

## Comparison of Three Survival Scores in a Series of Patients $\geq 80$ Years of Age Irradiated for Bone Metastases

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**Abstract.** *Background/Aim:* Very elderly patients irradiated for bone metastases likely benefit from individualized treatments. A specific survival score was created for this group and compared to existing instruments. *Patients and Methods:* Ninety-six patients aged 80+ irradiated for bone metastases were retrospectively evaluated. Dose-fractionation regimen plus twelve characteristics were evaluated for survival. *Results:* In the Cox regression model, performance status and tumor type were significant and used for the score, which included three groups (5-7, 8-12, and 14 points) with 6-month survival rates of 15%, 52%, and 90%. Positive predictive values (PPVs) regarding death  $\leq 6$  months were 85% (new score), 100% (previous 65+ score), and 84% (previous score for any age). The new instrument and the 65+ score were also very accurate regarding survival. Since PPV regarding death was calculated from only four patients for the 65+ score, this PPV may be less conclusive than that for the new instrument. *Conclusion:* The new score appears useful for patients aged 80+ irradiated for bone metastases.

Bone metastases represent a common complication in cancer patients (1-3). A considerable number of these patients receive radiotherapy, either alone or following surgical stabilization. For these situations, different dose-fractionation regimens are used including single-fraction, multi-fraction short-course, and longer-course regimens. Important indications for radiotherapy of bone metastases include pain

relief and re-calcification of osteolytic bone (2). Single-fraction radiotherapy is similarly effective with respect to pain relief as multi-fraction regimens, but multi-fraction regimens require re-irradiation for another episode of metastatic bone pain in the same area significantly less frequently and lead to better re-calcification (4-7). Radiation-induced re-calcification and stabilization of osteolytic bone can take several months (2). Moreover, the effect of pain relief often continues for several months or even longer than a year (2-7). Thus, patients with longer survival times would benefit from (longer course) multi-fraction radiotherapy. For this group, additional treatment with bisphosphonates or denosumab should also be considered. Both agents were shown to reduce the risk of skeletal-related events such as fractures, metastatic spinal cord compression (MSCC), and local re-treatment with surgery or radiotherapy (2, 3, 8, 9). In contrast, patients with a limited lifespan appear better treated with single-fraction radiotherapy, since symptom-control is comparable to multi-fraction treatment and patients have to spend less days receiving radiotherapy (2-7).

These data and considerations support individualization of radiotherapy for bone metastases considering several factors including the patient's survival prognosis. For estimation of a patient's remaining lifespan, survival scores are helpful. Of the scores that already exist for irradiation of bone metastases, the vast majority was created in patient cohorts treated 15 or more years ago or was limited to lesions of the spine or long bone alone (10-19). Only two survival scores were derived from data of elderly patients (65+), one in patients with symptomatic MSCC and another one in patients with bone metastases at any sites (18, 19). However, no instrument is available specifically for very elderly patients (80+), a constantly growing age group that requires particular attention due to significant comorbidities and decreased resilience to cancer therapies (20, 21). In this study, a survival score for patients aged 80+ was designed

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and compared for accuracy to the two previous scores considered most suitable for such a comparison (18, 19).

**Patients and Methods**

Ninety-six very elderly patients (aged 80+), who were treated with fractionated radiotherapy for bone metastases without neurologic deficits due to MSCC between 2009 and 2022, were retrospectively evaluated. The study was approved by the ethics committee at the University of Lübeck (22-062). Dose-fractionation regimens included 5 or 6x4.0 Gy (n=8), 10x3.0 Gy (n=48), 12 or 13x3.0 Gy (n=3), 14 or 15x2.5 Gy (n=30), and 18 or 20x2.0 Gy (n=7). The dose-fractionation regimen and 12 other characteristics were analyzed for potential associations with survival following radiotherapy (Table I). Primary tumor types with n<5 were included in the subgroup “other tumors”.

Univariate analyses were performed with the Kaplan-Meier method and the log-rank test (BlueSky Statistics LLC, Chicago, IL, USA). Significant characteristics (p<0.05) and those showing a trend (p<0.08) were subsequently included in a Cox regression model (multivariable analysis). Characteristics found significant (p<0.05) in this multivariable analysis were used for the prognostic instrument. The scoring points of these characteristics (6-month survival rate divided by 10) were summed for each patient (patient scores). Based on the patient scores, prognostic groups were designed.

