E-ISSN 2228-8082

Volume 74, Number 4, April 2022

SMJ

Siriraj Medical Journal

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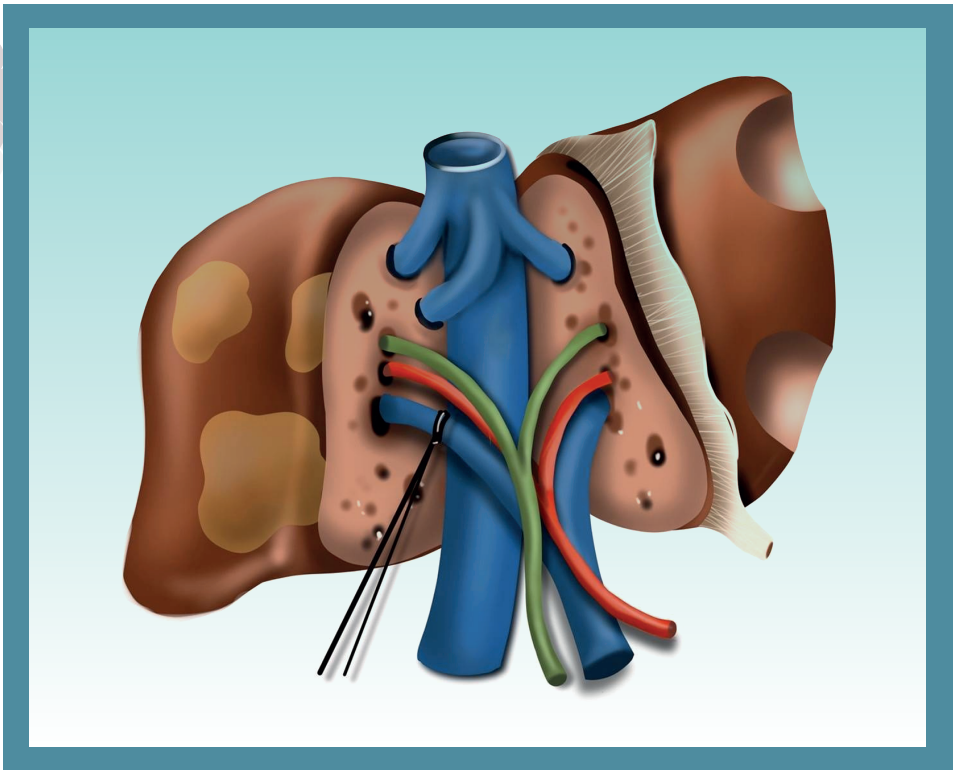

By Voramon Teranasthiarphan, et al.

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Siriraj Medical Journal SMJ

Volume 74, Number 4, April 2022

ORIGINAL ARTICLE

REVIEW ARTICLE

SIRIRAJ MEDICAL JOURNAL

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SIRIRAJ MEDICAL JOURNAL is published bimonthly, 6 issues a year (Jan-Feb, Mar-Apr, May-Jun, Jul-Aug, Sep-Oct and Nov-Dec) and distributed by the end of the last month of that issue.
SIRIRAJ MEDICAL JOURNAL is listed as a journal following the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM) by the International Committee of Medical Journal Editors (ICMJE) since 9 July 2010 [http://www.icmje.org/journals.html].

Long Term Outcomes and Durability of Bioprosthetic Valve for Valve Replacement at Siriraj Hospital

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ABSTRACT

Objective: Bioprosthesis has been used in cardiac valve replacement for a long time. However, structural valve deterioration is still a major cause of failure. There are several risk factors for valve deterioration. This study evaluates the risk factors of valve deterioration in the long term (10 years) at Siriraj Hospital.

Materials and Methods: We retrospectively reviewed the medical records of 249 patients who underwent mitral or aortic valve replacement between January 2006 and December 2012 using various tissue valves, comprising Carpentier–Edwards porcine, Carpentier–Edwards Perimount bovine pericardial, Carpentier–Edwards Perimount Magna bovine pericardial, and St Jude Trifecta bovine pericardial types. The information from each patient was entered into a database at the time of the operation and followed up regularly, with a mean follow-up of 10 years.

