Original Article
Male sexual health and dysfunction

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Erectile Dysfunction in Germ Cell Tumor Survivors

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Purpose: Germ cell tumors (GCTs) are the most common malignant neoplasms in adolescents and young adults, and most patients with these tumors can be completely cured. Therefore, maintaining quality of life (QOL) is important. Erectile dysfunction (ED) is one factor that reduces the QOL of GCT survivors. We aimed to clarify the relationship between ED and age, follow-up period, serum levels of hormones, and treatment methods for GCT survivors.
Materials and Methods: We evaluated ED using the Sexual Health Inventory for Men questionnaire (SHIM) and measured serum levels of hormones in survivors after GCT treatment. The relationships between the SHIM score responses and age, serum levels of hormones, follow-up period, and treatment methods were assessed using a logistic analysis.
Results: Fifty-two GCT survivors were enrolled and 46 survivors completed the SHIM. The median age, follow-up period, and SHIM score were 38 years, 35 months, and 18, respectively. Regarding the SHIM scores, 85% had scores <22 and 46% had scores <17. The percentage of SHIM scores <17 was 69% in patients with under 2 years of follow-up. It significantly improved to 33% in patients with over 2 years of follow-up. The multivariate analysis identified the follow-up period as an independent factor for SHIM scores <17. Age, serum levels of hormone, and treatment method were not significant factors for SHIM scores <17.
Conclusions: Improvement of SHIM score can be expected after GCT treatment regardless of age, serum levels of hormone, and treatment method.

Keywords: Erectile dysfunction; Neoplasms, germ cell and embryonal; Sexual health; Survivors

INTRODUCTION

Germ cell tumors (GCTs) are the most common malignant neoplasms in adolescents and young adults (AYAs). Thirty percent of patients with GCT have metastases. In Japan, patients with metastatic GCT are treated with cisplatin-based chemotherapy followed by retroperitoneal lymph node dissection (RPLND), and the prognosis is good. Because AYAs can survive after multimodal treatment, it has become more important to manage complications after treatment to maintain the survivors' quality of life (QOL). Long-term complications among GCT survivors include secondary malignant neoplasms, cardiovascular disease, neurotoxicity, nephrotoxicity, infertility, and sexual dysfunction including erectile dysfunction (ED) [1-3].

Information concerning sexual dysfunction is needed by the majority of patients with GCT [4]. Studies of GCTs have shown that QOL is comparable for GCT survivors and the general population [5-9]. The QOL

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of GCT patients worsens at the time of diagnosis and treatment but recovers afterward to the same level as that of the control group. However, GCT survivors have a significantly higher rate of ED [3], and those who do have ED have been reported to have worse QOL [5,6]. Previous studies reported that ED complications can persist for years but constantly improve [10,11]. The presence of hypogonadism has not been a predictor of ED [12-14], and the prevalence of ED has varied according to the treatment method [15]. These reports have focused on patients with gonadal GCTs, but not on patients with extragonadal GCTs. To clarify the important factors for ED after GCT treatment, we investigated the association between ED and age, follow-up period, serum levels of hormone, and treatment method. We also examined the association of ejaculatory dysfunction as well as ED with GCTs because GCT survivors also have a higher rate of ejaculatory dysfunction.

MATERIALS AND METHODS

1. Patients

A total of 52 Japanese patients with GCTs who visited Osaka University Hospital for follow-up after treatment from May 2017 to August 2017 were enrolled in this study. All patients were given one blood test and interviewed at the same time. Patients were informed about this study when they were interviewed, and informed consent was obtained.

2. Ethics statement

The study protocol was reviewed and approved by of the Institutional Review Board (IRB) of Osaka University Hospital (IRB no. 19175). Informed consent was confirmed by the IRB.

3. Laboratory tests

Blood samples were collected during the morning. Serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT) and free testosterone (FT) were measured. The reference ranges of LH, FSH, and TT are 1.7–10.0 mIU/mL, 1.5–17.2 mIU/mL, and 1.87–9.02 ng/mL, respectively. The normal ranges of FT are 7.6–23.8 pg/mL (age, 20–29 years), 6.5–17.7 pg/mL (age, 30–39 years), 4.7–21.6 pg/mL (age, 40–49 years), 4.6–19.6 pg/mL (age, 50–59 years), and 5.3–11.5 pg/mL (age, 60–69 years).

