Does neoadjuvant chemotherapy regimen affect sarcopenia status in patients with breast cancer?

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A R T I C L E   I N F O

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A B S T R A C T

Background: Low muscle mass, or sarcopenia, predicts poorer treatment outcomes in breast cancer. Neoadjuvant chemotherapy is the main treatment to improve surgical outcomes for breast cancer, yet few studies have assessed the relationships between different chemotherapy regimens and sarcopenia. This study compared body composition change between two neoadjuvant chemotherapy regimens: AC-T (anthracyclines and cyclophosphamide followed by a taxane) and TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab).

Methods: This study included 298 patients with breast cancer who received neoadjuvant chemotherapy between 2017 and 2020 at one university hospital. Body composition was assessed by computed tomography. Multiple linear regression was performed to examine predictors of SMI change.

Results: Patients receiving TCHP showed a significant mean skeletal muscle index (SMI) decrease of 1.6 cm²/m² (SD = 3.5, p < .001); patients receiving AC-T showed no significant change in mean SMI. The TCHP group also showed significantly decreased visceral and subcutaneous fat mass, while the AC-T group showed increases in both. The TCHP group had significantly more patients with newly diagnosed sarcopenia after neoadjuvant chemotherapy than the AC-T group (12% vs 1%, respectively). Chemotherapy regimen was the only significant predictor of muscle mass loss, and the TCHP group’s mean SMI decrease was 3.124 greater than that of the AC-T group (p = .015).

Conclusions: Patients receiving TCHP have a higher risk of muscle mass loss than those receiving AC-T. Considering the severe SMI decline observed in the TCHP group, further prospective studies are called for to examine treatment-induced sarcopenia and its relationship to body composition.

1. Introduction

Sarcopenia, or low muscle mass, has been recognized as having a negative impact on chemotherapy toxicities and cancer survival, and thus has become a meaningful indicator of mortality in oncology. Specifically, sarcopenia in breast cancer patients is unfavorable to clinical outcomes: it has been associated with chemotherapy toxicities [1–4], faster tumor progression [5], and higher overall mortality [6]. For example, breast cancer patients with sarcopenia have been found to have a 71% greater risk of mortality compared to patients without sarcopenia [7]. Conversely, greater muscle mass in breast cancer patients has been related to decreases in hematologic toxic effects such as neutropenia, anemia, and thrombocytopenia [8]. This is compelling evidence which supports the relationship between low muscle mass and poor treatment outcomes.

Neoadjuvant chemotherapy is the mainstay of treatment for breast cancer, and it has been proven indispensable for eradicating cancer and preventing tumor recurrence. Different types of neoadjuvant chemotherapy involving combinations of two or more drugs (e.g., representative anthracyclines and cyclophosphamide followed by a taxane [AC-T] or docetaxel, carboplatin, trastuzumab, and pertuzumab [TCHP]) have been applied in clinical settings depending on patient clinical characteristics such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression and tumor histology, stage, and grade [9,10]. Research findings indicate that sarcopenia may be an essential indicator of poor tolerance of
various types of chemotherapy as well as of increased mortality [11,12].
In a study of breast cancer patients undergoing taxane-based chemo-
therapy, patients with sarcopenia showed higher chemotherapy toxicity,
more toxicity-related hospitalizations, and reduced time to treatment
failure compared to patients without sarcopenia [3]. In a separate study
of breast cancer patients who were undergoing neoadjuvant epirubicin
plus cyclophosphamide therapy, those with sarcopenia showed signifi-
cantly more laboratory adverse events than those without sarcopenia
[13]. Furthermore, patients with metastasis breast cancer and sarcopen-
ia who received capetibactin treatment showed higher chemotherapy
toxicity and less time to tumor progression than patients without sar-
copenia [5]. Considering that the mechanisms, cycles, effectiveness, and
major toxicities related to different chemotherapy regimens vary, re-
search is needed into how different types of regimens affect sarcopenia
status post neoadjuvant chemotherapy.