Results: After 10 years follow-up time, the incidence of valve deterioration events were 1.2% and 8.43% in the first five and ten years, respectively. The overall death rate during follow-up was 2.41%. There were three statistically significant risk factors ($p < 0.05$) of valve deterioration: gender (female) ($p = 0.042$), age ≤ 60 years old ($p = 0.010$) and St Jude Trifecta bovine pericardial valve ($p = 0.004$).

Conclusion: In the surgical populations who underwent valve replacement at Siriraj Hospital with tissue valves, we found an acceptable long-term durability of the tissue valve. The risk factors of valve deterioration were female gender, age ≤ 60 years old, and St Jude Trifecta bovine pericardial valve.

Keywords: Tissue valve; bioprosthesis valve; structural valve deterioration (Siriraj Med J 2022; 74: 211-216)

INTRODUCTION

There are two types of prosthetic heart valves: the mechanical heart valve and the bioprosthetic tissue valve. The mechanical valve is recommended for young patients because of its durability, but the patient is required to take anticoagulants for life to prevent thromboembolism events; whereas the tissue valve is less durable than the mechanical valve, but the patient is not required to take anticoagulants for life; thus leading to a lower risk of bleeding events associated with the use of anticoagulants.

In 1966, Dr. Alain Carpentier invented the stented porcine valve and used glutaraldehyde solution as the chemical preservative for porcine valves by creating collagen cross-links. This preservation protected the denaturation of tissue leaflets and made the tissue immunologically inactive.[1]

Since 1980s, tissue valves have been improved through the use of low-pressure fixation to maintain a normal leaflet morphology. Anti-calcification and anti-mineralization treatment methodologies were developed to obtain longer durable leaflets.[2]

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http://dx.doi.org/10.33192/Smj.2022.26

Porcine and pericardial tissue valves have been used for cardiac valve replacement surgery for 20 years at Siriraj Hospital. However, it is known that these may suffer structural valve deterioration over time, which is the major cause of tissue valve failure worldwide. Data collected from 1970 to 2000 revealed that 30% - 40% of tissue valves at the mitral or aortic position require replacement within 15 years following implantation because of structural valve deterioration.[3] There are several risk factors for structural valve deterioration, such as a younger patient, renal insufficiency, hyperparathyroidism, hypertension, tissue valve at the mitral position, and an older generation of tissue valve.

Calcification is accelerated in younger patients, renal insufficiency, or hyperparathyroidism patients. Systemic hypertension damages tissue valves at the mitral and aortic positions due to the increased systolic and diastolic closing pressure. Older generations of tissue valves are less durable than the newer generation of tissue valves. Pericardial valves are more durable than porcine valves.[4,5]

The primary objective of this study was durability of tissue valve and secondary objective was the risk factors of long-term (10-year) structural valve deterioration in patients at Siriraj Hospital, which are essential to have a better understanding of in order to support selection of the proper tissue valve types for patients in terms of the position and timing of tissue valve replacement.

MATERIALS AND METHODS

This research was approved by the Ethical Committee on Research Involving Human Subjects, Faculty of Medicine Siriraj Hospital, Mahidol University on March 24, 2021.

We retrospectively reviewed the medical records of 249 patients who underwent mitral or aortic valve replacement since January 2006 to December 2012 using the Carpentier–Edwards porcine (porcine) (24 cases), Carpentier–Edwards Perimount bovine pericardial (PM) (165 cases), Carpentier–Edwards Perimount Magna bovine pericardial (PM magna) (57 cases), and St Jude Trifecta bovine pericardial (trifecta) (3 cases) tissue valves types and who survived the operation. The types of tissue valve were selected by the individual surgeon's preference and the valves available at that time. The case of structural valve deterioration was defined by clinical presentation, echocardiographic finding results and reoperation event.