In addition, the new instrument was compared for accuracy to two previous tools created for elderly patients (aged 65+) and patients of any age, respectively, with three groups each (18, 19). Accuracy was represented by the positive predictive values (PPVs) for correct prediction of death within 6 months (comparison of the least favorable groups) and survival for at least 6 months (comparison of the most favorable groups). Moreover, comparisons were performed with respect to prediction of death within 12 months and survival for at least 12 months.

PPVs for prediction of death ≤6 months and ≤12 months were calculated as follows (N=number of patients):

$$PPV = [N \text{ dying } \leq 6 \text{ months} / (N \text{ dying } \leq 6 \text{ months} + N \text{ not dying } \leq 6 \text{ months})] \times 100$$

$$PPV = [N \text{ dying } \leq 12 \text{ months} / (N \text{ dying } \leq 12 \text{ months} + N \text{ not dying } \leq 12 \text{ months})] \times 100$$

PPVs for prediction of survival ≥6 and ≥12 months were calculated as follows:

$$PPV = [N \text{ surviving } \geq 6 \text{ months} / (N \text{ surviving } \geq 6 \text{ months} + N \text{ not surviving } \geq 6 \text{ months})] \times 100$$

$$PPV = [N \text{ surviving } \geq 12 \text{ months} / (N \text{ surviving } \geq 12 \text{ months} + N \text{ not surviving } \geq 12 \text{ months})] \times 100$$

**Results**

ECOG-PS 1 (p=0.006) and favorable tumor type (breast or prostate cancer, p=0.002) were significantly associated with survival on univariate analyses (Table II). In addition, trends were found for female sex (p=0.076), interval from tumor diagnosis to RT of bone metastases of >24 months (p=0.065), and pre-RT treatment with bisphosphonates or denosumab (p=0.056). In the Cox regression model, ECOG-

Table I. Characteristics analyzed for associations with survival.

| Characteristic                                       | Subgroup          | N patients (%) |
|--|-------------------|----------------|
| Age  | 80-84 Years       | 70 (73)        |
|  | ≥85 Years         | 26 (27)        |
| Sex  | Female            | 42 (44)        |
|  | Male              | 54 (56)        |
| Eastern Cooperative Oncology Group performance score | 0-1               | 37 (39)        |
|  | 2                 | 41 (43)        |
|  | 3                 | 18 (19)        |
| Primary tumor type                                   | Breast cancer     | 24 (25)        |
|  | Prostate cancer   | 26 (27)        |
|  | Lung cancer       | 14 (15)        |
|  | Kidney cancer     | 10 (10)        |
|  | Colorectal cancer | 6 (6)          |
| Interval from tumor diagnosis to radiotherapy        | Other tumors      | 16 (17)        |
|  | ≤24 Months        | 49 (51)        |
| Visceral metastases                                  | >24 Months        | 47 (49)        |
|  | No                | 55 (57)        |
| Other bone metastases                                | Yes               | 41 (43)        |
|  | No                | 43 (45)        |
| Metastatic sites                                     | Yes               | 53 (55)        |
|  | Spine only        | 36 (38)        |
|  | Other sites only  | 31 (32)        |
| Number of irradiated sites                           | Both              | 29 (30)        |
|  | 1                 | 44 (46)        |
| Pathological fracture prior to radiotherapy          | ≥2                | 52 (54)        |
|  | No                | 75 (78)        |
| Bisphosphonates or denosumab prior to radiotherapy   | Yes               | 21 (22)        |
|  | No                | 66 (69)        |
|  | Yes               | 24 (25)        |
| Systemic therapy prior to radiotherapy               | Unknown           | 6 (6)          |
|  | No                | 39 (41)        |
| Dose-fractionation regimen                           | Yes               | 57 (59)        |
|  | 5 or 6x4.0 Gy     | 8 (8)          |
|  | 10x3.0 Gy         | 48 (50)        |
|  | 12 or 13x3.0 Gy   | 3 (3)          |
|  | 14 or 15x2.5 Gy   | 30 (31)        |
|  | 18 or 20x2.0 Gy   | 7 (7)          |

PS [hazard ratio (HR)=1.60, 95% confidence interval (CI)=1.11-2.32, p=0.012] and tumor type (HR=1.17, 95%CI=1.06-1.29, p=0.002) were significant (Table III) and, therefore, used for the survival score. The corresponding scoring points are given in Table IV. Patient scores ranged between 5 to 14 points (Figure 1); no patient achieved 13 points. Considering the 6-month survival rates of the patient scores, three groups were designed, namely 5-7 points (group A, n=23), 8-12 points (group B, n=63) and 14 points (group C, n=10). Median survival times were 3, 9, and 24 months, respectively (p<0.001), 6-month survival rates were 15%, 52%, and 90%, respectively, and 12-month survival rates 7%, 37%, and 90% (Figure 2, p<0.001).