4. Erectile dysfunction and ejaculatory dysfunction

ED was evaluated by the Sexual Health Inventory for Men questionnaire (SHIM). Patients were considered to have ED based on the SHIM score: severe ED, score 1–7; moderate ED, score 8–11; mild to moderate ED, score 12–16; or mild ED, score 17–21. Patients with a SHIM score of 22–25 were thought to not have ED. SHIM scores of 22 and 17 were used to divide GCT survivors into 2 groups. The presence of ejaculatory dysfunction was asked at the same time.

5. Statistical analysis

Differences in SHIM scores between groups were evaluated by Student's t-test or an analysis of variance. Categorical variables were compared using the χ^2 test or Fisher's exact test. Correlations between SHIM scores and serum levels of hormone were determined using Spearman's rank correlation coefficient. Predictive factors for SHIM scores <17 and ejaculatory dysfunction were analyzed using univariate and multivariate logistic regression models. The items selected for the multivariate analysis were those with $p<0.15$ according to the univariate analysis and those expected to be clinically relevant. For continuous variables, the odds ratio (OR) is expressed based on the regressor change over the entire range. Statistical analyses were performed with JMP® Pro 14.3.0 (SAS Institute Inc., Cary, NC, USA). All tests were 2-sided and $p<0.05$ was considered significant.

RESULTS

1. Patient demographics and laboratory tests

Of the 52 enrolled patients, 46 (88%) completed the SHIM and 28 (54%) patients provided responses regarding the presence or absence of ejaculatory dysfunction. The median age was 38 years (range, 21–66 years). The median follow-up period after the end of treatment was 35 months (range, 1–254 months). The International Germ Cell Consensus Classification, histological characteristics, history of treatment, and serum levels of hormone are shown in Table 1. All patients who had gonadal GCTs (83%) underwent orchiectomy. RPLND was performed for both seminoma and non-seminoma if clinical stage was stage II or higher according to the General Rule for Clinical and Pathological Studies on Testicular Tumors of the Japanese Urological Associa-

tion. All RPLNDs were template RPLNDs and nerves were preserved as much as possible. Laboratory test results showed abnormal LH, FSH, TT, and FT levels in 29% (13/45), 68% (30/44), 13% (6/45), and 9.1% (4/44), respectively.

Table 1. Patients' age, IGCCC, histological characteristics, history of treatment, serum levels of hormones (n=46)

Variable	Value
Age (y)	38 (21–66)
IGCCC	
Non-metastatic	11 (24)
Good	15 (33)
Intermediate	9 (20)
Poor	10 (22)
Unknown	1 (2)
Histopathology	
Gonadal seminoma	22 (48)
Extra gonadal seminoma	1 (2)
Gonadal non-seminoma	16 (35)
Extra gonadal non-seminoma	7 (15)
No. of chemotherapy cycles	
0	11 (24)
1–3	8 (17)
>4	27 (59)
History of RPLND	
Yes	28 (61)
No	18 (39)
Median serum levels of hormones	
LH (mUI/mL)	5.6 (1.3–68.3)
FSH (mUI/mL)	24.35 (5.8–166.6)
Total testosterone (ng/mL)	3.48 (0.15–7.25)
Free testosterone (pg/mL)	10 (0.9–17.4)

Values are presented as median (range) or number (%).
IGCCC: International Germ Cell Consensus Classification, RPLND: retroperitoneal lymph node dissection, LH: luteinizing hormone, FSH: follicle stimulating hormone.

Table 2. ED grade according to SHIM scores (n=46)

ED grade	Value
Not ED (score, 22–25)	7 (15)
Mild ED (score, 17–21)	18 (39)
Mild-moderate ED (score, 12–16)	5 (11)
Moderate ED (score, 8–11)	7 (15)
Severe ED (score, 1–7)	9 (20)

Values are presented as number (%).
ED: erectile dysfunction, SHIM: Sexual Health Inventory for Men questionnaire.

