Impact of postoperative reduced skeletal muscle on prognosis after recurrence in gastric cancer

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Received March 11, 2020; Accepted August 21, 2020

DOI: 10.3892/mco.2020.2165

Abstract. Little is known about the association between sarcopenia development after gastrectomy and gastric cancer prognosis after recurrence. The present study retrospectively examined the effects of decreased psoas muscle index (PMI) on post-recurrence prognosis after gastrectomy. A total of 67 patients with gastric cancer recurrence were included in the present study. PMI at pre-operation and recurrence were calculated, and 25 patients whose PMI reduction rate value was lower than the cutoff values (male=0.766 and female=0.704) were classified into the sarcopenia group and 42 patients into the non-sarcopenia group. There were no significant differences between the groups regarding age, sex, pathological stage, and nutrition and inflammation indices at the time of recurrence. Post-recurrence overall survival (OS) was significantly shorter in the sarcopenia group compared with the non-sarcopenia group (P<0.001). The post-recurrence survival rate was significantly worse in the sarcopenia group compared with the non-sarcopenia group (P<0.001). In multivariate analysis, sarcopenia (HR=5.04) and the total courses of chemotherapy after recurrence (HR=3.88) were independent unfavorable prognostic factors. In conclusion, sarcopenia and fewer total courses of post-recurrence chemotherapy were poor prognostic factors after gastric cancer recurrence. To improve prognosis, preventing sarcopenia development after gastrectomy is required.

Introduction

Despite ongoing advances in diagnostics, operative technique, and treatment strategy for the decades, gastric cancer remains one of the most common cancers in the world and a lethal disease (1). Gastrectomy for gastric cancer is essential for improving the survival rate, it may cause persistent functional disorders such as reduced amount of oral intake, insulin resistance, increased protein catabolism, and metabolic changes, leading to weight loss and the development of sarcopenia (2). It is reported that preoperative sarcopenia has been associated with long-term prognosis as well as short-term outcomes such as the development of postoperative pneumonia, poor activities of daily living, longer hospital stay, and the incidence of postoperative complications (3-10), which may restrict the following treatment options (11). Treatment option for patient with recurrence of gastric cancer after gastrectomy is limited to chemotherapy or best supportive care. It is known that sarcopenia could influence on pharmacokinetics of chemotherapy which could be associated with adverse effects of chemotherapy in several cancers (4). However, little is known about the effects of reduced skeletal muscle volume after gastrectomy on prognosis and treatment strategy after the recurrence of gastric cancer. In the present study, we investigated the effects of reduced skeletal muscle volume after gastrectomy on the treatment and prognosis in patients with recurrent gastric cancer.

Materials and methods

Patients. The study protocol was approved by the Institutional Review Board of National Defense Medical College (Saitama, Japan). Of the 553 patients who underwent radical gastrectomy for gastric cancer at the National Defense Medical College between 2011 and 2016, 67 patients who had gastric cancer recurrence were included in this study. We retrospectively evaluated the clinicopathological findings, serum albumin levels, C-reactive protein (CRP), total cholesterol, and neutrophil and lymphocyte counts at the time of preoperative and recurrence of gastric cancer. In addition, the neutrophil-lymphocyte ratio (NLR), the CRP-albumin ratio (CAR), the controlling nutrition status (CONUT) score, the prognostic nutritional index (PNI), and the modified Glasgow prognostic (mGPS) score were calculated as markers of nutrition or inflammation.

The tumor pathological findings were recorded in accordance with the third English edition of the Japanese Classification of Gastric Carcinoma, edited by the Japanese Gastric Cancer Association (12). All patients were followed-up using an oncologically appropriate plan on a per-patient basis.
For patients with stage II or III disease, postoperative adjuvant chemotherapy with S-1 (80 mg/m²/day) was recommended for 1 year. In 45 cases of pathological stage II or III gastric cancer patients, 26 cases (57.8%) received adjuvant chemotherapy. There was no significant correlation between age and receiving adjuvant chemotherapy.

