Prognostic Factors and Treatment Outcomes of Adult Patients With Rhabdomyosarcoma After Multimodality Treatment

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Abstract. *Background:* Adults with rhabdomyosarcoma (RMS) have a worse clinical outcome compared to pediatric cases. In the present study, the failure pattern and clinical outcome of adult patients with RMS who received multimodality treatment at our Institution was assessed. *Patients and Methods:* Data were retrospectively recorded and analyzed from 20 adult patients, aged 19 years or more, who were treated for RMS at our Institution between 2004 and 2015. Disease-free (DFS) and overall (OS) survival after starting treatment were calculated using the Kaplan–Meier method. The relationship of these outcome measures with the following variables was then assessed: Primary site, tumor stage, lymph node involvement, histological subtype, radiotherapy (RT), and duration of chemotherapy. *Results:* Sixteen patients had localized RMS, and four had metastatic disease. For the whole patient cohort, the 3-year DFS and OS rates were 20%, and 45%, respectively. Patients with alveolar histological subtype had a better 3-year OS than those with other subtypes ($p=0.038$). The median OS rates for those with localized and metastatic disease were 53.2 (95% confidence interval(CI)=14.7-91.8) months, and 21.7 (95% CI=0-45.7) months, respectively ($p=0.047$). In patients with localized RMS, those who received RT ($n=13$) had a better median DFS (24.6 versus 6.0 months, $p=0.009$) and OS (53.2 versus 11.4 months, $p=0.009$) than those who did not ($n=3$).

For patients receiving RT, concurrent chemotherapy with vincristine and cyclophosphamide ($n=11$) was associated with better 3-year DFS (36.4% versus 0%, $p<0.001$) and OS (81.8% versus 0%, $p<0.001$) compared with RT alone ($n=2$). Administration of chemotherapy for more than 19 weeks significantly correlated with better 3-year DFS (44% versus 0%, $p=0.001$) and OS (53.3% versus 0%, $p<0.001$) in those with localized RMS. Conclusion: In addition to staging and histological subtype, our results indicate that concurrent chemoradiotherapy and longer duration of chemotherapy were associated with significantly improved DFS and OS in adult patients with localized RMS.

Rhabdomyosarcoma (RMS) is the most common soft-tissue malignancy, accounting for 4-5% of cancer cases in children (1). In Taiwan, soft-tissue sarcoma accounted for approximately 40% of all pediatric cancers diagnosed between 1996 and 2010, with RMS comprising 6% of all pediatric soft-tissue sarcomas (2). RMS is far less common in adults (2). Although most cases occur in children younger than 10 years, adult RMS still accounted for 41% of all RMS cases in the Surveillance, Epidemiology and End Results (SEER) database between 1973 and 2005 (3). Pediatric patients with RMS are typically treated within clinical studies or by standard protocols. In the United States, the Intergroup Rhabdomyosarcoma Study Group (IRSG; now the Children's Oncology Group Soft-Tissue Sarcoma Committee) organized a series of studies incorporating multimodality treatment (chemotherapy, surgery, and radiotherapy) to treat pediatric RMS, and the 5-year overall survival (OS) after treatment clearly improved from 55% in IRS-I to over 71% in IRS-IV (4-6). However, the IRS studies enrolled only patients under 21 year of age, most of whom were under 14 years old, hence their results are not valid for adult patients with RMS (4-6). In contrast, treatment of adult

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RMS (age >19 years) is still non-standardized and depends on the experience and personal choice of different physicians. The treatment outcome of adult RMS has been demonstrated to be inferior to that of pediatric RMS (3, 7).

Tumor cells of RMS arise from progenitors of skeletal muscle cells throughout the body. The histology of adult RMS is much different from that of pediatric RMS, with the pleomorphic histological subtype (undifferentiated, adult spindle cell, and not otherwise specified) being most common (8, 9). In contrast, embryonal and alveolar RMS subtypes are most common in children (8, 9). The clinical presentation of RMS varies according to the site (10, 11). Tumors are usually detected as a painless or rapidly growing mass. Common symptoms of head and neck RMS include cranial nerve dysfunction, sinus pressure, rhinorrhea, nasal congestion, ear discharge, headache, and facial pain, whereas tumor of extremities presents as a rapidly enlarging, firm mass (10, 11). Tumors occurring in the retroperitoneum and mediastinum can become quite large before producing signs and symptoms (10, 11). The most common locations of adult RMS are the head and neck (40%), genitourinary tract (20%), and extremities (20%) (4).