Among patients with breast cancer, the prevalence of sarcopenia is
known to be high—it has been estimated at about 39.8% [12], 43.2% [11],
and 45.0% [7] in recent systematic reviews and meta-analyses. In the
wake of such findings, it is crucial to assess breast cancer patients for
sarcopenia before and after chemotherapy in order to optimize treat-
ment efficacy and tolerance and minimize adverse side effects. Yet
despite the significance of sarcopenia status to treatment outcomes, and
the different mechanisms and toxicities associated with various
chemotherapy regimens, little research attention has been given to act-
ual muscle mass loss during neoadjuvant chemotherapy. There has
been no prior research with a large sample of breast cancer patients to
investigate the possibility that body composition changes during neo-
adjuvant chemotherapy might vary by treatment regimen. Conse-
quently, the purpose of this study was to compare changes in body
composition among two groups of breast cancer patients receiving
neoadjuvant chemotherapy—one receiving an AC-T regimen and the
other receiving a TCHP regimen—and to examine predictors of muscle
mass loss in these groups.

2. Material and methods

2.1. Study design and setting

This was a retrospective cohort study of breast cancer patients who
were treated in one university hospital in South Korea between January
2017 and November 2020. The institutional review board of the hospital
of the Yonsei University Health System approved the study protocol (#4-
2021-0452).

2.2. Study population

The hospital’s big data team extracted patient data from the hospi-
tal’s dataset based on ICD-10-CM Code C50 (malignant neoplasm of
breast). Guided by our study’s eligibility criteria, the team extracted
data for patients with breast cancer who were women aged 20 years or
older, had completed neoadjuvant chemotherapy, and had received at
least two abdominal computed tomography (CT) scans which provided
images of the third lumbar spine vertebra (L3) before and after neo-
adjuvant chemotherapy. We excluded patients who had stage IV cancer,
did not receive the AC-T or TCHP chemotherapy regimen, or had
inadequate CT images that did not allow analysis of body composition.

2.3. Data collection and measurement

As part of our comprehensive information collection effort, we
reviewed participants’ medical records for demographic and clinical
data, including cancer- and chemotherapy-related information. In
addition, we collected body composition data generated by the uni-
versity’s Convergence Medical Technology Center, which performed
body composition analysis using Aquarius iNtuition viewer version
4.4.13. P6 software (TeraRecon, Durham, North Carolina). The
Hounsfield unit (HU) values used for measurements ranged from
–29HOU to +150HOU for skeletal tissue, –190HOU to –30HOU for subcu-
taneous fat, and –150HOU to –50HOU for visceral fat.

We assessed abdominal CT scans that provided images of L3 before
and after neoadjuvant chemotherapy. The mean time until CT follow-up
(from before to after neoadjuvant chemotherapy) was 6 months, with
periods ranging from 3 to 9 months. The first CT was taken when pa-
ients visited the hospital to undergo biopsy, and the time interval be-
tween each patient’s first neoadjuvant chemotherapy session and the
first CT averaged 14 days (SD: 8.5). The second CT was taken after all
neoadjuvant chemotherapy was completed (before surgery), and this
time interval averaged 11 days (SD: 3.4). A single axial CT slice at the L3
level—a vertebral landmark previously validated in sarcopenia studies
of cancer patients [14–18]—was selected for body composition analysis.

We applied the sarcopenia cut-off value of 38.5 cm²/m² for women [19].
We calculated the skeletal muscle index (SMI) as cm²/m² by measuring
the skeletal muscle mass cross-sectional area (in cm²) at L3 and then
normalizing the results for patient height in meters squared (m²).
Similar to the SMI, we calculated the subcutaneous fat index (SFI) and
visceral fat index (VFI) by dividing each related cross-sectional area by
height squared. Fig. 1 shows the change in body composition before and
after neoadjuvant chemotherapy in one patient who received the TCHP
regimen.

Finally, using the body mass index (BMI) classifications for Asia [20,
21], we assigned four BMI categories: underweight (BMI < 18.5), normal
weight (BMI 18.5–22.9), overweight (BMI 23.0–24.9), and obese (BMI
≥25.0).

2.4. Statistical analysis

All statistical analyses were performed using STATA IC version 16.
We employed chi-square tests to describe and compare the distributions
of demographic and clinical data between a patient group receiving AC-
T chemotherapy and a group receiving TCHP chemotherapy. A paired t-
test was applied to examine body composition changes before and after
the neoadjuvant chemotherapy regimens. Multiple linear regression was
used to examine predictors of SMI change after neoadjuvant chemother-
apy; p values lower than .05 were considered significant.