Statistical analysis

The baseline demographic continuous data were presented as number or percentage, mean and standard deviation were carried out as normal distribution. Categorical data was presented as percentage or ratio/ In inferential statistic, 95%CI was used. In case of time to deterioration in univariate analysis, deterioration was obtained from Kaplan-Meier survival curves and log-rank test for compared each group. For multivariate analysis using Cox (Proportional Hazards) regression analysis was performed after adjusted controlling confounding factors with p-value < 0.2 from univariate analysis using backward elimination for variable selection. The statistical significance was accepted if the p-value was < 0.05.

Table 1 summarizes the preoperative clinical characteristics of all the patients. The male gender represented 48.2% of cases and the female gender 51.8%. The mean age was 69.2 years old (range 15–98 years old), with 203 patients (81.5%) being more than 60 years old. Overall, 148 patients underwent aortic valve replacement (AVR) (59.4%), 84 patients underwent mitral valve replacement (MVR) (33.7%), and 17 patients underwent double valve replacement (DVR) (6.8%).

Also, 79 patients (31.7%) with significant coronary artery disease who received preoperative angiography underwent concomitant coronary artery bypass graft surgery were included in this study. The data obtained from all the patients were entered into a database at the time of the operation and then those patients were followed up regularly.

TABLE 1. Preoperative clinical characteristics.

Variables (n=249)	Number (%) or Mean ± SD
Gender; Male	120 (48.2%)
Female	129 (51.8%)
Age (years)	69.2 ± 11.4
≤ 60 years	46 (18.5%)
> 60 years	203 (81.5%)
Follow-up time (years)	10.0 (4.0-15.0)
Diagnosis	
Regurgitation	153 (61.4%)
Stenosis	79 (31.7%)
Mixed	17 (6.8%)
Operation	
AVR	148 (59.4%)
MVR	84 (33.7%)
DVR	17 (6.8%)
Type of tissue valve	
PM	165 (66.3%)
PM magna	57 (22.9%)
Porcine	24 (9.6%)
Trifecta	3 (1.2%)
Concomitant CABG	79 (31.7%)

RESULTS

After 10 years (range 4-15 years) follow-up time, the incident of structural valve deterioration events was 1.2% (95%CI: 0.25-3.47) and 8.43% (95%CI: 5.27-12.56) in the first five and ten years, respectively (Fig 1). The overall death rate during follow-up was 2.41% (95%CI: 0.97-5.66). A summary of the incidence of structural valve deterioration is shown in Table 2.

According to Table 3, there were three statistically significant risk factors ($p < 0.05$) of structural valve deterioration, i.e., female gender, age ≤ 60 years old, and St Jude Trifecta bovine pericardial valve. The risk of structural valve deterioration was 2.75 times (95%Cl: 1.04 to 7.28 times) higher significant ($p = 0.042$) in females compared to males, and the risk of structural valve deterioration is 3.33 times (95%Cl: 1.34 to 8.29 times) more significant ($p = 0.010$) in the adult group (age ≤ 60 years old) compared with the elderly group (age > 60 years old). The St Jude Trifecta valve was also found to be a significant risk factor of structural valve deterioration ($p = 0.004$)

DISCUSSION

The expanding use of tissue valves for valve replacement has been supported by evidence of their long term durability and freedom from structural valve deterioration. In this present study at Siriraj Hospital, we followed 249 cases of tissue valve replacement in the aortic and mitral valve positions. During the early years of our experience, the main reasons for using a tissue valve were patients having a contraindication to taking anticoagulants, elderly patients, and women of reproductive age. Nowadays, patient preference has become one of the most important factors for choosing the proper valve. In our series, the freedom from structural valve deterioration at 10 years was 91.57% (Fig 1). There were three statistically significant risk factors ($p < 0.05$) of structural valve deterioration identified in our study: female gender, age ≤ 60 years old and St Jude Trifecta bovine pericardial valve (Table 3, Fig 2, Fig 3).