In the present study, we assessed the failure pattern and clinical outcome of adult patients with RMS who were treated with multimodality treatment, including surgery, chemotherapy, and radiotherapy (RT) at our Institution over a 15-year period, starting in 2004. We also reviewed the clinical outcome of previously published reports of adult patients with RMS. From our patient data and other investigators' studies, we hope to develop an appropriate treatment strategy for improving the outcome of adult patients with RMS.

Patients and Methods

Data collection. We retrospectively analyzed registry data from our Institution's Cancer Administration and Coordination Center. This facility was founded in 1976 with the purpose of collecting, managing, and analyzing the data of all cancer patients treated in our institution. Data from patients newly diagnosed with RMS between March 2004 and March 2015 were collected and reviewed. Seventy-seven patients with RMS were initially identified. Pediatric patients (age <19 years), patients with Ewing sarcoma, and patients who were treated at another hospital or received no treatment were excluded. Additionally, we excluded those with insufficient data and an inadequate follow-up period. We finally included and analyzed data from 20 adult patients with RMS aged ≥19 years. No patient included in the study had a secondary malignancy.

Multimodality treatment. The treatment flowchart of these 20 adult patients with RMS is shown in Figure 1. Only one out of 20 patients did not receive chemotherapy, due to rapid disease progression after surgery and RT. Thirteen patients (65%) received a multidrug regimen, including vincristine, actinomycin D (dactinomycin), and cyclophosphamide (VAC), alternating with ifosfamide and etoposide

Table I. *Intergroup Rhabdomyosarcoma Study Group surgical/pathological clinical grouping system and risk stratification of rhabdomyosarcoma.*

Group	Description
I	Localized disease, completely resected
II	Gross total resection with a. Microscopic positive margins b. Regional lymph node involvement and resected c. Both
III	Incomplete resection of gross disease
IV	Metastatic disease
Risk	Description
Low	Localized, embryonal subtype, any resected site (Group II or III) or favorable sites Group III
Intermediate	Any localized alveolar subtype (Group I-III) or any unfavorable site Group III
High	Metastatic disease

(IE). During RT, the addition of concurrent chemotherapy with vincristine and cyclophosphamide (VC) was prescribed in 10 patients (Figure 1). Two patients received chemotherapy with doxorubicin and ifosfamide. One patient received the Taiwan Pediatric Oncology Group protocol RMS 95D (VAC and vincristine alternating with IE for 1 year plus RT) treatment (12), and another received the modified POG9354/CCG7932 protocol (mainly VAC, VC and IE) treatment (13). ARST0431 (including irinotecan) was prescribed for one patient with stage IV disease (14). One patient with a uterine RMS received cisplatin and paclitaxel prescribed by her gynecologist.

RT was delivered by a cobalt-60 machine, linear accelerator or Tomotherapy system using photon or electron beam energies with fractionated schedules of 1.8 to 2.2 Gray (Gy) daily for 5 days per week. The RT techniques included three-dimensional (3D) conformal RT, intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT) planning system. Overall, 14 patients received RT, with only one for palliation. Among the 13 patients receiving RT for curative purpose, the total dose of RT ranged from 50 to 63 Gy, with a median dose of 56 Gy. RT fields included the initial volume of the tumor plus 2 cm margins, as well as any involved lymph nodes.

Statistical methods. Patient variables were stratified by age, sex, site of origin, tumor size, stage, histology, chemotherapy duration, clinical groups, and risk level. Patients were also divided into two categories, those with favorable and unfavorable sites, according to the primary tumor site. Favorable sites included the orbit, non-parameningeal head and neck, non-bladder/non-prostate genitourinary tract, and biliary tract. All other sites were considered unfavorable. Before treatment, the patients were categorized using the IRSG staging system, in which stage I to III indicates localized disease and stage IV indicates metastatic spread; patients were also categorized using the IRSG surgical/pathologic clinical grouping system (Table I) (15, 16). In addition, the data from IRS-III and IRS-IV provided rationale for risk stratification into low-risk, intermediate-risk, and high-risk groups, which is highly predictive

Figure 1. Treatment flowchart of total adult patients with rhabdomyosarcoma (RMS). Chemo: Chemotherapy; RT: radiotherapy.

of outcome in patients with RMS (Table I) (17-19). Disease-free survival (DFS) was measured from the date of the original surgery for RMS to the date of local or distant recurrence, or death from any cause. OS was calculated from the day of surgery or biopsy to the day of death from any cause, or the day of last follow-up. Survival was calculated according to the Kaplan–Meier method. DFS and OS curves were compared between variables using the log-rank test. All tests were two-sided with $p < 0.05$ indicating significance.

