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The incidence of and risk factors for axillary web syndrome with limited shoulder movement after surgery for breast cancer, and the effect of early physical therapy intervention

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Abstract

Background The aims of this cohort study were to identify (1) the incidence and risk factors for axillary web syndrome (AWS) with shoulder movement limitation within 4 weeks after axillary lymph node dissection (ALND) for Asian women with breast cancer (BC), and (2) whether early intervention with physical therapy (PT) could improve AWS, and how many PT sessions would be needed.

Methods A cohort study of patients with BC receiving ALND was performed at Changhua Christian Hospital, Taiwan, between January 2019 and December 2020. Those patients who were diagnosed with AWS with shoulder movement limitation were referred to receive PT twice weekly at the Department of Physical Medicine and Rehabilitation.

Results A total 173 BC patients receiving ALND were enrolled. The incidence of AWS with shoulder movement limitation was 18%, and the time to diagnosis was 26.3 days. In a subsequent multivariate analysis, younger age (OR = 0.95; 95% CI = 0.91–0.99; $p = 0.019$), higher number of removed lymph nodes (OR = 1.09; 95% CI = 1.03–1.16; $p = 0.007$) and receiving neoadjuvant chemotherapy (NAC) (OR = 2.96; 95% CI = 1.25–6.98; $p = 0.013$) were associated with an increased risk of developing AWS with shoulder movement limitation. The corresponding area under the curve was 0.762. Initial shoulder flexion and abduction were 132.1° and 123.4°, respectively. After 14.8 PT sessions, shoulder flexion and abduction improved to 172.3° and 171.8°, respectively. Improvement in shoulder range of motion was 40.2° and 48.4° in flexion and abduction, respectively, which was significant ($p < 0.001$).

Conclusions In conclusion, we demonstrated a prediction model for AWS with shoulder movement limitation using 3 risk factors: younger age, a higher number of removed lymph nodes, and receiving NAC. Approximately 18% of BC survivors will have AWS with shoulder function limitation during the first month after ALND. An early intervention protocol with a PT program could effectively restore shoulder function.

Keywords Breast cancer · Axillary web syndrome · Physical therapy · Neoadjuvant chemotherapy · Rehabilitation

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1 Background

Axillary web syndrome (AWS) is a common morbidity among breast cancer (BC) patients following surgery [1]. AWS, also known as cording or axillary cording, is a clinical condition that affects the soft tissues of the axilla and arm [2]. Moskovitz et al. reported that AWS presented as lymphovenous injury, stasis and hypercoagulability in axillary vessels, resulting in thrombosis of the large superficial veins or lymphatics of the arm [3]. Leduc et al., Reedijk et al. and Rashtak et al. concluded that the origin of the cords in AWS was lymphatic pathologenesis [4–6].

The incidence of AWS in patients with BC receiving axillary lymph node dissection (ALND) was about 5–6% in 2 retrospective studies [3, 7]. In 2 review articles (Mullen et al. [2] and Yeung et al. [1]), the incidence of AWS varied significantly: from 5.2% [7] to 72% [8] in patients undergoing ALND, and from 0.9% [7] to 45% [2] in patients undergoing sentinel lymph node biopsy (SLNB). Variations in AWS incidence is due to differing definitions and follow-up periods. Some studies have reported that AWS typically appears within the first 3 months after surgery, with a higher frequency observed within the first 60 days [9, 10]. Koehler et al. found 47.2% of women with BC developed AWS within 12 weeks after surgery11, 12. Ryans et al. and Yeung et al. reported that AWS occurred within the first 8 weeks postoperatively [1, 13].

Among patients with a history of BC, the reported risk factors for developing AWS varied. The higher incidence in patients undergoing ALND, compared to those undergoing SLNB [7, 12, 14], is more established. Agreement on the effect of age and body mass index (BMI) on AWS occurrence is not unanimous. Fukushima et al.[9], O'Toole et al.[14], and Torres Lacomba et al. [10] found that younger individuals were at greater risk for AWS. In contrast, Ryans et al. concluded that older women (over 60 years old) had a higher incidence of AWS [13]. Some research has indicated that a low BMI is associated with a higher risk of AWS [2, 8–11, 15]; the researchers reasoned that patients with a lower BMI tended to have less body mass, which makes it easier to detect the cords in these individuals [2, 8, 12, 13]. Leidenius et al. [8], Torres Lacomba et al. [10], and Bergmann et al. [15] found that obese patients showed less risk for AWS.