3. Results

3.1. Demographic and clinical characteristics

A total of 298 patients with breast cancer were included in this study.
The demographic and clinical characteristics of the two participant
groups (by AC-T or TCHP chemotherapy regimen) are shown in Table 1.
The participants’ mean age of approximately 53 years was similar in
each group, and most patients had stage II cancer (n = 212, 71.4%).
In the AC-T group, mean BMI before chemotherapy was 23.7 ± 3.2 kg/
m², with 56.6% of the participants categorized as overweight (BMI
23.0–24.9) or obese (BMI >25.0). For the TCHP group, the mean BMI
before chemotherapy was 23.5 ± 3.3 kg/m², with 51.2% of participants
categorized as overweight or obese. There was no significant heteroge-
neity between the groups except for the duration of neoadjuvant
chemotherapy and the tumor subtype. For treatment period, the AC-T
group had a median value of 161 days, and the TCHP group had a me-
dian value of 105 days (p < .001). With respect to tumor subtypes, all
participants with triple-negative breast cancer received the AC-T
regimen (p < .001).

3.2. Body composition and sarcopenia status before and after
chemotherapy in AC-T and TCHP groups

Table 2 shows changes in body composition during neoadjuvant
chemotherapy for the two treatment groups.

At the beginning of neoadjuvant chemotherapy, we observed no
significant heterogeneity in body composition parameters (SMI, VFI, SFI, BMI, and body surface area [BSA]) between the groups. However, there were significant between-group differences in body composition changes after chemotherapy. In the AC-T group (n = 214), the mean SMI was 24.4 cm²/m² (SD = 5.4) before neoadjuvant chemotherapy and did not significantly change after chemotherapy (at 42.4 cm²/m² [SD = 5.9]); t(213) = −0.22, p = .830. However, in the TCHP group, a significant difference in SMI was observed from before to after chemotherapy (t(83) = 4.00, p = .0001). In that group, the mean SMI was 42.6 cm²/m² (SD = 5.8) before chemotherapy and decreased considerably (by almost 1.6 cm²/m²) to 41.0 cm²/m² (SD = 5.6) after chemotherapy. In addition, based on a two-sample t-test between the AC-T and TCHP groups, we observed a significant difference in the groups’ SMI changes during chemotherapy (t(296) = 3.41, p = .0007).

In addition, after neoadjuvant chemotherapy, the mean VFI in the AC-T group showed a significant increase of 2.55 cm²/m², but the mean VFI in the TCHP group showed a significant decrease of 2.390 cm²/m² (SD = 17.3). Similarly, the mean SFI in the AC-T group showed a significant increase of 1.745 cm²/m² post chemotherapy, but the mean SFI in the TCHP group showed a significant decrease of 2.17 cm²/m². Based on a paired t-test between the AC-T and TCHP groups, there were thus significant differences in both VFI and SFI changes during chemotherapy (t(296) = 4.26, p = .0000 and t(296) = 4.83, p = .0000, respectively).

### 3.3. Distributions of SMI change during chemotherapy in AC-T and TCHP groups

![Fig. 1. Body composition evaluation via CT images for one 55-year-old woman before and after neoadjuvant TCHP. Axial CT images of the third lumbar vertebral region show the different proportions of skeletal muscle (green), visceral fat (yellow), and subcutaneous fat (purple) mass before and after TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab). This patient received six cycles of the TCHP regimen during neoadjuvant chemotherapy. Body mass index was 27.06 kg/m² (obese) before THCP and 24.56 kg/m² (overweight) after TCHP. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)](image1)

![Fig. 2. Distribution of absolute SMI, VFI, and SFI changes during neoadjuvant chemotherapy. This figure illustrates the different distribution characteristics of the two groups. The median value of SMI change in the TCHP group showed a considerably greater skeletal muscle mass loss than the median value in the AC-T regimen group (median: 1.6 vs. −0.05, respectively). In addition, the skewness of SMI change in the TCHP group was higher than that in the AC-T group (skewness: .191 vs. 0.055, respectively). Similarly, the median VFI and SFI changes in the TCHP group showed decreases during neoadjuvant chemotherapy, but the median VFI and SFI changes in the AC-T group showed increases. Accordingly, the distribution graph in Fig. 2 reveals a greater loss of skeletal muscle and fat in the TCHP group.](image2)