The risk of structural valve deterioration in the mitral position has been considered to be higher than in the aortic position because the systolic closing pressure at the mitral position is higher than the diastolic closing pressure at the aortic position. In an Edinburgh study[6], after 15 year tissue valve follow-up, a reoperation rate of 29% due to structural valve deterioration was observed in the AVR group and 44% in the MVR group. In our series, after 10 year tissue valve follow-up, we found a rate of structural valve deterioration of 6.8% in the AVR group and 10.7% in the MVR group. However, the statistical difference was insignificant ($p = 0.183$).

Regarding gender, as far as we know there has been no report about the effects of gender associated with structural valve deterioration after tissue valve replacement, but we found a structural valve deterioration rate of 11.6% in females and 5.0% in males. The risk of structural valve deterioration was 2.75 times (95%Cl: 1.04-7.28) more significant ($p = 0.042$) in female compared to male. The suggested reason behind this result might be the use of a smaller valve in female patients, which carries a higher risk of structural valve deterioration.[4]

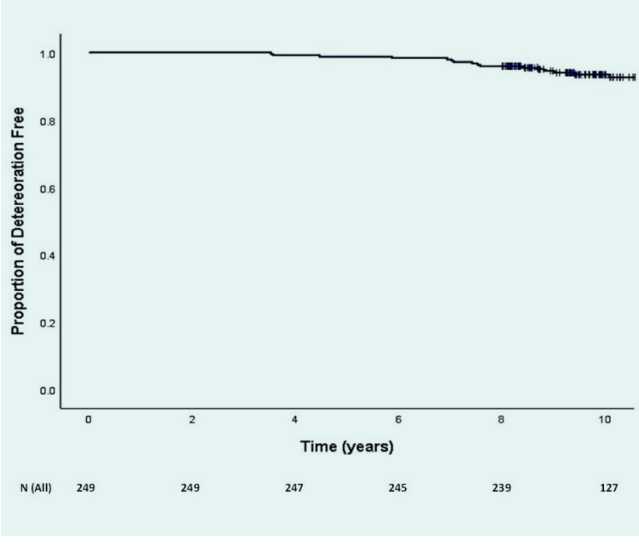

Fig 1. Freedom from structural valve deterioration for all tissue valves.

TABLE 2. Incidence of structural valve deterioration.

Variables (n=249)	Number of Deterioration	Incident of Deterioration (95%CI)
Deterioration		
at 5 years	3	1.20% (0.25-3.47)
at 10 years	21	8.43 % (5.27-12.56)
Died during follow-up	6	2.41% (0.97-5.66)

TABLE 3. Risk factors of structural valve deterioration.

Variable	Number (%) or Mean ± SD		Log-rank test (p-value)	Multivariate Adjusted HR (95%CI)	Cox regression (p-value)
	Non-deterioration (n=228)	Deterioration (n=21)			
Gender					
Male (n=120)	114 (95.0)	6 (5.0)	0.069	1	
Female (n=129)	114 (88.4)	15 (11.6)		2.75 (1.04-7.28)	0.042 *
Age (year)	69.8 ± 10.7	63.05±15.7			
Adult group; age ≤ 60 year (n=46)	38 (82.6)	8 (17.4)	0.021	3.33 (1.34-8.29)	0.010 *
Elderly group; age > 60 year (n=203)	190 (93.6)	13 (6.4)		1	
Diagnosis					
Regurgitation (n = 153)	137 (89.5)	16 (10.5)	0.930		
Stenosis (n = 79)	75 (94.9)	4 (5.1)			
Mixed (n = 17)	16 (94.1)	1 (5.9)			
Operation					
AVR (n=148)	138 (93.2)	10 (6.8)	0.183		
MVR (n=84)	75 (89.3)	9 (10.7)			
DVR (n=17)	15 (88.2)	2 (11.8)			
Type					
PM (n=165)	153 (92.7)	12 (7.3)	0.052	1	
PM magna (n=57)	53 (93.0)	4 (7.0)		1.53 (0.47-5.00)	0.479
Porcine (n=24)	20 (83.3)	4 (16.7)		2.22 (0.70-7.01)	0.173
Trifecta (n=3)	2 (66.7)	1 (33.3)		23.71 (2.69-209.09)	0.004 *
CABG					
yes (n=79)	75 (94.9)	4 (5.1)	0.176		
no (n=170)	153 (90.0)	17 (10.0)			