2. Sexual Health Inventory for Men questionnaire scores

The median SHIM score was 18 (range, 2–25). The ED grades according to the SHIM scores are shown in Table 2. In the SHIM, the 3rd, 4th, and 5th items include a choice of "0", which was chosen by 28% of survivors (13/46); this choice indicated that 28% of the survivors did not attempt intercourse over the 6 months before completing the SHIM. Even among patients with over 2 years of follow-up, 23% of them chose "0" as the response to the 3rd, 4th, and 5th items. There was no significant difference in SHIM scores between patients in different age groups (Fig. 1).

The percentages of SHIM scores <22 and SHIM scores <17 were 85% (39/46) and 46% (21/46), respectively. The percentages of SHIM scores <22 for patients with under 2 years of follow-up and for patients with over 2 years of follow-up were 88% (14/16) and 83% (25/30), respectively. No significant difference in the percentages of SHIM scores <22 was found between the two groups based on the number of years of follow-up. The percentage of SHIM scores <17 was 69% for patients with under 2 years of follow-up. The percentage of SHIM scores <17 was significantly improved to

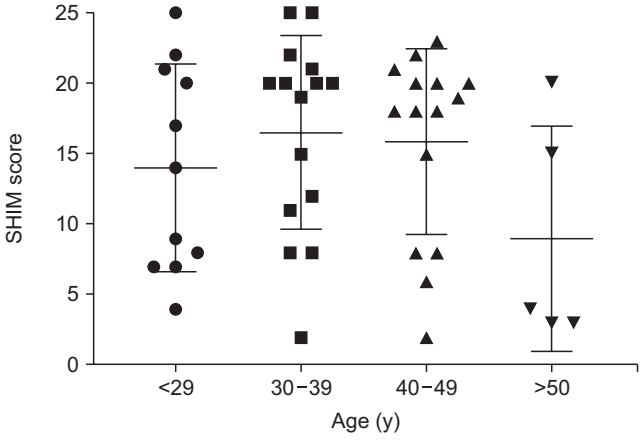

Fig. 1. Sexual Health Inventory for Men questionnaire (SHIM) scores according to age.

Table 3. SHIM scores <22 and <17 according to follow-up period

SHIM score	Follow-up period		p-value
	Under 2 years	Over 2 years	
<22	88%	83%	NS
<17	69%	33%	0.02

SHIM: Sexual Health Inventory for Men questionnaire, NS: not significant.

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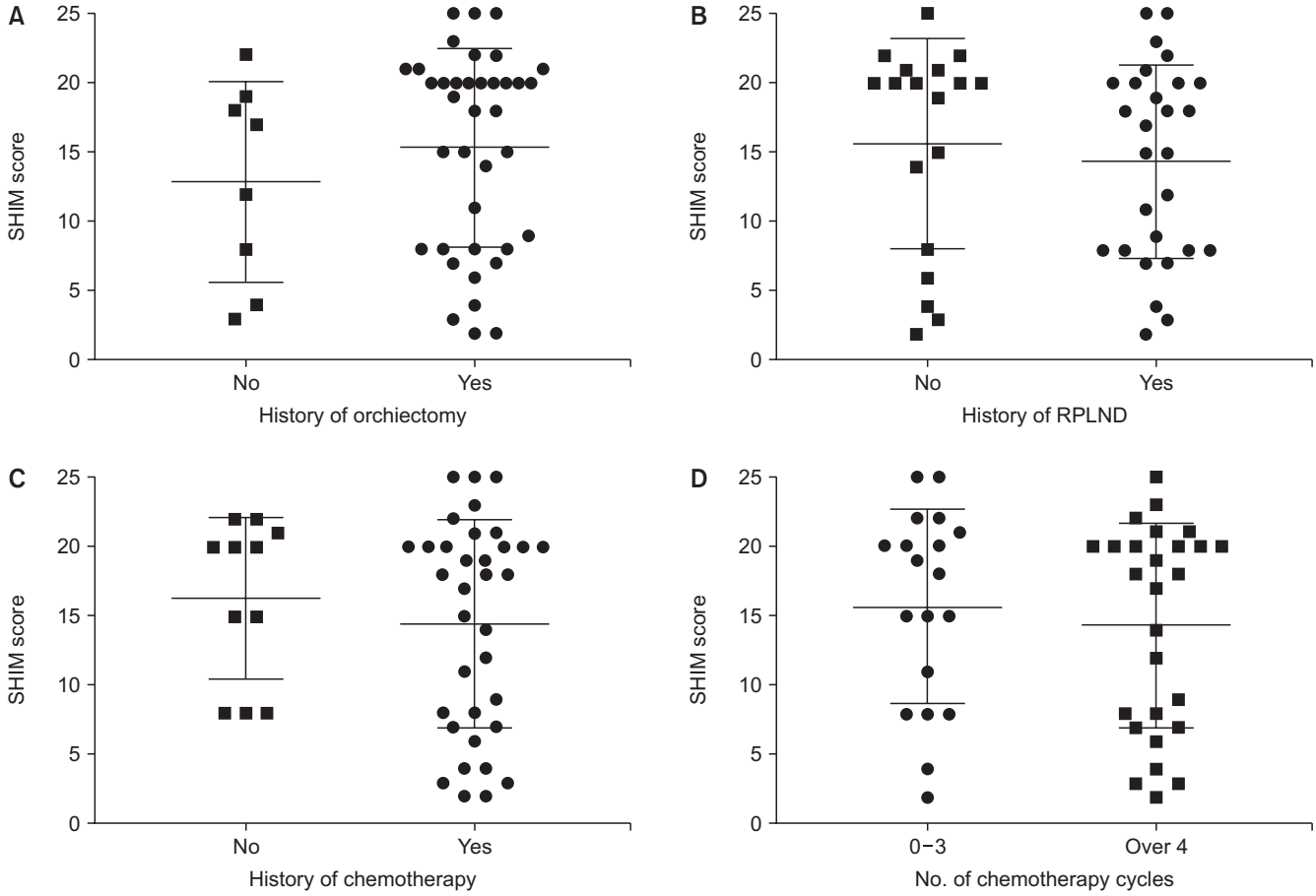