Results

Clinicopathological features of adult RMS. The clinicopathological features of the 20 patients in this study are listed in Table II. Median follow-up time was 44 months, and median age at diagnosis was 34 (range=19-79) years. Sixteen presented with localized disease (four stage I, four stage II, and 8 stage III disease), and four presented with metastases at initial diagnosis (two with extremities primary site and two with genitourinary primary site). Among all patients, the most frequent primary site was the head and neck (12 patients, 60%). According to the IRSG risk stratification,

most patients were at intermediate risk (15/20, 75%). Of the 20 patients, 14 received RT treatment for primary sites due to residual disease, whereas three patients with localized disease did not receive RT. Nineteen patients (95%) received chemotherapy; of these, 13 (55%) received chemotherapy for >19 weeks.

Clinical outcomes and prognostic factors in all adult RMS patients. Twelve out of the 20 (60%) patients died of their disease. By tumor histology, 7/9 (77.8%) with pleomorphic subtype, 2/8 (25%) with alveolar subtypes, and all three embryonal cases died. For the whole patient cohort, the 3-year DFS and OS rates were 20% and 45%, respectively (Figure 2). The respective stage I, II, III, and IV 3-year DFS rates were 50%, 25%, 12.5% and 0%; the 3-year OS rates were 75%, 50%, 50%, and 0%, respectively. The median OS for those with localized and those with metastatic disease were 53.2 [95% confidence interval (CI)=14.7-91.8] months and 21.7 (95% CI=0-45.7) months, respectively ($p=0.047$) (Figure 3).

Table II. Patient characteristics and demographic data of adult patients with rhabdomyosarcoma (n=20).

Variable	Value
Age at diagnosis, years	
Median (range)	34 (19-79)
Gender, n (%)	
Male	11 (55%)
Female	9 (45%)
Year of diagnosis, n (%)	
2004-2010	9 (45%)
2011-2015	11 (55%)
Site, n (%)	
Head & neck	12 (60%)
Parameningeal	11
Non-parameningeal	1
Genitourinary	6 (30%)
Bladder/prostate	2
Non-bladder/prostate	4
Limb	2 (10%)
Stage, n (%)	
Localized	16 (80%)
Metastatic	4 (20%)
LN involvement, n (%)	
No	9 (45%)
Yes	10 (50%)
Unknown	1 (5%)
Size, n (%)	
≤5 cm	5 (25%)
>5 cm	13 (65%)
Unknown	2 (10%)
Histology, n (%)	
Embryonal	3 (15%)
Alveolar	8 (40%)
Pleomorphic	9 (45%)
Postsurgical group, n (%) [*]	
2 (R1 resection or involved LNs)	3 (15%)
3 (Gross residuals)	13 (65%)
4 (Metastasis)	4 (20%)
Risk group, n (%) [#]	
Low	1 (5%)
Intermediate	15 (75%)
High	4 (20%)
Chemotherapy duration, n (%)	
None	1 (5%)
≤19 Weeks	6 (30%)
>19-45 Weeks	11 (55%)
>45 Weeks	2 (10%)
Radiotherapy, n (%)	
No	6 (30%)
Yes	14 (70%)
VC-CCRT, n (%)	
No	2 (14.3%)
Yes	12 (85.7%)
Radiation technology, n (%)	
3DRT	3 (21.4%)
IMRT/VMAT/Tomo	11 (78.6%)

LN: Lymph node; VC: vincristine and cyclophosphamide; CCRT: concurrent chemoradiotherapy; 3DRT: three-dimensional conformal RT; IMRT: intensity-modulated radiation therapy; VMAT: volumetric-modulated arc therapy; Tomo: tomotherapy. ^{*}According to the Intergroup Rhabdomyosarcoma Study Group (15,16); [#]according to the Children's Oncology Group (17-19).