**Definition of sarcopenia.** The psoas muscle index (PMI: cm²/m²) was calculated from CT images (Aquilion 64; Toshiba Medical Systems) and the psoas muscle cross-sectional area at the third lumbar vertebra (L3) normalized length preoperatively and at the recurrence of gastric cancer by a physician who was blinded to the clinicopathological characteristics of the patients (Fig. 1) (13,14). The reduction rate of PMI from the preoperative value to that at the recurrence of gastric cancer was calculated. The patients were divided into two groups by the cutoff value using area under the receiver operating characteristic curves (ROC); the sarcopenia group (n=25 patients) had less than the cutoff value of the reduction rate of PMI (male=0.766 and female=0.704), and the non-sarcopenia group (n=42 patients) had more than the cutoff value (Fig. 2). The median value of the total cohort was 0.793.

**Statistical analyses.** All statistical analyses were performed using the JMP® Pro 14.0.0 software package (SAS Institute Inc.). The Student's t-test and Pearson's Chi-square test were performed, as appropriate. A receiver operating characteristic curves (ROC) curve was constructed to estimate the optimal cutoff value of the reduction of PMI. Survival rates were obtained by the Kaplan-Meier method, and the statistical significance was determined by the log-rank test.

Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. The data are expressed as mean ± standard deviation. A P-value of <0.05 was considered statistically significant.

**Results**

**Patient characteristics.** Patients' clinical factors at the recurrence of gastric cancer and pathological factors diagnosed from resected specimens are shown in Table I. There were no significant differences in age, sex, Charlson Comorbidity Index score, and surgical procedure including reconstruction methods between the two groups. The sarcopenia group had a higher body weight and body mass index (BMI) than did the non-sarcopenia group. In addition, the reduction rates of body weight and BMI due to the recurrence of gastric cancer in the sarcopenia group were higher than those of the non-sarcopenia group. There was no significant difference in the pathological factors between the two groups except for tumor depth. The NLR, CAR, CONUT score, PNI, and mGPS at the recurrence of gastric cancer were not significantly different between the two groups (Table II). There was no significant difference in the time between gastrectomy and recurrence, the number of patients who received adjuvant chemotherapy and chemotherapy after the recurrence, the number of discontinued chemotherapies due to adverse effect, the number of chemotherapy regimens after recurrence, the kind of basic chemotherapy after recurrence, and the total courses of chemotherapies between the two groups. The sarcopenia group had a significantly shorter OS from recurrence than did the non-sarcopenia group (median survival time, interquartile range: 118, 43.5-180.5 vs. 300, 133.8-636.3 days, P<0.001).

**Prognostic factors.** The survival rate from the time of recurrence in the sarcopenia group was significantly worse than that in the non-sarcopenia group (3-year OS 6.0% vs. 21.0%, P<0.001; Fig. 3). Univariate and multivariate analyses that might affect the survival rate from the time of the recurrence of gastric cancer were shown in Table III. Univariate analysis demonstrated that the total courses of chemotherapy after recurrence <5 [hazard ratio (HR)=3.82], sarcopenia (HR=2.66), NLR ≥3.0 (HR=2.63), and PNI ≤40 (HR=2.59) were significantly associated with the prognosis after recurrence. The sarcopenia group more frequently had peritoneal recurrence, which didn't affect prognosis.

Multivariate analysis revealed that sarcopenia at the recurrence (HR=5.04) and the total courses of chemotherapy after recurrence (HR=3.88) were independent unfavorable prognostic factors.

Table IV shows univariate and multivariate analysis for the OS from the time at recurrence among the difference time.
of sarcopenia. Sarcopenia at the recurrence and the reduction rate of PMI from surgery to the recurrence were selected as the independent poor prognostic factors via multivariate analysis, but preoperative sarcopenia was not.

Discussion

In the present study, we demonstrated that the high reduction rate of PMI from the preoperative value to that at the recurrence of gastric cancer and the fewer courses of chemotherapy performed after recurrence were independently associated with poor prognosis after the recurrence.

Since Rosenberg has reported the concept of sarcopenia in 1997, and many studies have evaluated the associations between sarcopenia and clinical factors, such as poor quality of life, aspiration pneumonia, osteoporosis, swallowing function, and respiratory function (15). In patients with malignancies, sarcopenia is more likely to be developed due to increased protein catabolism, inflammatory reactions, metabolic abnormalities, and poor oral intake and may be associated with cancer cachexia. Many recent studies have shown that the frequency of serious postoperative complications was high and the long-term prognosis was poor in gastric cancer patients with preoperative sarcopenia (5-7,9,10). In addition, postoperative loss of the muscle mass affects the continuation rate of postoperative adjuvant chemotherapy, especially in the elderly, because of increased severe adverse events (16,17). However, no study has evaluated the relationship between prognosis after the recurrence and the reduction of skeletal muscle mass after gastrectomy. This study indicated that the reduction of PMI was a risk factor of poor OS after the recurrence of gastric cancer, which is consistent with a previous report that skeletal muscle loss during postoperative adjuvant chemotherapy is associated with poor prognosis (18).