Fig. 2. Sexual Health Inventory for Men questionnaire (SHIM) scores according to treatment methods and chemotherapy cycles. (A) SHIM scores according to history of orchiectomy. (B) SHIM scores according to history of retroperitoneal lymph node dissection (RPLND). (C) SHIM scores according to history of chemotherapy. (D) SHIM scores according to number of chemotherapy cycles.

33% for patients with over 2 years of follow-up (Table 3). There was no significant difference in the SHIM scores for those with and without a history of orchiectomy (Fig. 2A), RPLND (Fig. 2B), or chemotherapy (Fig. 2C). There was no significant difference in the SHIM scores of patients who underwent 3 or fewer cycles of chemotherapy and those who underwent 4 or more cycles (Fig. 2D). According to the laboratory test results, only LH was significantly correlated with the SHIM score ($p=0.038$; $\rho=-0.32$).

3. Ejaculatory dysfunction

Ten out of 28 patients (36%) had ejaculatory dysfunction. For patients with under 2 years of follow-up, 78% (7/9) had ejaculatory dysfunction, and this percentage was significantly improved to 16% (3/19) for patients with over 2 years of follow-up ($p=0.003$). There was no significant difference in the presence of ejaculatory dysfunction for those with or without a history of orchiectomy ($p=0.36$), RPLND ($p=1.0$), chemotherapy ($p=0.28$). The SHIM scores were not significantly different between patients who underwent 3 or fewer cycles of chemotherapy and patients who underwent 4 or more cycles of chemotherapy ($p=0.70$). According to the laboratory test results, only LH was significantly correlated with ejaculation dysfunction ($p=0.02$; $\rho=-0.36$).

4. Predictive factors for Sexual Health Inventory for Men questionnaire scores <17 and ejaculatory dysfunction

Logistic analyses of age, follow-up period, serum levels of hormone, and treatment methods as predictive factors for SHIM scores <17 and ejaculation dysfunction were performed. The follow-up period was the only significant predictive factor for SHIM scores <17 according to the univariate logistic analysis ($p=0.03$). The follow-up period was also the only significant predictive factor for SHIM scores <17 according to the

Table 4. Logistic analysis for factors predictive of SHIM scores <17 (n=46)