The median OS for head and neck, and genitourinary primary sites was 53.2 (95% CI=19.7-91.8) months and 6.1 (95% CI=17.9-41.2) months, respectively ($p=0.21$). The 3-year DFS and OS rates were 11.1% and 33.3%, respectively, for the nine cases diagnosed before and including 2010, and were 27.3% and 54.5%, respectively, for the 11 diagnosed after 2010 (DFS, $p=0.318$; OS, $p=0.296$). High-risk patients (n=4) had lower 3-year DFS (0% versus 26.7%; $p=0.616$) and OS (0% versus 53.5%; $p=0.12$) than intermediate-risk group patients (n=15). The prognostic variable analysis of DFS and OS for adult patients with RMS is listed in Table III. There were no differences in DFS in terms of sex, year of diagnosis, primary site, favorable site, bulky size, lymph node involvement, stage, histology subtype, postsurgical group, and risk group (Table III). Similarly, sex, year of diagnosis, primary site, favorable site, bulky size, lymph node involvement, stage, postsurgical group, and risk group did not affect OS. However, patients with alveolar histological subtype had a better OS ($p=0.035$, Table III).

Clinical outcome of patients with localized RMS. Regarding failure patterns in 16 patients with localized RMS (stage I to III), four had local failure, three had distant metastasis, two had regional recurrences, and one had both local and distant failure. In patients with localized RMS, the 3-year DFS rates for those with pleomorphic (n=8), alveolar (n=6) and embryonal (n=2) subtypes were 12.5%, 50%, and 0%, respectively ($p=0.167$). The respective 3-year OS rates were 25%, 100%, and 50% ($p=0.017$). The 3-year DFS and OS rates were 12.5% and 37.5%, respectively, for the eight patients diagnosed from 2004 up to and including 2010, and 37.5% and 75% for the eight diagnosed after 2010 (DFS, $p=0.415$; OS, $p=0.21$). No secondary malignancy was found during follow-up of these patients. As shown in Figure 4A, patients receiving RT (n=13) had a significantly better median DFS than those without RT (n=3) (24.6 versus 6.0 months, $p=0.009$). Similarly, patients receiving RT had a significantly better median OS than those not receiving RT (53.2 versus 11.4 months, $p=0.009$) (Figure 4B). Among the three patients who did not receive RT, one had post-surgical group II disease, another had complete response after chemotherapy, and the other had stage I with primary uterine disease.

There were no significant differences in DFS and OS found between patients receiving 3D RT or IMRT/VMAT/tomotherapy (Table III). Regarding chemotherapy regimens, we found that four out of five patients who received chemotherapy cycles for ≤19 weeks' duration died, while seven out of nine patients who received longer chemotherapy (≤45 weeks) were still alive. The 3-year DFS rate was significantly better for patients who received chemotherapy for more than 19 weeks than those who received chemotherapy ≤19 weeks

Figure 2. Disease-free survival (DFS) (A) and overall survival (OS) (B) outcomes of the whole patient cohort (n=20).

Figure 3. Disease-free survival (DFS) (A) and overall survival (OS) (B) outcomes of patients with rhabdomyosarcoma (n=20) by stage (localized/metastatic).

(40% versus 0%, $p=0.009$, Figure 4C). The corresponding 3-year OS rates were 90% and 0% for these two groups ($p=0.009$) (Figure 4D). When compared to those receiving RT alone, patients receiving RT concurrent with VC had a significantly better 3-year DFS (36.4 versus 0%; $p<0.01$) and OS (81.8% versus 0%; $p<0.01$) (Table III).

Discussion

In this study, our cohort of 20 patients with adult RMS were treated with multidisciplinary treatment, including surgery, chemotherapy, or RT in the modern era. Nineteen patients received chemotherapy, with 60% of them receiving it for more

Table III. Univariate analysis of disease-free (DFS) and overall (OS) survival.