AWS has been reported to cause morbidity and is associated with reduced shoulder range of motion (ROM) and an increased risk of long-term functional impairment [12]. In a longitudinal study of BC survivors conducted 7 years after surgery, Kootstra et al. found that shoulder-arm function at 6 weeks post-surgery is the strongest predictor of long-term shoulder-arm function [16]. So early intervention for AWS to restore shoulder function is critical. Torres Lacomba et al. [17] and Cho et al. [18] reported that a PT program (including manual lymph drainage (MLD) and arm exercise) could effectively improve shoulder function, pain, and quality of life (QOL) in women after BC surgery. Physical therapy (PT) intervention for AWS may prove beneficial in limiting subsequent shoulder dysfunction, but there is no consensus in the PT literature regarding optimal treatment or timing of treatment [10, 19].

Based on the findings of previous studies, the purposes of this cohort study were to identify (1) the incidence and risk factors for AWS with shoulder movement limitation within 4 weeks after ALND for Asian women with BC, and (2) whether early intervention with PT could improve AWS, and how many PT sessions would be needed to treat AWS.

2 Methods

2.1 Data source and study participants

At Changhua Christian Hospital in Taiwan, patients with BC who received ALND were scheduled into the BC rehabilitation protocol, as follows. During the period of admission, they would consult the physiatrist (SF Liao) and the physical therapist. Every patient would then be given an appointment with the same physiatrist (SF Liao) 4 weeks after surgery. All patients were evaluated for ROM of the shoulder, educated on lymphedema prevention, and requested to return to SF Liao's clinics if AWS appeared in the follow-up period. Patients with AWS without ROM deficits were monitored at Dr. SF Liao's clinic 1 month post-initiation.

AWS with shoulder movement limitation was diagnosed by the same physiatrist, with the criteria of a palpable or visible band on the axillary area, medial arm or lateral chest wall [3, 12], and limited affected shoulder motion with elbow extension. Limited shoulder mobility was defined as a difference of 10 degrees or more in ROM when compared with the other shoulder [20, 21]. Patients with AWS with limited affected shoulder motion were referred to receive PT twice weekly until the ROM of the shoulder returned to normal and the AWS disappeared.

The 60-min physical therapy program included the following components: (1) MLD using the Vodder technique, performed for 25 min to facilitate lymph fluid drainage to the contralateral axillary or ipsilateral inguinal lymph nodes [22]; (2) 15 min of cord mobilization and release, which involved (a) thumb MLD to mobilize the cords, as described by Torres Lacomba et al. [10], and (b) shoulder in abduction, extension, and external rotation, elbow extension and forearm supination, and wrist and finger extension with thumb abduction, simulating a median nerve neurodynamic glide to mobilize the cords [17]; (3) 20 min of mobilization, coupled with strengthening and stabilization exercises for the shoulder and scapula. Patients were also instructed in a home exercise program, which included wall climbing, free weights, and 0.6 kg weight-lifting exercises for the affected shoulder. If lymphedema was present, MLD was also incorporated into the home program.

For the purpose of this study, patients who had a history of affected side shoulder injury or limited shoulder ROM before surgery were excluded. The data on BC diagnosis and treatment were derived from the hospital's cancer registry, which contains data on all cancer patients diagnosed at Changhua Christian Hospital since 2005. The study was approved by the Institutional Review Board Committee of Changhua Christian Hospital (IRB 220636), and the need for informed consent was waived. This study was conducted in compliance with the principles of the Declaration of Helsinki.

2.2 Outcome

Data on each patient, including the surgical method, cancer stage, neoadjuvant chemotherapy (NAC), and length of PT, were obtained. The clinical symptoms of pain, tension and heaviness were evaluated using the visual analog scale (VAS). The VAS provided quantifiable, reliable measurements ranging from 0 to 10, with 0 reflecting no symptoms and 10 indicating the worst symptoms. The VAS scale has consistently shown sensitivity to changes in cancer pain associated with treatment or time [23]. A minimal detectable change (MDC) of 0.9 to 1.1 is required for clinical relevance [24]. The affected side passive ROM for shoulder flexion and abduction was assessed in the sitting position, with the elbow fully extended, using a standard goniometric (Baseline Plastic Goniometers, Fabrication Enterprises Inc., White Plains, NY, USA) method in agreement with Dougherty et al. [25], by the same physical therapist (YH Chou). The elbow was held in full extension and elbow flexion avoided during the assessment of shoulder ROM to maintain the tension of the AWS cords, as Koehler et all suggested [12]. Rasmussen et al. reported that ROM of the shoulder can be measured reliably on the affected shoulder in patients with BC [26]. An MDC of 20.8 degrees for abduction and 10.2 degrees for flexion are required for clinical relevance [26].