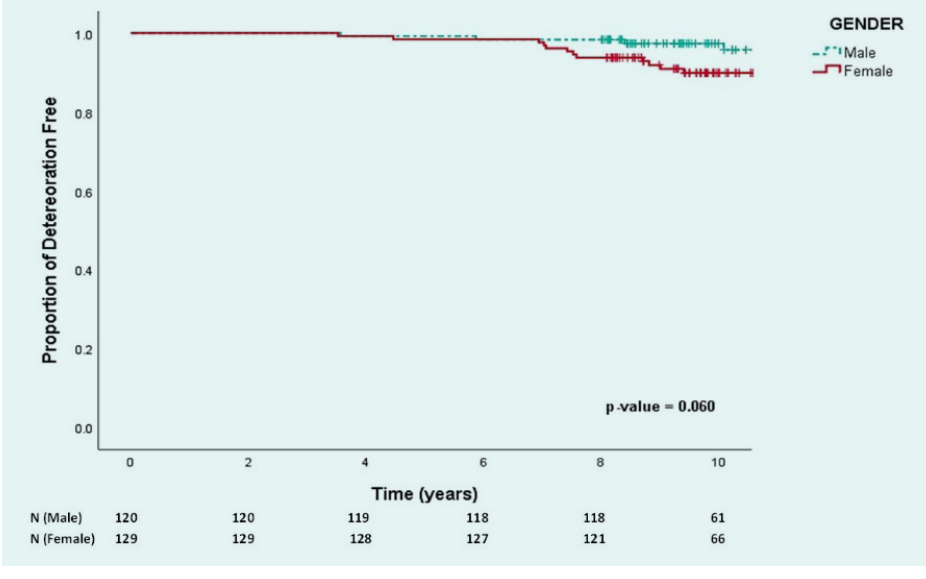

Fig 2. Freedom from structural valve deterioration for male and female patients.

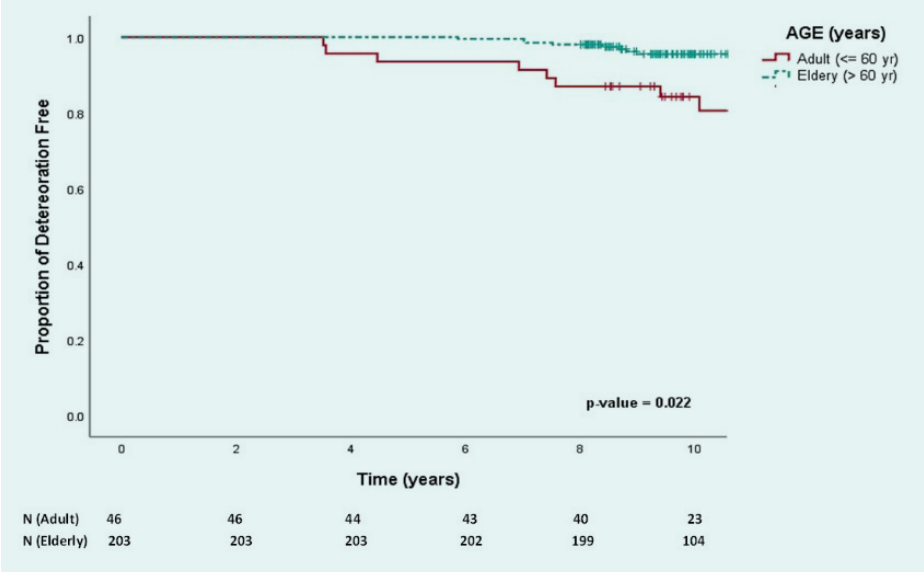

Fig 3. Freedom from structural valve deterioration for adult and elderly patients.