We also demonstrated that patients who failed to continue chemotherapy more than five courses after the recurrence of gastric cancer had a poor prognosis. There are several factors affecting the continuity of chemotherapy after the recurrence, i.e., adverse events, age, performance status, the amounts of oral intakes, economic problem, and other social circumstances (19). Physicians can intervene the continuity of chemotherapy by providing appropriate nutritional management and preventing loss of skeletal muscle mass at the time of recurrence, which may be associated with longer survival after the recurrence of gastric cancer.

Preoperative exercises and nutritional support programs were effective for increasing total caloric intake, protein, and grip strength, maintaining skeletal muscle volume and
Table I. Patient's clinicopathological factors.

| Characteristic                        | Sarcopenia (n=25, 37.3%) | Non-Sarcopenia (n=42, 62.7%) | Total (n=67) | P-value |
|---------------------------------------|---------------------------|-----------------------------|--------------|---------|
| Age                                   | 72.1±7.8                  | 70.0±8.6                    | 70.8±8.3     | 0.393   |
| Sex                                   |                           |                             |              |         |
| Male                                  | 20                        | 32                          | 52           |         |
| Female                                | 5                         | 10                          | 15           |         |
| Body weight (kg)                      |                           |                             |              |         |
| Preoperatively                        | 55.4±8.9                  | 59.5±9.8                    | 57.9±9.6     | 0.082   |
| At the time of recurrence             | 46.2±8.1                  | 51.2±7.9                    | 49.3±8.3     | 0.014*  |
| Recurrence/preoperatively             | 0.8±0.1                   | 0.9±0.1                     | 0.9±0.1      | 0.422*  |
| Body mass index (kg/m²)               |                           |                             |              |         |
| Preoperatively                        | 21.3±2.9                  | 22.6±3.2                    | 22.1±3.1     | 0.071   |
| At the time of recurrence             | 17.7±2.2                  | 19.5±2.6                    | 18.8±2.6     | 0.010*  |
| Recurrence/preoperatively             | 0.8±0.1                   | 0.9±0.1                     | 0.9±0.1      | 0.338   |
| Psoas muscle index                    |                           |                             |              |         |
| Preoperatively                        | 3.9±0.9                   | 3.7±1.1                     | 3.8±1.0      | 0.223   |
| At the time of recurrence             | 2.5±0.8                   | 3.2±1.0                     | 3.0±1.0      | 0.005*  |
| Recurrence/preoperatively             | 0.6±0.1                   | 0.9±0.1                     | 0.8±0.2      | <0.001* |
| CCI score 2≤                           |                           |                             |              | 0.630   |
| Yes                                   | 6                         | 8                           | 14           |         |
| No                                    | 19                        | 34                          | 53           |         |
| Tumor location U/M/L                  |                           |                             |              | 0.579   |
| U                                     | 11                        | 15                          | 26           |         |
| M                                     | 9                         | 12                          | 21           |         |
| L                                     | 5                         | 15                          | 20           |         |
| Histology int/dif/other               |                           |                             |              | 0.210   |
| Int                                   | 14                        | 18                          | 32           |         |
| Dif                                   | 8                         | 22                          | 30           |         |
| Other                                 | 3                         | 2                           | 5            |         |
| Tumor depth                           |                           |                             |              | 0.418   |
| pT1                                   | 4 (16.0%)                 | 3 (7.1%)                    | 7 (10.5%)    |         |
| pT2                                   | 3 (12.0%)                 | 3 (7.1%)                    | 6 (9.0%)     |         |
| pT3                                   | 7 (28.0%)                 | 19 (45.2%)                  | 26 (38.8%)   |         |
| pT4                                   | 11 (44.0%)                | 17 (40.5%)                  | 28 (41.8%)   |         |
| Lymph node metastasis                 |                           |                             |              | 0.978   |
| pN0                                   | 5 (20.0%)                 | 8 (19.1%)                   | 13 (19.4%)   |         |
| pN1                                   | 4 (16.0%)                 | 8 (19.1%)                   | 12 (17.9%)   |         |
| pN2                                   | 6 (24.0%)                 | 11 (26.2%)                  | 17 (25.4%)   |         |
| pN3                                   | 10 (40.0%)                | 15 (35.7%)                  | 25 (37.3%)   |         |
| Pathological cancer stage             |                           |                             |              | 0.267   |
| pStageI                               | 3 (12.0%)                 | 3 (7.2%)                    | 6 (9.1%)     |         |
| pStageII                              | 6 (24.0%)                 | 12 (28.6%)                  | 18 (27.3%)   |         |
| pStageIII                             | 16 (64.0%)                | 27 (64.3%)                  | 43 (63.6%)   |         |
| Lymphatic invasion                    |                           |                             |              | 0.613   |
| Ly0                                   | 2                         | 5                           | 7            |         |
| Ly1                                   | 23                        | 37                          | 60           |         |
| Venous invasion                       |                           |                             |              | 0.429   |
| V0                                    | 4                         | 4                           | 8            |         |
| V1                                    | 21                        | 38                          | 59           |         |
| DG/TG/other                           |                           |                             |              | 0.161   |
| DG                                    | 6                         | 19                          | 25           |         |
| TG                                    | 17                        | 22                          | 39           |         |
| Other                                 | 2                         | 1                           | 3            |         |
Table I. Continued.