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.4 (0.11–18)	0.80	1.0 (2.6×10^{-2}–40)	0.99
Follow-up period (over/under 2 years)	0.23 (6.2×10^{-2}–0.83)	0.03	0.13 (2.6×10^{-2}–0.65)	0.01
LH	1.4×10^{2} (0.61–3.1×10^{5})	0.07	2.7×10^{2} (0.56–1.3×10^{5})	0.08
FSH	9.3 (0.38–2.2×10^{5})	0.14		
TT	5.7×10^{-2} (2.4×10^{-3}–1.4)	0.08		
FT	0.32 (2.8×10^{-2}–3.7)	0.37		
History of chemotherapy (yes/no)	1 (0.26–3.9)	0.99		
History of RPLND (yes/no)	1.6 (0.47–5.2)	0.46		
History of orchiectomy (yes/no)	1.2 (0.27–5.7)	0.79		

SHIM: Sexual Health Inventory for Men questionnaire, OR: odds ratio; CI: confidence interval, LH: luteinizing hormone, FSH: follicle stimulating hormone, TT: total testosterone, FT: free testosterone, RPLND: retroperitoneal lymph node dissection.

Table 5. Logistic analysis for factors predictive of ejaculation dysfunction (n=28)

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.66 (3.7×10^{-2}–12)	0.78		
Follow-up period (over/under 2 years)	5.4×10^{-2} (7.3×10^{-2}–0.39)	0.004	2.1×10^{-2} (1.1×10^{-3}–0.40)	0.01
LH	8.5×10^{2} (0.21–3.1×10^{5})	0.11	4.1×10^{2} (0.11–1.6×10^{12})	0.09
FSH	19 (0.27–1.4×10^{3})	0.18		
TT	0.70 (1.3×10^{-2}–38)	0.86		
FT	4.0 (0.15–1.1×10^{2})	0.41		
History of chemotherapy (yes/no)	0.24 (1.8×10^{-2}–3.0)	0.26		
History of RPLND (yes/no)	1.1 (0.17–7.7)	0.89	2.4 (9.7×10^{-2}–59)	0.60
History of orchiectomy (yes/no)	2.0×10^{8} (1.0–∞)	1.0		

OR: odds ratio; CI: confidence interval, LH: luteinizing hormone, FSH: follicle stimulating hormone, TT: total testosterone, FT: free testosterone, RPLND: retroperitoneal lymph node dissection.

multivariate logistic analysis adjusted for age, follow-up period, and serum levels of LH (p=0.01) (Table 4). According to the univariate logistic analysis for factors predictive of ejaculatory dysfunction, the follow-up period was the only significant predictive factor (p=0.004). The multivariate logistic analysis for factors predictive of ejaculatory dysfunction was adjusted for the follow-up period, LH, and history of RPLND (p=0.01) (Table 5).

DISCUSSION

We examined ED in GCT survivors by using SHIM and elucidated the association between ED in GCT survivors and age, follow-up period, serum levels of hormone, and treatment methods. This is the first study to show that ED in GCT survivors not only improves over time but also improves significantly over time regardless of age, serum levels of hormone, and treatment methods. Furthermore, this study also showed that ejaculatory dysfunction in GCT survivors improves significantly over time regardless of age, serum levels of hormone, and treatment methods.

The prevalence of ED after GCT treatment has been reported to be 18% to 25% [3,16]. These 2 reports and ours included sexually inactive survivors in the assessment. Rossen et al [3] used six questions from the European Organisation for Research and Treatment of Cancer QLQ-PR25. Capogrosso et al [16] used the international index of erectile function (IIEF). In our study, the percentages of SHIM scores <22 and <17 were 85% and 47%, respectively. These percentages seem to be higher than those reported previously. It may need to be considered that some patients have had symptoms of ED before treatment. Tal et al [12] reported that 25% of patients after testicular cancer treatment had ED symptoms even before their diagnosis. According to a

Japanese community-based study, the ED rates were 44.6%, 63.7%, 78.2%, and 90.3% for men aged younger than 40, 40–49, 50–59, and 60 years or older, respectively [17]. The higher rates of SHIM scores <22 and SHIM scores <17 in this study may partly because Japanese males, even those without GCTs, tend to have low SHIM scores.