Elderly patients have been shown to be the most powerful determinants of tissue valve longevity.[7] Rizzoli et al.[3] reported the actual freedom from structural valve deterioration in patients younger than 65 years old was less than that seen in older patients (84.5% vs. 95%). Similarly, we found the rate of structural valve deterioration was 17.4% in the adult group (age ≤ 60 years old) and 6.4% in the elderly group (age > 60 years old). The risk of structural valve deterioration was 3.33 times (95%Cl: 1.34-8.29) more significant (p = 0.010) in the adult group (age ≤ 60 years old) compared to the elderly group (age > 60 years old).

The newer generations of tissue valves are more durable than older generations of tissue valves. Likewise, pericardial valves are more durable than porcine valves.[5] Bourguignon et al.[8,9] reported the long-term outcomes of patients fitted with a Carpentier–Edwards Perimount valve in the aortic or mitral position. They found that the expected valve durability was 19.7 years in the aortic position and 14.2 years in the mitral position.

In our series, after 10 year tissue valve follow-up, we found structural valve deterioration in 7.3% of cases in the Perimount group, 7.0% in the Perimount Magna group, 16.7% in the porcine group, and 33.3% in the Trifecta group. However, the statistical difference was insignificant for the Carpentier–Edwards porcine compared to the Carpentier-Edwards Perimount bovine pericardial type (p = 0.173, 95%Cl: 0.70-7.01). Conversely, the St Jude Trifecta bovine pericardial type was found to be a significant risk factor of structural valve deterioration (p = 0.004, 95%Cl: 2.69-209.09), but it should be noted that the total number of cases in the Trifecta group was very small (n = 3) compared to in the other groups. So, we cloud not conclude that they were more likely to deteriorate than other types.

When reoperation is required, reoperative AVR or MVR can be done safely. The recent mortality outcomes were 5%-7% in reoperative AVR or reoperative MVR.[10,11] Besides, in the future, valve in valve transcatheter aortic valve replacement (TAVR) and transcatheter mitral valve replacement (TMVR) may be the second optional treatments for patients who develop structural tissue valve deterioration. In our series, there were 7 cases who underwent reoperative AVR or reoperative MVR without mortality and 2 cases who underwent TAVR without mortality, while 12 structural valve deterioration cases were still waiting for their definitive treatment soon.

CONCLUSION

In surgical populations that underwent valve replacement at Siriraj Hospital with tissue valves, we found an acceptable long-term durability of the new tissue valve. The risk factors of structural valve deterioration were the female gender and age ≤ 60 years. The freedom from reoperation was not significantly different in terms of the valve position. However, we need to further re-evaluate the data in the next 5-10 years to obtain longer term results.

ACKNOWLEDGMENTS

The authors thank Miss Nachasa Khongchu of Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand for her professional statistical analysis.

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The Reliability of the Thai Version of the Toddlers' Temperament Questionnaire

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ABSTRACT

Objective: To evaluate the reliability of the Early Childhood Behavior Questionnaire (ECBQ)-very short form, Thai version; and to investigate Thai toddlers' temperaments

Materials and Methods: The English version of the very short form ECBQ was translated into Thai language. The primary caregivers of 360 healthy, 18-36 months old children, were asked to fill the questionnaire from the period of April, 2018 to June, 2019. The scores were calculated to determine the child's temperament. The reliability of the very short form ECBQ- Thai version was assessed by Cronbach's alpha coefficient for internal consistency and Intraclass correlation coefficient (ICC) for inter-rater reliability, two-week and six-month test-retest reliability.