2.3 Statistical analysis

Descriptive statistics (including mean, range, frequency, and percent) are presented for demographic and clinical/treatment factors of interest. The continuous and categorical variables of the 2 groups (patients with AWS and shoulder movement limitation Vs without AWS) were analyzed using an independent T-test and chi-squared test. Factors and a p value < 0.05 were chosen to decide the final predictive factors for logistic regression analysis. Multiple logistic regression was used to identify those patients that were significantly associated with AWS with shoulder movement limitation after adjusting for the effects of other factors in the model. The preliminary prediction model was based on the results of multiple logistic regression. The area under the receiver operating characteristic (ROC) curve (AUC) was the index of prediction accuracy. Prediction accuracy or the equivalent AUCs were assessed using STATA/SE V 14.1 (Stata Corporation, College Station, TX). The comparison of shoulder ROM between before and after PT was calculated using repeated ANOVA. All analyses were performed using SPSS Version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). A p value less than 0.05 was considered statistically significant.

3 Results

A total of 173 patients with BC that had undergone ALND were enrolled in the study. The mean age was 55.7 ± 12.3 years old, BMI was 24.5 ± 4.1 kg/m^2, and the number of removed lymph nodes was 9.5 ± 6.6. With regard to treatment, 36.4% (63/173) of the patients received NAC, and 53.2% (92/173) received Taxotere therapy (Table 1).

Thirty-one patients were diagnosed with AWS with shoulder movement limitation, with an incidence of 18%. The mean age of the patients was 50.2 ± 10.7 years, BMI was 24.3 ± 5.5 kg/m^2, and the number of removed lymph nodes was 12 ± 5.8. The time to diagnosis of AWS with shoulder movement limitation was 26.3 ± 5.6 days. The mean symptoms of

Table 1 Demographic and clinical characteristics in participants with and without AWS

Variables	All (n = 173)	AWS (n = 31)	No AWS (n = 142)	*p*
Mean (SD) age (years)	55.7 (12.3)	50.2 (10.7)	56.8 (12.3)	0.004*
Mean (SD) body mass index (BMI) kg/m^2	24.5 (4.1)	24.3 (5.5)	24.6 (3.8)	0.747
Onset time after surgery (days)		26.3(5.6)		
Type of surgery				0.198
Breast-conserving surgery	63 (36.4%)	13 (42%)	50 (35.2%)	
Modified radical mastectomy	53 (30.6%)	12 (38.7%)	41 (28.9%)	
Nipple-sparing mastectomy	57 (32.9%)	6 (19.4%)	51 (35.9%)	
Breast reconstruction surgery	50 (28.9%)	11 (35.5%)	39 (27.5%)	0.115
Mean (SD) number of removed lymph nodes	9.5 (6.6)	12 (5.8)	9 (6.6)	0.018*
Neoadjuvant chemotherapy	63 (36.4%)	19 (61.3%)	44 (31%)	0.002*
Taxotere use	92 (53.2%)	15 (48.4%)	77 (54.2%)	0.559
Stage				0.789
I	50 (28.9%)	9 (29%)	41 (28.9%)	
II	72 (41.6%)	15 (48.4%)	57 (40.1%)	
III	35 (20.2%)	5 (16.1%)	30 (21.1%)	
IV	16 (9.2%)	2 (6.5%)	14 (9.9%)	
Tension		0.5 (1)		
Pain		0.9 (1.5)		
Heaviness		0.1 (0.5)		

AWS axillary web syndrome, *SD* standard deviation, *BMI* body mass index

*$p < 0.05$

pain, tension, and heaviness, using the VAS, were 0.5 ± 1, 0.9 ± 1.5, and 0.1 ± 0.5, respectively (Table 1) There was a predominant difference in age ($p = 0.004$), number of removed lymph nodes ($p = 0.044$), and whether NAC had been provided or not ($p = 0.002$) between the patients with AWS and shoulder movement limitation and without AWS. However, there were no differences in BMI, type of surgery (including reconstruction), chemotherapy use (including Taxotere), or other relevant factors between these 2 groups (Table 1).