| Characteristic                          | Sarcopenia (n=25, 37.3%) | Non-Sarcopenia (n=42, 62.7%) | Total (n=67) | P-value |
|----------------------------------------|--------------------------|------------------------------|--------------|---------|
| Open/laparoscopy                       |                          |                              |              |         |
| Open                                   | 18                       | 23                           | 41           | 0.161   |
| Laparoscopy                            | 7                        | 19                           | 26           |         |
| Billroth-I/Roux-en-Y/other             |                          |                              |              | 0.130   |
| Billroth-I                             | 6                        | 15                           | 21           |         |
| Roux-en-Y                              | 2                        | 27                           | 44           |         |
| Other                                  | 17                       | 0                            | 2            |         |
| Recurrence pattern                     |                          |                              |              | 0.455   |
| Peritoneal                             | 9 (36.0%)                | 9 (7.1%)                     | 18 (26.9%)   |         |
| Hematogenous                           | 6 (24.0%)                | 17 (7.1%)                    | 23 (34.3%)   |         |
| Lymph node                             | 6 (24.0%)                | 11 (7.1%)                    | 17 (25.4%)   |         |
| Local                                  | 2 (8.0%)                 | 1 (7.1%)                     | 3 (4.5%)     |         |
| Other                                  | 2 (8.0%)                 | 4 (45.2%)                    | 6 (8.9%)     |         |

U, upper third; M, middle third; L, lower third; Int, intestinal type; Dif, diffuse type; DG, Distal gastrectomy; TG, Total gastrectomy; CCI, Charlson comorbidity index; *P<0.05. Data are expressed as the mean ± standard deviation.

Table II. Patient's characteristics at the time of recurrence of gastric cancer.