ED after GCT treatment has been reported to improve over time. Pallotti et al [10] reported that the percentage of ED progressively decreased from 37.8% to 16.0% for 2 years after orchiectomy. Tuinman et al [11] found low IIEF scores post orchiectomy and 3 months post treatment, with significant improvement after 1 year of follow-up. Our data also suggested SHIM scores improved after treatment.

In addition to the follow-up period, age, changes in body image [3], partnership status [18], and adverse effects of treatment [15,19] have been described as factors of ED after GCT treatment. On the other hand, no clear association with hypogonadism has been found [12-14]. Undergoing 4 or more cycles of chemotherapy has not been found as a factor of ED, but it is associated with delayed recovery of spermatogenesis [20]. Changes in body image, mainly caused by orchiectomy, include a loss of sense of manhood and, assuming that, a loss of physical strength [21,22]. In contrast to previous reports, we included patients with extragonadal GCTs in this study, thereby allowing us to examine the effects of orchiectomy on ED. Controversy exists regarding the relationship between GCT treatment and ED. Several reports have found that radiation therapy is a risk factor for ED [15,16]. Another report found that chemotherapy, radiation therapy, and multimodal treatment increased the risk of ED [23]. Other studies have found that treatment method and treatment intensity for GCT had no association with ED [13]. RPLND is not related to ED, but retrograde ejaculation [3]. Serum levels of gonadotropins and testosterones are altered by orchiectomy or toxicity of chemotherapy [14,24]. The percentage of patients with high LH levels is 22% to 55%, but alterations in testosterone are generally within the normal range [25-27]. The lower limit of the reference value for TT is 1.87 ng/mL in Osaka University Hospital. When we set the lower limit of the reference value for TT to 3 ng/mL, the percentage of patients with abnormal levels was 34%. However, TT was not a significant factor for SHIM scores <17 when the lower limit of the reference value was set to 3 ng/mL (p=0.35; OR=0.52). We also measured FT levels because TT levels did not decrease with age in Japanese men [28,29] and therefore, measuring FT levels is recommended. In our study, the factor predicting SHIM scores <17 and ejaculatory dysfunction was only the follow-up period for both. Age, serum levels of hormone, and treatment methods were not significant factors according to the univariate or multivariate analyses.

Follow-up period and LH were subjected to a multivariate analysis for factors predictive of SHIM scores <17 because of p<0.15 according to the univariate analysis. Although TT also has a p<0.15, TT was excluded from the multivariate analysis because TT was correlated with LH (p=0.001; r=-0.47), and FT measurement is recommended rather than TT in Japan as mentioned above. Age was subjected to a multivariate analysis because it is generally considered to be associated with ED, although the p-value was not <0.15 in the univariate analysis. In the multivariate analysis for factors predictive of ejaculatory dysfunction, follow-up period and serum levels of LH were subjected due to p<0.15. RPLND was subjected to a multivariate analysis because it is a known risk factor [30].

There are several limitations to the present study. First, the number of cases is small. Follow-up period might not be the only predictive factor for ED. There might be hidden factors that are undiscovered because of the small number of cases. Second, our data misses the information on changes in body image, partnered or unpartnered, and SHIM scores before GCT treatment began. All of these data have been mentioned as predictors of ED after GCT treatment. Third, the lack of information on the SHIM score before treatment makes it unclear to what extent GCT treatment affects ED. Some patients might have had ED before treatment, and the lack of this information may have added to the complications of analyzing the effects on ED due to treatment. Future studies are suggested to be longitudinal that include pre-treatment data, and may be better with information such as the presence or absence of partners and changes in body image.

CONCLUSIONS

The majority of GCT survivors have ED after treatment, but gradually the symptoms of ED improve after treatment regardless of age, serum levels of hormone,

and treatment methods. These findings should help health providers to counsel GCT survivors as the majority of them may need information about sexuality.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: KF. Data curation: KO, KF. Formal analysis: KO, KF. Funding acquisition: KF. Investigation: KF. Methodology: KF. Project administration: KF. Resources: KF. Software: KO, KF. Supervision: SF, HK, MU, RI, NN. Validation: KO, KF. Visualization: KO, KF, SF. Writing – original draft: KO. Writing – review & editing: KF, SF.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/BEZILA.

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