In a subsequent multivariate analysis (Table 2), younger age (OR = 0.95; 95% CI = 0.91–0.99; $p = 0.019$), higher number of removed lymph nodes (OR = 1.09; 95% CI = 1.03–1.16; $p = 0.007$), and receiving NAC (OR = 2.96; 95% CI = 1.25–6.98; $p = 0.013$) were associated with an increased risk of developing AWS with shoulder movement limitation. For those receiving NAC, the odds of developing AWS with shoulder movement limitation increased by a factor of 2.96. After controlling for stage of BC, younger age (OR = 0.95; 95% CI = 0.91–1; $p = 0.029$), higher number of removed lymph nodes (OR = 1.1; 95% CI = 1.03–1.18; $p = 0.004$) and receiving NAC (OR = 3.07; 95% CI = 1.29–7.3; $p = 0.011$) were still risk factors for AWS. To demonstrate the accuracy of the prediction model using these 3 predictors in multiple logistic regression, the predicted values were used as the test variable. The ROC curve, shown in Fig. 1, had an AUC of 0.762.

There was no correlation between age and number of removed lymph nodes in the AWS ($p = 0.155$) and shoulder movement limitation and without AWS groups ($p = 0.237$). The mean age of patients receiving NAC was significantly

Table 2 Factors associated with axillary web syndrome with shoulder movement limitation

	Odds Ratio	Lower 95% CI	Upper 95% CI	*p* value
Age	0.950	0.910	0.991	0.019*
Number of removed lymph nodes	1.092	1.025	1.164	0.007*
Neoadjuvant chemotherapy	2.956	1.252	6.980	0.013*

Multiple logistic regression was used to identify the factors associated with AWS with shoulder movement limitation

CI confidence interval

*$p < 0.05$

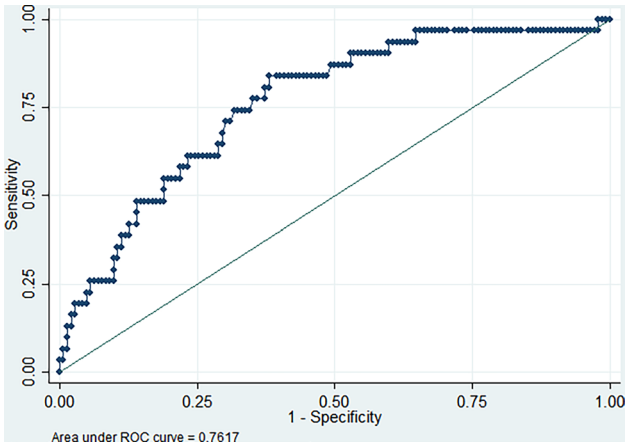

Fig. 1 ROC curves based on the multiple logistic regression prediction model. The younger age, higher number of removed lymph nodes and receiving NAC were still risk factors for AWS. The corresponding AUC was 0.762. *ROC* receiver operating characteristic, *NAC* neoadjuvant chemotherpy

younger than that of those not receiving NAC among all patients ($p = 0.003$), but not in the AWS with shoulder movement limitation group ($p = 0.152$).

Initial shoulder flexion and abduction were 132.1 ± 37.6° and 123.4 ± 35.7°. After 14.8 ± 14.8 PT sessions, shoulder flexion and abduction improved to 172.3 ± 16.2° and 171.8 ± 14.9°, respectively, with a statistically significant difference ($p < 0.001$) as determined by repeated measures ANOVA. Improvement in shoulder ROM was 40.2 ± 33.1° and 48.4 ± 32° in flexion and abduction, respectively (Table 3).