In addition, the new instrument (80+) was compared to two previous tools that were developed for patients of any age (Table V) and patients aged 65+ (Table VI), respectively

Table II. Six- and 12-month survival rates of the investigated characteristics.

| Characteristic                                       | Subgroup          | 6-month survival (%) | 12-month survival (%) | p-Value      |
|--|-------------------|----------------------|-----------------------|--------------|
| Age  | 80-84 Years       | 47                   | 37                    | 0.88         |
|  | ≥85 Years         | 48                   | 34                    |              |
| Sex  | Female            | 54                   | 41                    | 0.076        |
|  | Male              | 42                   | 32                    |              |
| Eastern Cooperative Oncology Group performance score | 0-1               | 65                   | 55                    | <b>0.006</b> |
|  | 2                 | 40                   | 26                    |              |
|  | 3                 | 27                   | 20                    |              |
| Primary tumor type                                   | Breast cancer     | 70                   | 65                    | <b>0.002</b> |
|  | Prostate cancer   | 54                   | 42                    |              |
|  | Lung cancer       | 36                   | 21                    |              |
|  | Kidney cancer     | 30                   | 15                    |              |
|  | Colorectal cancer | 44                   | 22                    |              |
|  | Other tumors      | 23                   | 11                    |              |
| Interval from tumor diagnosis to radiotherapy        | ≤24 Months        | 36                   | 29                    | 0.065        |
|  | >24 Months        | 59                   | 43                    |              |
| Visceral metastases                                  | No                | 52                   | 41                    | 0.46         |
|  | Yes               | 41                   | 29                    |              |
| Other bone metastases                                | No                | 48                   | 42                    | 0.58         |
|  | Yes               | 47                   | 32                    |              |
| Metastatic sites                                     | Spine only        | 50                   | 40                    | 0.99         |
|  | Other sites only  | 50                   | 39                    |              |
|  | Both              | 40                   | 28                    |              |
| Number of irradiated sites                           | 1                 | 52                   | 43                    | 0.77         |
|  | ≥2                | 43                   | 30                    |              |
| Pathological fracture prior to radiotherapy          | No                | 47                   | 41                    | 0.16         |
|  | Yes               | 48                   | 16                    |              |
| Bisphosphonates or denosumab prior to radiotherapy   | No                | 41                   | 28                    | 0.056        |
|  | Yes               | 58                   | 53                    |              |
| Systemic therapy prior to radiotherapy               | No                | 42                   | 25                    | 0.14         |
|  | Yes               | 51                   | 43                    |              |
| Dose-fractionation regimen                           | 5 or 6×4.0 Gy     | 13                   | 13                    | 0.19         |
|  | 10×3.0 Gy         | 40                   | 33                    |              |
|  | 12 or 13×3.0 Gy   | 100                  | 0                     |              |
|  | 14 or 15×2.5 Gy   | 62                   | 49                    |              |
|  | 18 or 20×2.0 Gy   | 57                   | 43                    |              |

Significant p-values are shown in bold.

Table III. Results of the multivariable analysis (Cox regression model).

| Characteristic                      | Hazard ratio | 95% confidence interval | p-Value      |
|-------------------------------------|--------------|-------------------------|--------------|
| Sex                                 | 1.28         | 0.75-2.21               | 0.37         |
| ECOG performance score              | 1.60         | 1.11-2.32               | <b>0.012</b> |
| Primary tumor type                  | 1.17         | 1.06-1.29               | <b>0.002</b> |
| Interval from tumor diagnosis to RT | 0.77         | 0.47-1.27               | 0.30         |
| Pre-RT bisphosphonates or denosumab | 0.97         | 0.52-1.83               | 0.94         |

ECOG: Eastern Cooperative Oncology Group; RT: radiotherapy. Significant p-values are shown in bold.