### 3.4. Sarcopenia prevalence during neoadjuvant chemotherapy

![Fig. 3 presents the sarcopenia prevalence in the AC-T and TCHP groups before (at baseline) and at completion of neoadjuvant chemotherapy. Using the sarcopenia cut-off value for women [19], we observed no significant difference in sarcopenia prevalence between the groups before chemotherapy: both groups had a sarcopenia prevalence of about 25%. However, although only 1% of the AC-T group showed newly diagnosed sarcopenia after chemotherapy, the TCHP group showed a significant increase in newly diagnosed sarcopenia, of 12%. Thus, the group that received the TCHP regimen had a much higher proportion of patients experiencing sarcopenia status than the group that received the AC-T regimen (37% vs. 26%, respectively; χ²(1) = 128.215, p < .001).](image3)

### 3.5. Predictors of SMI change during neoadjuvant chemotherapy

![Table 3 shows multiple linear regression results for SMI change during neoadjuvant chemotherapy. This regression included patient age, BMI at diagnosis, cancer stage, tumor subtype, chemotherapy regimen, and chemotherapy duration as independent predictors. The model fit statistics were significant (at F (9,278) = 2.66, p < .01), with 7% of the variance in SMI change explained with this model. Chemotherapy regimen was the only significant predictor of decreased SMI, and the](image4)
Table 1: Demographic and clinical characteristics of the AC-T and TCHP treatment groups (N = 298).

| Characteristic                  | AC-T group (n = 214) | TCHP group (n = 84) | χ² or t (p value) |
|---------------------------------|----------------------|--------------------|-------------------|
| Mean ± SD (range) or No. (%)    | Mean ± SD (range) or No. (%) |
| Age (years)                     | 52.86 ± 10.54 (26-77) | 53.06 ± 9.49 (35-82) | 0.1512 (0.880)    |
| Stage of tumor                  | I                    | II                 | III               |
|                                | 3 (1.4)              | 2 (2.4)            | 0.358             |
| Initial clinical T stage        | I                    | II                 | III               |
|                                | 21 (9.8)             | 20 (23.8)          | 20 (23.8)         |
| Initial clinical N stage        | 0                    | 1                  | 2                 |
| Duration of neoadjuvant         | 160 ± 7.13           | 107 ± 5.84         | 4.346             |
| chemotherapy                   |                      |                    |                   |
| Tumor subtype                   | HR+/HER2             | HR+/HER2+          | HR+/HER2-          |
|                                | 100 (46.7)           | 12 (5.6)           | 9 (4.2)           |
|                                | 3 (3.6)              | 36 (42.9)          | 45 (53.6)         |
| Ki-67                           | Low (<14%)           | 25 (11.7)          | 8 (9.5)           |
|                                | 8.95                 | 0.258              |
| High (>14%)                     | 181 (84.6)           | 72 (85.7)          | (1.612)           |
| BMI at baseline                 | !<.18.5              | 5 (2.3)            | 4 (4.8)           |
|                                | (underweight)        | 2.650              |                   |
|                                | 18.5-22.9 (normal)   | 88 (41.1)          | 37 (44.0)         |
|                                | 23.0-24.9 (overweight)| 59 (27.6)          | 17 (20.2)         |
|                                | 25.0+ (obese)        | 62 (29.0)          | 26 (31.0)         |

Notes. AC-T regimen = combination of an anthracycline and cyclophosphamide (AC) followed by a taxane; BMI = body mass index; HER2+/− = human epidermal growth factor receptor 2-positive/-negative; HR+/− = hormone receptor-positive/-negative; TCHP regimen = docetaxel, carboplatin, trastuzumab, and pertuzumab; TNBC = triple negative breast cancer.

mean SMI decrease in the TCHP group was 3.124 greater than in the AC-T group (β = −3.124 vs. β = 1.000, p = .015).