	Variable	Number	3-Year DFS (%)	p-Value	3-Year OS (%)	p-Value
All patients (n=20)						
Gender	Male	11	18.2	0.798	45.5	0.862
	Female	9	22.2		44.4	
Diagnostic year	2004-2010	9	11.1	0.318	33.3	0.296
	2011-2015	11	27.3		54.5	
Tumor site	Head & neck	12	25.0	0.621	58.3	0.140
	Non-head & neck	8	12.5		25.0	
	Parameningeal	11	18.2	0.219	54.5	0.450
	Non-parameningeal	1	100		100	
Bulky size	Bladder/prostate	2	0	0.207	0	0.207
	Non-bladder/prostate	4	25		50	
	Favorable site	4	50	0.251	50	0.950
	Unfavorable site	16	12.5		43.8	
	≤5 cm	5	20	0.771	40	0.735
	>5 cm	13	23.1		46.2	
LN Involvement	No	9	22.2	0.542	44.4	0.524
	Yes	10	20		50	
Stage	Localized	16	25	0.574	56.3	0.089
	Metastatic	4	0		0	
Histology	Embryonal	3	0	0.166	33.3	0.038
	Alveolar	8	37.5		75	
	Pleomorphic	9	11		22.5	
Postsurgical group*	2 (R1 resection or involved LNs)	3	0	0.294	33.3	0.114
	3 (Gross residuals)	13	30.8		61.5	
	4 (Metastasis)	4	0		0	
Risk group#	Low	1	0	0.852	100	0.182
	Intermediate	13	26.7		53.3	
	High	4	0		0	
Localized disease (n=16)						
Diagnostic year	2004-2010	8	11.1	0.318	33.3	0.296
	2011-2015	8	27.3		54.5	
Histology	Embryonal		0	0.166	33.3	0.038
	Alveolar		37.5		75	
	Pleomorphic		11		22.5	
Chemotherapy duration	≤19 Weeks	6	0	<0.01	0	<0.01
	>19-45 Weeks	9	44.4		53.3	
	>45 Weeks	1	0		100	
Radiotherapy	No	3	0	<0.01	0	<0.01
	Yes	13	30.8		69.2	
RT Technology	3DRT	3	33.3	0.732	66.7	0.951
	IMRT/VMAT/Tomo	10	30		70	
Concurrent VC RT	No	2	0	<0.01	0	<0.01
	Yes	11	36.4		81.8	

LN: Lymph node; VC: vincristine and cyclophosphamide; CCRT: concurrent chemoradiotherapy; 3DRT: three-dimensional conformal RT; IMRT: intensity-modulated radiation therapy; VMAT: volumetric-modulated arc therapy; Tomo: tomotherapy. *According to the Intergroup Rhabdomyosarcoma Study Group (15, 16); #according to the Children's Oncology Group (17-19).

than 19 weeks, and 14 patients received RT for residual disease or involved lymph nodes. However, the 3-year DFS and OS were 30% and 45%, respectively, considering all 20 patients. The 3-year OS rate for those with localized disease was higher than that for metastatic disease (56.3% versus 0%; $p=0.089$).

From the retrospective study conducted at the MD Anderson Cancer Center from 1957 through 2003, the

median OS for patients with nonmetastatic disease was 45.6 months, and 16.8 months for those with metastatic disease (20). In their study, approximately 73% of patients received at least bimodality treatment (20). The improved median OS of the patients with localized RMS seen in our study may result from the fact that a majority of our patients were treated with VAC-based chemotherapy, intensive medical

Figure 4. The disease-free (DFS) (A, C) and overall (OS) (B, D) survival outcomes of patients with localized rhabdomyosarcoma according to receipt of radiotherapy (RT) (A, B) and by duration of chemotherapy administration (C, D).

care, and precise RT dose–volume metrics. However, when compared to pediatric patients, the survival of our adult patients with RMS was still poor. The IRS-IV reported that 3-year OS was 86% in pediatric patients with non-metastatic RMS (6). In addition, a recent published study from our Institution showed that the 5-year OS rate was 54.7% for pediatric patients under 18 years old (12).

Much of the published literature from single- or multiple-institution series has presented similar results of inferior outcome in adult RMS (summarized in Table IV) (3, 8, 9, 20–24, 25, 26). When compared with other series, which

reported regional lymph node metastasis rates ranging from 14% to 46% and unfavorable sites in approximately 53% at initial presentation (21, 22, 24), our study found a higher rate of both initial lymph node involvement (50%) and unfavorable sites (75%). This may explain why our patients had lower 3-year DFS and OS. However, after incorporating multidisciplinary team care after 2010, the 3-year OS for our patients improved. Our colleagues also previously reported that a multidisciplinary team approach improved event-free survival in patients with high-risk neuroblastoma (27). These findings indicate that the incorporation of a

Table IV. Published cohort studies of adult rhabdomyosarcoma.

