This simplified risk score is easy to use with readily available clinical, demographic, and laboratory values in primary healthcare services. To our knowledge, this is the first score designed to predict the incidence of developing erosive esophagitis in an asymptomatic population.

As erosive esophagitis is assumed an initial step in the development of esophageal adenocarcinoma, screening to identify patients with erosive esophagitis may be an effective strategy to prevent progression. However, in terms of cost effectiveness of endoscopic screening, trying to identify patient groups in an entire population, as of now, is not recommended. With respect to Barrett esophagus as a long-term complication of erosive esophagitis, guidelines recommend selective screening for erosive esophagitis patients with multiple risk factors. However, unlike symptom-based analysis of factors associated with progression to Barrett esophagus, analysis to predict the incidence of erosive esophagitis should be conducted in a population without symptoms or endoscopic erosivitis. Indeed, there is an inflammatory change in the cardiac mucosa in the asymptomatic, moderately overweight population, without evidence of typical symptom, suggesting the limitation of symptom-based risk stratification. Therefore, comprehensive analysis for every possible factor is required for the development of a prediction model for developing erosive esophagitis.

Various epidemiologic studies regarding risk factors for erosive esophagitis pointed out that parameters including male sex, overweight, obesity, or smoking were consistently associated with erosive esophagitis. Apart from this, clinical factors such as alcohol intake or dietary fat intake were suggested by some cross-sectional analyses. However, these included factors have been derived from patients who were already diagnosed with erosive esophagitis. Therefore, these are not suitable for selecting high-risk patients beforehand and for making preemptive modifications of lifestyle-related factors. Recent prospective cohort studies, even if these were symptom-based studies rather than endoscopic studies showed BMI gain and smoking to be risk factors; therefore, smoking cessation or weight reduction might be beneficial providing preventive intervention or education at the time of negative endoscopy and using a prediction model with baseline clinical parameters are of vital importance, and may be worthwhile in the primary care setting.

DISCUSSION

In our cohort study, the triglyceride level and diagnosis of hypertension as individual components of metabolic syndrome were independently associated with the incidence of erosive esophagitis. Clinical parameters such as current smoker, male sex, and BMI were also definite risk factors for developing erosive esophagitis. In contrast to a previous cross-sectional study on a healthy population, the influence of waist circumference in our data was not evident. Overall, this cohort analysis elucidated the temporal relationship between these putative risk factors and the eventual development of esophagitis. In particular, male sex, which has been suggested by many other studies, was identified as strong contributing factors invested with 2 points of risk score. The attributable risk of other factors was similar, given 1 point. Regarding performance measurement, even if this risk-prediction scoring system yielded moderate discrimination, this prediction model is of high value, considering there has never been a model like this, and it was derived from an asymptomatic population. Moreover, the present model was well calibrated overall, as verified by the validation set, which means that the observed risk of erosive esophagitis fit the predicted risk well. In the present model, there was a distinct difference in the incidence of erosive esophagitis among groups classified according to the risk score, giving the approximate 20% incidence in the high-risk group.
Clinical relevance of this risk-prediction model may lead to active participation in future endoscopic screening and correction of modifiable lifestyle factors in a selected high-risk group. Furthermore, for predicting progression from nonerosive reflux disease to erosive esophagitis, this risk score may be useful after combining the key symptom-based parameter to this scoring system in the future.

Regarding the clinical use of this prediction model, it is crucial to consider the epidemiologic aspect, as there is a significant difference in the incidence rate of erosive esophagitis between western and Asian populations. Whereas the reported prevalence of erosive esophagitis has varied from 3.4% to 16.3% in Asia, western studies revealed a rate of 12.1% to 28.5%. Barrett esophagus is regarded as a complication of chronic erosive esophagitis and has the potential to develop into esophageal adenocarcinoma. A population-based cohort study found the annual risk of esophageal adenocarcinoma to be 0.12% among patients with Barrett esophagus.\(^45\) In the United States, however, the prevalence of Barrett esophagus was reported to be 6.8%.\(^46\) Moreover, the incidence of esophageal adenocarcinoma in the United States increased by more than 460% in white men and 335% in white women between 1975 and 2004, outpacing squamous cell carcinoma to become the most predominant esophageal cancer in that country.\(^47\) On

![Figure 5](image)

**FIGURE 5.** Ratio of expected-to-observed risk for developing erosive esophagitis. The simplified score is used in the validation cohort (n = 5770).

| Risk Groups | Derivation Cohort (n = 5765) | Validation Cohort (n = 5770) |
|-------------|-----------------------------|-----------------------------|
|             | n (%)                       | Incidence % (95% CI)        | P*          | n (%)                       | Incidence % (95% CI)        | P*          |
| Low         | 2487 (43.1)                 | 5.0 (4.1–5.9)               | Reference   | 2501 (43.3)                 | 6.2 (5.2–7.1)               | Reference   |
| Intermediate| 2576 (44.7)                 | 15.2 (13.5–16.7)            | <0.0001     | 2474 (42.9)                 | 15.1 (13.5–16.6)            | <0.0001     |
| High        | 702 (12.2)                  | 22.7 (19.1–26.2)            | <0.0001     | 795 (13.8)                  | 18.2 (15.2–21.3)            | <0.0001     |

CI = confidence interval.
*By testing the difference incidence rate between low-risk group and other groups.
the contrary, the reported prevalence of Barrett esophagus in Asia shows that the disease is still rare across most of the continent. A Korean nationwide prospective multicenter study showed that Barrett esophagus was diagnosed in 1% of the population. Among Asian BMIs lower than 25 kg/m².
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