4. Discussion

Oncology research studies have shown increased interest in sarcopenia over the past decade, with the recognition that it has a negative impact on cancer treatment and survival. Sarcopenia has thus become a meaningful indicator for mortality in oncology. However, few studies have examined actual muscle mass loss during neoadjuvant chemotherapy, let alone the effects of different chemotherapy regimens on changes in body composition in a large cohort of patients with breast cancer. Our study contributes new insights in that the TCHP regimen was associated with a large increase in newly diagnosed sarcopenia during neoadjuvant chemotherapy as well as 3.124 greater loss of muscle mass than was seen with the AC-T regimen. These findings highlight the importance of closely monitoring muscle mass loss among breast cancer patients who receive the TCHP chemotherapy regimen.

Our study findings have several clinical implications. First, we found that the TCHP group showed greater loss of muscle mass during neoadjuvant chemotherapy than the AC-T group, even though they showed no significant SMI differences at baseline. A previous systematic review and meta-analysis reported an average SMI reduction of 2.7 cm²/m² during chemotherapy (and/or radiotherapy) treatment for various cancer types [22]. Although cancer treatments such as chemotherapy, surgery, and radiotherapy are known to cause muscle mass loss, it is worrisome that we observed a mean SMI decrease of 1.6 cm²/m² in just 3-4 months (6 cycles, median: 105 days) of TCHP neoadjuvant chemotherapy.

One previous study involving 119 patients with breast cancer in France reported a mean SMI of 42.3 cm²/m² before chemotherapy [23], as measured by CT scan. That value is slightly lower than the mean baseline SMI of our TCHP group (42.6 cm²/m²). In another previous study, this one involving patients with metastatic breast cancer who received first-line taxane-based chemotherapy in the United States, the mean SMI measured by CT scan before chemotherapy was 41.2 cm²/m² [3], which is lower than our TCHP group’s mean SMI before chemotherapy but slightly higher than their mean SMI of 41.0 cm²/m² after neoadjuvant chemotherapy. Also, another study involving 49 patients with metastatic breast cancer in France [24] found a mean SMI of 41.7 cm²/m² before chemotherapy, as measured by CT scan. No previous breast cancer studies in South Korea have specified how much muscle mass was lost during neoadjuvant chemotherapy, but compared to studies performed in other countries, we observed a slightly higher SMI at baseline and a slightly lower SMI after chemotherapy, despite the fact that no metastatic cancer was present in our patients. As decreased SMI after neoadjuvant chemotherapy poses a threat to disease-free survival [25], decreased SMI should be given attention when determining the direction of clinical treatment and evaluating treatment effectiveness.

A second finding with clinical implications is that chemotherapy regimen was a significant predictor of SMI decrease. Compared to the AC-T group, the TCHP group showed 3.124 greater decrease in SMI. These findings indicate that muscle mass loss may differ depending on the chemotherapy regimen applied. As these two groups obviously differed in their tumor biology, such as ER, PR, and HER2, their differences in SMI change should be interpreted in light of the fact that chemotherapy regimens are selected according to the specific tumor biology present. A TCHP neoadjuvant regimen is generally used for patients with early or locally advanced breast cancer and with HER2-positive breast cancer to improve survival and achieve pathologically complete response; patients undergoing this regimen have reported experiencing adverse events such as mucositis, pain, diarrhea, fatigue, and anorexia [26,27]. A previous study involving patients with early
breast cancer has also reported that the proportion of patient-reported toxicities differed by chemotherapy regimen: a group receiving the AC-T regimen most frequently experienced fatigue over the entire course of chemotherapy, whereas a group receiving docetaxel/carboplatin with anti-HER2 therapy most frequently experienced diarrhea [28]. The fact that chemotherapy-related adverse events can vary by regimen due to the actions of the particular chemical combination involved could be indirectly or directly related to muscle mass loss. For example, the diarrhea and anorexia frequently associated with chemotherapy toxicities of the TCHP regimen could be related to loss of muscle or fat. Given the multiple causes of muscle loss in cancer patients—further examination of the degree of muscle mass loss by chemotherapy regimen, in addition to other factors, is called for.