| Characteristic                          | Sarcopenia (n=25, 37.3%) | Non-Sarcopenia (n=42, 62.7%) | Total (n=67) | P-value |
|----------------------------------------|--------------------------|------------------------------|--------------|---------|
| Neutrophil lymphocyte ratio            |                          |                              |              |         |
| Preoperatively                         | 3.0±2.4                  | 3.5±2.8                      | 3.3±2.6      | 0.828   |
| At the time of recurrence              | 4.2±3.1                  | 4.6±4.7                      | 4.5±4.1      | 0.589   |
| CAR                                    |                          |                              |              |         |
| Preoperatively                         | 0.3±0.4                  | 0.1±0.2                      | 0.2±0.3      | 0.213   |
| At the time of recurrence              | 0.7±1.0                  | 0.5±0.6                      | 0.6±0.8      | 0.474   |
| CONUT score                            |                          |                              |              |         |
| Preoperatively                         | 2.3±1.1                  | 2.5±1.3                      | 2.4±1.2      | 0.597   |
| At the time of recurrence              | 4.8±2.8                  | 3.0±1.7                      | 3.9±2.5      | 0.062   |
| Prognostic nutritional index           |                          |                              |              |         |
| Preoperatively                         | 37.2±9.5                 | 35.9±13.3                    | 36.4±11.7    | 0.746   |
| At the time of recurrence              | 39.7±7.5                 | 43.7±9.0                     | 42.1±8.6     | 0.114   |
| Modified GPS score                     |                          |                              |              |         |
| Preoperatively                         | 0.4±0.7                  | 0.5±0.7                      | 0.5±0.7      | 0.927   |
| At the time of recurrence              | 1.2±0.7                  | 1.0±0.6                      | 1.1±0.7      | 0.180   |
| Adjuvant chemotherapy                  |                          |                              |              | 0.874   |
| Yes                                    | 8                        | 16                           | 24           |         |
| No                                     | 17                       | 26                           | 43           |         |
| Discontinued adjuvant chemotherapy due to adverse effect | 6 (75.0%) | 10 (62.5%) | 16 (66.7%) | 0.540 |
| Duration from gastrectomy to recurrence (day) | 572.9±513.2 | 444.8±331.0 | 492.6±409.5 | 0.484 |
| Chemotherapy after recurrence          |                          |                              |              | 0.729   |
| Yes                                    | 12                       | 22                           | 34           |         |
| No                                     | 13                       | 20                           | 33           |         |
| 1st line regimen after recurrence      |                          |                              |              | 0.100   |
| Pyrimidine fluoride                    | 8                        | 20                           | 28           |         |
| Taxane                                 | 2                        | 2                            | 4            |         |
| Other                                  | 2                        | 0                            | 2            |         |
Table II. Continued.

| Characteristic                                      | Sarcopenia (n=25, 37.3%) | Non-Sarcopenia (n=42, 62.7%) | Total (n=67) | P-value |
|----------------------------------------------------|--------------------------|-----------------------------|--------------|---------|
| Number of chemotherapy regimens after recurrence  | 1.6±0.8                  | 1.7±1.0                     | 1.7±0.9      | 0.855   |
| Total courses of chemotherapy after recurrence     | 3.7±2.4                  | 7.5±5.6                     | 6.3±5.1      | 0.092   |
| Discontinued chemotherapy due to adverse effect     | 6 (30.0%)                | 7 (31.8%)                   | 13 (38.2%)   | 0.297   |
| Overall survival from the recurrence of gastric cancer (day) | 169.0±52.8               | 492.9±83.4                  | 372.0±58.8   | <0.001  |

CAR, C-reactive protein Albumin ratio; CONUT, controlling nutrition status; GPS, Glasgow Prognostic Score. Data are expressed as the mean ± standard deviation.

Table III. Prognostic factor for the overall survival from the time at recurrence.

| Characteristic                                               | Univariate analysis | Multivariate analysis |
|--------------------------------------------------------------|---------------------|-----------------------|
|                                                             | HR                 | 95% CI                | P-value   | HR                 | 95% CI                | P-value   |
| Age ≥70 years old                                            | 1.69                | 0.91-3.22             | 0.096     |                    |                      |           |
| Body weight reduction rate ≥Median                           | 1.24                | 0.67-2.28             | 0.490     |                    |                      |           |
| Body mass index reduction rate ≥Median                       | 1.21                | 0.65-2.23             | 0.530     |                    |                      |           |
| CCI score ≥2                                                 | 0.90                | 0.37-1.92             | 0.802     |                    |                      |           |
| Tumor depth ≥pT3                                             | 0.71                | 0.35-1.66             | 0.404     |                    |                      |           |
| Lymph node metastasis ≥pN2                                   | 1.65                | 0.88-3.24             | 0.117     |                    |                      |           |
| Lymphatic invasion Ly1                                       | 0.99                | 0.45-2.62             | 0.984     |                    |                      |           |
| Venous invasion V1                                           | 0.95                | 0.43-2.52             | 0.908     |                    |                      |           |
| Neutro Lymph ratio ≥3.0                                      | 2.63                | 1.28-5.53             | 0.008*    | 1.48               | 0.40-5.01             | 0.544     |
| CONUT score ≥4                                               | 2.26                | 0.90-6.20             | 0.084     |                    |                      |           |
| Prognostic Nutritional Index ≤40                            | 2.59                | 1.23-5.50             | 0.012*    | 1.25               | 0.33-5.01             | 0.746     |
| modified GPS score ≥1                                        | 1.91                | 0.90-4.70             | 0.097     |                    |                      |           |
| Sarcopenia Yes                                               | 4.18                | 2.17-8.07             | <0.001*   | 5.04               | 1.28-22.61             | 0.021*    |
| Adjuvant chemotherapy                                        | 1.05                | 0.58-1.93             | 0.872     |                    |                      |           |
| Recurrence site Peritoneal                                   | 1.49                | 0.75-2.80             | 0.246     |                    |                      |           |
| Chemotherapy after recurrence No                            | 1.32                | 0.71-2.43             | 0.376     |                    |                      |           |
| Chemotherapy regimen after recurrence No                     | 0.45                | 0.16-1.59             | 0.192     |                    |                      |           |
improving postoperative outcomes in patients with gastric cancer (19,20). However, there were few reports on the effects of postoperative nutritional supports on the postoperative development of sarcopenia and outcome. In addition, it has been reported that subtotal gastrectomy for the upper third of gastric cancer had advantages over total gastrectomy in terms of maintaining weight and nutritional status (20,21). Thus, it will be essential to ensure thorough nutritional management after surgery, as well as surgical procedures, for maintaining skeletal muscle volume and nutritional status at the recurrence of gastric cancer.