Table IV. Six-month survival rates and scoring points of the new score developed in patients aged 80+.

| Characteristic         | Subgroup          | Survival rate at 6 months (%) | Scoring points |
|------------------------|-------------------|-------------------------------|----------------|
| ECOG performance score | 0-1               | 65                            | 7              |
|                        | 2                 | 40                            | 4              |
|                        | 3                 | 27                            | 3              |
| Primary tumor type     | Breast cancer     | 70                            | 7              |
|                        | Prostate cancer   | 54                            | 5              |
|                        | Lung cancer       | 36                            | 4              |
|                        | Kidney cancer     | 30                            | 3              |
|                        | Colorectal cancer | 44                            | 4              |
|                        | Other tumors      | 23                            | 2              |

ECOG: Eastern Cooperative Oncology Group.

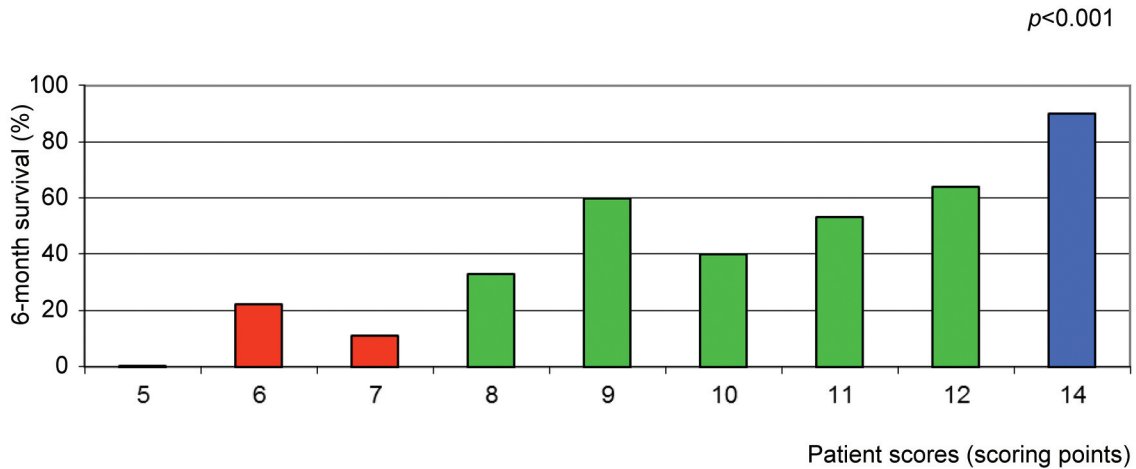


Figure 1. Patient scores (scoring points) and corresponding 6-month survival rates (Kaplan-Meier method). The *p*-value was obtained using the log-rank test.

Table V. Characteristics and scoring points of the score developed in patients of any age (18).

| Characteristic              | Subgroup          | Scoring points |
|-----------------------------|-------------------|----------------|
| Age                         | ≤60 Years         | 5              |
|                             | 61-70 Years       | 4              |
|                             | >70 Years         | 4              |
| Karnofsky performance score | ≤70               | 2              |
|                             | 80-100            | 6              |
| Primary tumor type          | Breast cancer     | 6              |
|                             | Prostate cancer   | 5              |
|                             | Lung cancer       | 3              |
|                             | Kidney cancer     | 6              |
|                             | Colorectal cancer | 3              |
|                             | Other tumors      | 2              |

Table VI. Characteristics and scoring points of the score developed in patients of any age (18).

| Characteristic         | Subgroup                  | Scoring points |
|------------------------|---------------------------|----------------|
| Sex                    | Female                    | 7              |
|                        | Male                      | 5              |
| ECOG performance score | 0-1                       | 7              |
|                        | 2-3                       | 4              |
| Primary tumor type     | Breast cancer             | 8              |
|                        | Prostate cancer           | 7              |
|                        | Lung cancer               | 3              |
|                        | Kidney cancer             | 5              |
|                        | Colorectal cancer         | 5              |
|                        | Cancer of unknown primary | 3              |
| Visceral metastases    | Other tumors              | 4              |
|                        | No                        | 6              |
|                        | Yes                       | 5              |

ECOG: Eastern Cooperative Oncology Group.