Another meaningful implication for the clinical oncology field is our research in the concept of sarcopenia during neoadjuvant chemotherapy. A prior study found greater visceral fat mass to be related to poor growth factor receptor 2-positive/-negative; TNBC = triple-negative breast cancer.

| Variable                  | Coef   | 95% CI interval | t     | p value |
|---------------------------|--------|-----------------|-------|---------|
| Chemotherapy regimen      |        |                 |       |         |
| AC-T                      | 1.000  |                 |       |         |
| TCHP                      | -3.124 | -5.646 to -0.603| -2.44 | .015    |
| Tumor subtype             |        |                 |       |         |
| HR-/HER2+                 | 1.000  |                 |       |         |
| HR+/HER2+                 | -0.440 | -1.251 to 2.132 | 0.51  | .609    |
| HR-HER2-                  | -0.450 | -2.505 to 1.604 | -0.43 | .666    |
| TNBC                      | -0.483 | -1.566 to 0.600 | -0.88 | .381    |
| Chemotherapy duration     |        |                 |       |         |
| Baseline BMI <50          | -0.108 | -0.257 to 0.041 | -1.42 | .156    |
| Stage                     |        |                 |       |         |
| I                         | 1.000  |                 |       |         |
| II                        | 2.114  | -2.962 to 7.191 | 0.82  | .413    |
| III                       | 1.281  | -3.839 to 6.400 | 0.49  | .623    |

Notes. BMI = body mass index; Coef = coefficient; CI = confidence interval; HR-+/+ = hormone receptor-positive/negative; HER2+/+ = human epidermal growth factor receptor 2-positive/negative; TNBC = triple-negative breast cancer. F(9,278) = 2.66, p < .01, pseudo r = 0.0717.

in the AC-T group). Particularly for patients with breast cancer, not only muscle mass loss but also increased body fat could be a crucial factor affecting treatment outcomes and patient survival. Furthermore, because different types of chemotherapy have different mechanisms, their effects on patients’ changes in body composition may vary during treatment. In future studies of changes in body composition—ideally with larger samples of breast cancer patients, more specific chemotherapy regimens should be considered along with other pertinent factors such as use of hormone agents and steroids.

A prior study found greater visceral fat mass to be related to poor distant disease-free survival after neoadjuvant chemotherapy in patients with advanced breast cancer, especially those who are postmenopausal [30]. In patients with nonmetastatic breast cancer, those with high total adipose tissue have shown higher overall mortality [6]. To support understanding of the combination of low muscle mass and high fat mass, research in the oncology field has been turning to the concept of sarcopenic obesity. Our study findings suggest that different chemotherapy regimens may make different contributions to body composition...
changes that lead to either sarcopenia or sarcopenic obesity. In terms of clinical relevance, our findings of the risk and severity of muscle mass loss in our TCHP group suggest a need for careful monitoring of body composition among breast cancer patients receiving this regimen. This study has some limitations that should be recognized. First, our retrospective study collected all patient data from a single medical center. Accordingly, our results may have limited generalizability, and we could not determine cause-and-effect relationships. Second, we could not include skeletal muscle density as a variable due to the possibility that the use of CT contrast agents would produce inaccurate muscle density results. Third, although sarcopenia is generally associated with a negative prognosis, this does not directly apply to treatment-induced sarcopenia. Further prospective studies involving chemotherapy-related clinical outcomes should be performed to investigate the causes and clinical significance of treatment-induced sarcopenia. Furthermore, employing comprehensive datasets, future researchers should pursue a greater understanding of the relationships between sarcopenia and nutritional patterns, physical activity, toxicity differences by Funding, and other factors in characterizing sarcopenia and related variables, accurate measurement of skeletal muscle density should be ensured in future studies.

5. Conclusion

Our study of 298 breast cancer patients found that those receiving a neoadjuvant TCHP regimen experienced greater loss of muscle mass than those receiving a neoadjuvant AC-T regimen. This study’s TCHP group lost both muscle and fat, whereas the AC-T group had no significant change in muscle but gained fat, which suggests that the type of chemotherapy regimen may be an important predictor of sarcopenia severity as well as body composition changes in breast cancer patients undergoing neoadjuvant chemotherapy. Given the higher risk and the severity of SMI decline observed in our TCHP group, and the known relationships between sarcopenia and poor treatment outcomes, careful monitoring of body composition is necessary for breast cancer patients receiving a TCHP regimen.

Ethical approval

The institutional review board of the hospital of the Yonsei University Health System approved the study protocol (#4-2021-0452).

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Declaration of competing interest

The authors have no conflict of interest to declare in relation to the work described in this article.

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