In the present study, we also evaluated the NLR, CAR, PNI, CONUT, and mGPS at the recurrence of gastric cancer, which were well known to be preoperative prognostic markers in various malignancies (22‑26). We demonstrated that these markers were not associated with prognosis when the values at the recurrence were used, indicating the importance of preoperative value but not at the recurrence.

We compared the clinical importance of the sarcopenia preoperatively, at the recurrence, and the reduction rate of PMI from surgery to the recurrence. Sarcopenia at the recurrence and the reduction rate of PMI from surgery to the recurrence were selected as the independent poor prognostic factors by multivariate analysis.

This study has several potential limitations. The retrospective design of the study and relatively small number of patients in this study may have resulted in bias. In addition, we did not evaluate the relation of amounts of oral intake and the exercise after gastrectomy to the occurrence of gastric cancer, which made it difficult to determine whether skeletal muscle loss was caused by eating disorder after gastrectomy or with the progression of cancer.

In conclusion, fewer total courses of chemotherapy after recurrence and sarcopenia were poor prognostic factors for patients with gastric cancer recurrence. Our data suggested that prospective interventional study to prevent the reduction of skeletal muscle volume should be promising for improving survival after the recurrence of gastric cancer.

### Acknowledgements

Not applicable.

### Funding

No funding was received.

### Availability of data and materials

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

### Authors contributions

KK, HT, HS, YIt, YIs, ST, YK and HU contributed to the study conception and design. Material preparation and data collection and analysis were performed by KK. The first draft of the manuscript was written by KK and HT, and all

| Characteristic                              | Univariate analysis | Multivariate analysis |
|---------------------------------------------|---------------------|-----------------------|
| Number of regimens after recurrence <2     | 1.13                | 0.50-2.58             | 0.762                   |
| Total courses of chemotherapy after recurrence <5 | 3.82                | 1.33-11.42            | 0.013*                 |

HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; CONUT, controlling nutrition status; GPS, Glasgow Prognostic Score; CCI, Charlson comorbidity index. *P<0.05.

### Table IV. Univariate and multivariate analysis for the overall survival from the time at recurrence among the difference time of sarcopenia.

| Characteristic                              | Univariate analysis | Multivariate analysis |
|---------------------------------------------|---------------------|-----------------------|
| Sarcopenia by skeletal muscle mass reduction rate | Yes                 | 4.18                  | 2.17-8.07             | <0.001* |
| Preoperative sarcopenia                     | Yes                 | 0.93                  | 0.51-1.73             | 0.813   |
| Sarcopenia at the time of recurrence        | Yes                 | 3.58                  | 1.78-7.42             | <0.001* |

HR, hazard ratio; CI, confidence interval. *P<0.05.
authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures followed were in accordance with the Helsinki Declaration of 1964 and later versions. The study protocol was approved by the Institutional Review Board of the National Defense Medical College, and written informed consent was obtained from every patient.

Patient consent for publication

Informed consent for publication was obtained from every patient.

Competing interests

The authors declare that they have no competing interests.

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