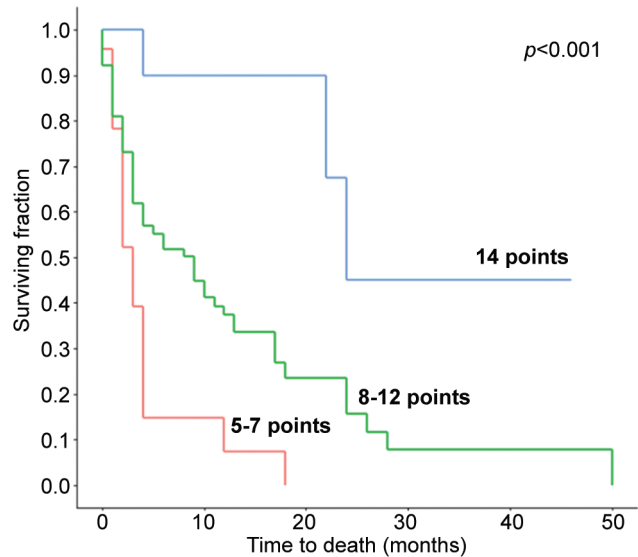


Figure 2. Kaplan-Meier curves for survival of the three prognostic groups (5-7, 8-12, and 14 points) of the new score. The *p*-value was obtained using the log-rank test.

(18, 19). The PPVs for correct prediction of death ≤6 months were 85% with the new score, 100% with the 65+ score, and 84% with the score for any age, respectively, and PPVs regarding death ≤12 months were 93%, 100%, and 95%, respectively (Table VII). Moreover, PPVs were 90%, 90%, and 70%, respectively, for prediction of survival ≥6 months, and 90%, 90%, and 65%, respectively, for prediction of survival ≥12 months. All three scores achieved high accuracy for prediction of death, the new score and the 65+ score also for prediction of survival.

Table VII. Prognosis-groups of the compared tools with scoring points and survival rates.

| Prognosis    | New score developed in patients aged 80+ |                      |                       | Score developed in patients of any age (18) |                      |                       | Score developed in patients aged 65+ (19) |                      |                       |
|--------------|--|----------------------|-----------------------|---|----------------------|-----------------------|---|----------------------|-----------------------|
|              | Scoring points                           | Survival at 6 months | Survival at 12 months | Scoring points                              | Survival at 6 months | Survival at 12 months | Scoring points                            | Survival at 6 months | Survival at 12 months |
| Poor         | 5-7<br>(n=23)                            | 15%                  | 7%                    | 8-9<br>(n=22)                               | 16%                  | 5%                    | 17<br>(n=4)                               | 0%                   | 0%                    |
| Intermediate | 8-12<br>(n=63)                           | 52%                  | 37%                   | 10-14<br>(n=51)                             | 50%                  | 35%                   | 18-25<br>(n=82)                           | 44%                  | 31%                   |
| Favorable    | 14<br>(n=10)                             | 90%                  | 90%                   | 15-17<br>(n=23)                             | 70%                  | 65%                   | 27-28<br>(n=10)                           | 90%                  | 90%                   |

n: Number of patients.

## Discussion

Very elderly patients (80+) including those irradiated for bone metastases benefit from individualized treatments. As stated in the introduction, the regimen of radiotherapy ideally becomes attuned to a patient's expectancy. Patients with a short remaining lifespan would benefit from treatment with a single fraction, which was shown in several randomized trials and meta-analyses to results in similar rates of complete and overall pain relief as fractionated regimens (4-7). Single-fraction treatment was found inferior to fractionated treatment with respect to longer-term pain control and remineralization of osteolytic lesions (4-7). However, since successful remineralization takes several months, both outcomes are less important for patients with poor prognoses. When selecting a radiation regimen consistent with the patient's individual setting, it is crucial to have an idea of his or her remaining survival time. To support treating physicians in this connection, survival scores can do a great service. Several such instruments are already accessible for patients with osseous metastases scheduled for radiation therapy (10-19). However, no instrument so far was designed especially for patients aged 80+. Since this age group is biologically different from younger patients and constantly growing, a specific instrument for patients  $\geq 80$  years of age appears advisable.