4 Discussion

The incidence of AWS with shoulder movement limitation was 18% in our study, which was lower than that in other studies [2, 8, 11–13]. Ryans et al. reported that AWS occurred in 30% of breast cancer survivors in the first year after surgery [13]. Koehler et al. defined AWS as the presence of a cord in the upper extremity or trunk during maximal shoulder abduction. Although these cords did not affect shoulder ROM, they found that 47.2% of women with BC developed AWS within 12 weeks after surgery [11, 12]. This lower incidence of our results is attributed to our study's definition of AWS with shoulder movement limitation, which includes not only palpable or visible bands but also a reduction in shoulder ROM of more than 10 degrees [20, 27]. We aimed to determine the incidence of AWS associated with restricted shoulder motion in patients with BC. Fukushima et al. also reported an AWS incidence of 28.86%, because more of their patients received modified radical mastectomy (71% vs 30.6%) [9]. Conversely, the incidence of AWS was lower in Wernicke's research [7]. He reported in a retrospective study that only 5.2% of early-stage BC participants who received ALND suffered from AWS [7]. In our study, 30% of patients had advanced BC, and our prospective cohort study design might have contributed to a higher incidence of AWS compared to Wernicke's findings.

We found that younger age, a higher number of removed lymph nodes, and receiving NAC were associated with an increased risk of developing AWS with shoulder movement limitation. We utilized these 3 factors to construct a prediction model for AWS. The accuracy of this predictor is denoted by an AUC of 0.762. The purpose of this prediction model was to provide a corresponding reference index for the accuracy of the prediction of AWS with shoulder movement limitation. Fukushima et al. [9], Torres Lacomba et al. [10], and O'Toole et al. [14] also reported that younger patients had

Table 3 Shoulder range of motion of patients with AWS

Variable (mean (SD))	Pre-PT	Post-PT	*p* value
Flexion	132.1 (37.6)°	172.3 (16.2)°	< 0.001*
Improvement of flexion		40.2 (33.1)°	
Abduction	123.4 (35.7)°	171.8 (14.9)°	< 0.001*
Improvement of abduction		48.4 (32)°	
Duration of PT (sessions)		14.8 (14.8)	

AWS axillary web syndrome, *SD* standard deviation, *PT* physical therapy

*$p < 0.05$

an increased risk of developing AWS. Fukushima's result is similar to our finding [9], in that he reported that the average age of patients with and without AWS was 50.5 and 57.6 years, respectively. Torres Lacomba et al. [10] concluded that the mean age of those with AWS was lower than that of those without AWS, and they considered that this might be related to older people being more prone to gaining weight and having higher BMI [28]. Much research has shown that low BMI is associated with a higher risk of AWS [2, 8–11, 15]. Bergmann et al. reported that obese women have 15% less risk of developing AWS, and they proposed that fibrous lymph cords were difficult to find at the thick subcutaneous layer, which could hinder the diagnosis of AWS [15]. Torres Lacomba et al. had another hypothesis: the lymph vessels were cushioned by the adipose tissue in the arm and thereby decreased the signs and symptoms of AWS [10].

In our study, BMI was not a risk factor for development of AWS. BMI was almost the same in the AWS (24.3 kg/m^2) and non-AWS (24.6 kg/m^2) groups. Our patients were slimmer than those in other studies [9, 10, 12], in which most participants were obese or overweight, no matter whether in the AWS (25 kg/m^2) or non-AWS (29 kg/m^2) group. This could reflect the difference in the body composition of Asian women compared to Western women. We did not find a correlation between age and number of removed lymph nodes, either NAC or not. This means that younger age is an independent risk factor for AWS, and that it is not associated with lower BMI, more removed lymph nodes, and receiving NAC. We consider that this might be another factor influencing the development of AWS with shoulder movement limitation in younger women that we need to explore in the future. Thus, our result revealed that younger age is still a risk factor for AWS with shoulder movement limitation in slender women with breast cancer.

The mean number of removed lymph nodes was 12 in the AWS with shoulder movement limitation group and 9 in the non-AWS group in our study. We concluded that a greater number of removed lymph nodes was associated with the risk of developing AWS with shoulder movement limitation, similar to the findings of a review article [2] and O'Toole et al. [14]. Many articles have reported a higher incidence of AWS in patients undergoing ALND, compared to those undergoing SLNB [2, 7, 8]. However, Huang HC found there was no difference in the number of removed lymph nodes between the AWS and non-AWS groups; the reason for this may be that more lymph nodes were dissected in Huang's study (17.3/14.7 in the AWS/non-AWS groups, respectively) than among our patients [29].