Author (Ref)	Source	No. of patients	Time	Median age (range), years	5-Year OS		Overall OS	
					All patients	M+	M–	M+
Sultan <i>et al.</i> (3)	SEER database	1071	1973-2005	>19 years	27%	33%	47%	
Bompas <i>et al.</i> (8)	France	157	1980-2010	37 (18-86)	31%	46%	43%	5%
Hawkins <i>et al.</i> (9)	MSKCC	84	1982-1999	23 (16-76)	35%	44%		
Dumont <i>et al.</i> (20)	MSKCC	239	1957-2003	10-102 (19)		32%	44.1%	18%
Esnaola <i>et al.</i> (21)	Brigham & Women's Hospital	39	1973- 1996	26 (16-82)	31%	33%		
Little <i>et al.</i> (22)	MDACC	82	1960-1998	27 (17-84)	-	-	44%	-
Ferrari <i>et al.</i> (23)	Milan	171	1975-2001	27 (19-83)	39.6%	18%		4.3%
Gerber <i>et al.</i> (24)	MDACC	148	1990-2011	27 (19-83)	34%	32%	45%	
Elsebaie <i>et al.</i> (25) (M–)	Database search	553	Search on 2015/1/15	30 (16-87)	-	-	52.7%	-
Noujaim <i>et al.</i> (26) (pleomorphic)	UK, Switzerland, Germany	49	1995-2014	72 (28-93)		29%	31.2%	0%
Present study	NTUH, Taiwan	20	2004-2015		45% (3-years)	20%	56.25% (3-years)	0%

N: Number; OS: overall survival; M+: metastatic disease; M–: non-metastatic; MSKCC: Memorial Sloan Kettering Cancer Center; MDACC: MD Anderson Cancer Center; NTUH: National Taiwan University Hospital.

multidisciplinary team approach in adult RMS may improve local control and improve OS.

A possible reason for lower survival in adult RMS is that the most common histological subtype in adults (pleomorphic) is not as responsive to chemotherapy as the embryonal or alveolar subtypes (8, 21, 25, 26). Another possibility is that the frequency of the pleomorphic subtype increases with advancing age and stage (9). In our cohort, the pleomorphic subtype accounted for nine out of 20 (45%) patients, and seven (77.8%) of these died. In a larger study conducted by the French Sarcoma Group, Bompas *et al.* reported that 44% of 449 patients had adult-type P-RMS (pleomorphic, spindle cell RMS, not otherwise specified), and a median OS of 16 months (8). This study also showed that RT significantly improved OS for patients with localized adult RMS (8), similar to our study. In addition to the use of RT in localized RMS, previous studies have suggested that longer duration of chemotherapy may have an impact by providing an improved survival benefit (28, 29). Most patients in our series undergoing chemotherapy for 19 weeks or less died, while almost 90% of patients who received chemotherapy for more than 19 weeks survived more than 3 years. Bisogno *et al.* from the European Paediatric Soft Tissue Sarcoma Study Group also demonstrated a better DFS in the standard and maintenance therapy group than the standard therapy group, indicating the importance of maintenance chemotherapy in high-risk non-metastatic RMS (29).

Despite the retrospective design and small sample size, we have presented the first single-institution series of adult RMS in Taiwan, and demonstrated that adult RMS is much

different histologically (mainly pleomorphic subtype), and behaves more aggressively compared to pediatric RMS. In addition to IRSG stage, risk level, and histological subtype, our data indicate that adult patients with localized RMS may achieve improved survival when they receive concurrent chemotherapy and RT, and longer duration of systemic chemotherapy (>19 weeks). Future studies with larger patient cohorts may validate the prognostic factors we identified, warranting further investigation of novel multimodality treatment strategies to improve outcomes of adult RMS.

Conflicts of Interest

The Authors have no conflicts of interest to declare in regard to this study.

Authors' Contributions

YTL collected the data, conducted all statistical analyses and wrote the article; CWW and RLH contributed data, and SHK conceived, designed the work and revised the article. All authors reviewed and approved the final article.

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