In the current study, such an instrument including three survival groups (5-7, 8-12, and 14 points, respectively) was produced. Median survival in the 5-7 points-group was only 3 months, and only 15% of the patients survived  $\geq 6$  months. Thus, most patients of this group should be treated with 1x8-10 Gy (2-7). Some patients, *e.g.*, with a large soft tissue component, may be considered for 20-24 Gy in 5-6 fractions. In the 8-12 points-group, median survival was considerably longer (9 months) than that in the 5-7 points-group, and 37% of these patients lived for  $\geq 12$  months following irradiation of their osseous lesions. Thus, longer-term pain control and remineralization gain importance. Therefore, fractionated

radiotherapy is a better option than 1x8-10 Gy. In a randomized trial from The Netherlands, 6x4 Gy resulted in significantly fewer pathological fractures and re-treatments at the initially irradiated sites than 1x8 Gy (22). In addition, in two randomized trials, 10x3 Gy was associated with fewer re-treatments than 1x8 Gy (23, 24). Therefore, 6x4 Gy and 10x3 Gy appear good options for the 8-12 points-group. In addition, patients of this group should be considered for denosumab or bisphosphonates that were demonstrated to postpone the need for re-irradiation (8, 9). The potential benefit and risks including osteonecrosis of the jaw need to be discussed with patients. The median survival time in the 14 points-group was 24 months, and the 12-months survival rate was as high as 90%. Therefore, these patients should receive fractionated radiotherapy. In the multivariable analysis of the recently published retrospective study of Jensen *et al.*, the biological effective radiation dose was the only independent predictor of increased bone-density (25). Thus, patients of the 14 points-group should receive higher-dose fractionated treatment such as 35-37.5 Gy in 14-15 fractions or 36-40 Gy in 18-20 fractions. Moreover, lower doses per fraction are generally associated with a lower risk of radiation-related late sequelae (26). Patients of the 14 points-group would also benefit from denosumab or bisphosphonates. When intending to follow these recommendations, physicians should regard the limitations of the current score including the lack of its validation and the retrospective study design. Moreover, the score may not be used for patients with symptomatic compression of the spinal cord.

The new instrument was compared for precision to two already available tools that were designed in patients aged 65+ and a cohort not limited to a certain age, respectively. These two scores were selected for comparison, because they were not limited to either lesions of the spine or long bones like the current score and were created in patient cohorts unexceptionally treated during the last 15 years. Accuracy achieved with the new instrument regarding survival  $\geq 6$  and

≥12 months was high (90% and 90%, respectively) and the same as with the 65+ score (90% and 90%, respectively) (19). Regarding survival, the new and the 65+ scores were superior to the score not limited to an age group (70% and 65%, respectively) (18). Accuracy of the new instrument regarding death ≤6 and ≤12 months was also high (85% and 93%, respectively) and similar compared to the score not limited to a certain age group (84% and 95%, respectively) (18). The accuracy of the 65+ score to predict death was even higher (100% and 100%, respectively). However, the rates for the 65+ score were obtained from only four patients who fell in the worst-prognosis group. In the current score, the worst-prognosis group included 23 patients. Therefore, the PPVs of the new score are likely more conclusive than the PPVs of the 65+ score. Thus, the new score appears useful for patients aged 80+, although the PPVs of the 65+ score regarding prediction of death were higher. To predict death in patients ≥80 years as precisely as possible, both scores may be used and considered supplementary.

In summary, the first instrument was designed to predict survival of patients aged 80+ assigned to radiotherapy of bone metastases. The score was compared to two previous instruments. PPVs were chosen as indicators of accuracy. All three scores achieved high accuracy regarding estimation of death ≤6 and ≤12 months. The new and the 65+ score were also very accurate regarding estimation of survival ≥6 and ≥12 months. Since the PPVs regarding death were calculated from only four patients for the 65+ score, these PPVs may be less conclusive than the PPVs of the new instrument that were calculated from 23 patients. The new score can be considered useful in addition to the 65+ score for patients aged 80+ scheduled for radiotherapy of bone metastases. It may not be used for patients with symptomatic compression of the spinal cord. Moreover, validation of the new instrument in a prospective study is required.

### Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

### Authors' Contributions

D.R., C.D., S.E.S., C.K., S.T., and S.J. participated in the design of the study. D.R. and C.D. provided the data, which were analyzed by D.R. and S.E.S. Funding was acquired by D.R., S.T., and S.J. The article drafted by D.R. and S.E.S. was reviewed and finally approved by all Authors.

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