In our study, undergoing NAC was associated with the highest risk of developing AWS with shoulder movement limitation, with a factor of 2.96. Ryans et al. reported that NAC increased the risk of AWS and found that women with AWS had a 44% higher risk of developing lymphedema during the first postoperative year [13]. Some studies have linked AWS to lymphovenous injury, lymphatic disruption, and tissue injury following ALND [2–6, 8, 13]. There are similarities in the etiology and risk factors related to BC-related lymphedema (BCRL) and AWS, both pathologies appear to be associated with lymph node removal and an inflammatory process impacting the lymphatic system in the involved quadrant [13]. NAC may have increased body fluid accumulation and the incidence of AWS [30]. Park et al. found that taxanes are associated with fluid retention and potentially with lymphedema [30]. Additionally, Armer et al. reported that a longer duration of NAC was associated with a higher incidence of lymphedema [24]. However, Fukushima et al. found no difference in the incidence of AWS between patients who received NAC and those who did not [9].

The time between diagnosis of AWS with shoulder movement limitation and referral to PT was 26.3 days in our study, because women with BC must visit the physiatrist within the first postoperative month in our hospital. This was compatible with the findings of Yeung et al. [1] and Ryans et al. [13]. Shoulder abduction ROM was significantly lower in the AWS with shoulder movement limitation group in the early postoperative period, which is consistent with Koehler's result [11]. Patients with AWS with shoulder movement limitation could achieve full shoulder ROM and return to regular ADL after 14.8 PT sessions. This means that a 7-week PT program could lead to successful improvement in AWS and shoulder ROM. Our PT sessions are similar to those in Cho et al.'s study [18]. They reported 12 PT sessions (4 weeks, 3 times/week) could improve shoulder function, pain, and QOL in BC patients with AWS, and combined with MLD, decrease arm lymphedema. Torres Lacomba et al.'s study showed fewer PT sessions could achieve a satisfactory result; they concluded that 9 PT sessions (3 weeks, 3 times/week) could effectively improve pain, shoulder ROM and function, and QOL, even 3 months after PT intervention [17]. Our study was a prospective cohort study of a rehabilitation protocol in women with BC, and was not a randomized trial, so the decision to end PT was made by the therapist.

In our study, the last AWS with shoulder movement limitation was diagnosed at 37 days after BC surgery, and there was no AWS recurrence after 5 weeks. This indicates that early intervention might reduce the long-term incidence of AWS, as reported in the studies by Koehler et al. [12] and Torres Lacomba et al. [10]. However, Koehler et al. concluded that AWS is not self-limiting; it could persist longer than 18 months and recur after it has subsided [12]. Although early intervention could effectively improve shoulder function, we should still encourage women with BC to pay attention to the affected shoulder, as Wernicke et al. reported, the chronic complication of decreased ROM of the shoulder was found in 80.0% of ALND BC patients at the 10-year follow-up [7].

However, there were some limitations to our study, as described below. (1). Since this was a cohort study, the spontaneous recovery of AWS with shoulder movement limitation could not be excluded. (2). These patients potentially could have had AWS as a result of their cancer prior to their surgery because they did not receive shoulder ROM measurements prior to surgery. (3). The evaluation and treatment therapist was the same person, so there was a possible bias regarding measurement. In the future, a randomized-controlled trial including a control group and blinded measurements are suggested to evaluate the efficacy of PT in this population. (4) The follow-up period for the patients was not well defined, and should be extended to 2 years after surgery to evaluate the long-term incidence and other risk factors (e.g., radiotherapy) of AWS, because AWS might appear in the medium-to-long-term period after surgery [17].

5 Conclusion

In conclusion, we reported a prediction model for AWS with shoulder movement limitation using 3 risk factors: younger age, a higher number of removed lymph nodes, and receiving NAC. Approximately 18% of BC survivors will have AWS with shoulder function limitation during the first month after ALND. An early intervention protocol with a PT program could effectively restore shoulder function.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by YHC, SFL, DRC,STC and WTW. YHC and SFL interpreted data and wrote the manuscript. SFL analyzed the data. All authors approved the concept of this study and have read and made critical revision to the drafted manuscript.

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Data availability The original data of the study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate Approval for the study was granted by the Ethics Committee of Changhua Christian Hospital Institutional Review Board (IRB 220636). The need for informed consent was waived. This study was conducted in compliance with the principles of the Declaration of Helsinki.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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