Results: The Cronbach's alpha coefficients were 0.627-0.692, which indicated questionable internal consistency, but almost reach those of the original ECBQ. The inter-rater ICCs were 0.463-0.670, which were comparable to those in the original English version. The two-week ICCs were 0.602-0.750, which indicated moderate reliability, whereas the six-month ICCs decreased to 0.459-0.602. However, these values almost reached those of the original English version. Most toddlers were reported to have a surgency temperament. Boys significantly had more surgency temperament and had higher mean surgency scores, whereas girls exhibited a more effortful-control temperament.

Conclusion: The very short-form ECBQ, Thai version can be implemented in assessing Thai toddlers' temperament. The majority of Thai toddlers in this study demonstrated surgency temperament. Boys tended to be more surgency, while girls tended to be more effortful control.

Keywords: temperament, ECBQ questionnaire, Thai toddlers (Siriraj Med J 2022; 74: 217-224)

INTRODUCTION

Temperament is defined as an inborn difference in reactivity and self-regulation when a child interacts with his or her environment. Reactivity is the child's reaction to changes in the environment. Self-regulation is a process to modulate one's reactivity. Although one's temperament persists throughout life, heredity, maturation, and experiences influence it over time[1], for example, parental discipline and responses to a child's behavior can affect the child's expressions and habits. The most popular temperament concept among pediatricians has been Thomas and Chess's approach, which was introduced in 1977.[2] This concept has included nine dimensions of temperament, which were activity level, rhythmicity or regularity of physical functions, approach to or withdrawal from a new situation, adaptability, one's sensory threshold to external stimuli, intensity of reactions, quality of mood, distractibility, and attention span or persistent focus on tasks. Children are categorized from the nine dimensions into three groups, which are easy, difficult, and slow-to-warm up ones. The "easy child" is easy to raise and care for, exhibits regular sleep, waking

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http://dx.doi.org/10.33192/Smj.2022.27

and feeding times, good moods, and high adaptability. The "difficult child" has characteristics that are opposite to those in the first category. The "slow-to-warm-up child" demonstrates initial withdrawal from new stimuli and needs more time to adapt to those new situations, though eventually he or she can adjust to such stimuli.

Some behavioral problems have been claimed to be associated with temperament. The child who has a very high activity level and is very distractible might mimic the one with attention deficit/ hyperactivity disorder (ADHD). Toddlers with autism exhibited more sensitivity to stimuli and have more negative moods, compared to their typically developing peers.[3] Moreover, the child's temperament may have bidirectional interactions with the parents' responses and psychopathology. Parents of negative-mood and low-impulse-control children tended to report a history of anxiety.[4] One study found that the authoritative parenting style - when parents were always sensitive to the child's needs and give him or her freedom to make decisions in general situations while limiting the child's decision-making in more serious ones, especially potentially dangerous activities - was correlated with more patience and less irritability among their children.[5] This highlights the fact that a successful management strategy for behavioral problems based on temperamental origin should harmonize with the child's temperament. Thus, a correct interpretation of the child's temperament helps pediatricians and other medical personnel to assist parents in better understanding their children's characteristics and to guide parents in dealing with his or her problems.

Although Thomas and Chess's temperament concept is clinically practical for the evaluation of children's behavior and in terms of offering recommendation to parents, however, the Toddler Temperament Scale questionnaire developed by Fullard et al, in 1984[6] to measure the nine dimensions of temperament contains 97 question items which is not clinically practical for Thai context. Most of Thai-version questionnaires developed for time-constraint clinical use consists of 15-40 question items.[7-9]

There is also the concept of temperament developed by Rothbart in 1981. Rothbart's temperament is defined as biologically-rooted individual differences in reactivity and self-regulation in one's emotional, activational, and attentional processes.[1] In their effort to measure children's temperaments, Putnam et al.[10] formulated 18 scales of temperamental components based on Rothbart's temperamental concept, which are shown in the appendix. The children were classified into three groups: "surgency," which refers to the ones with a high activity level and positive anticipation regarding new activities; "negative affectivity," referring to children who display fear and frustration; and "effortful control," which applies to those with high impulse control and attentiveness to tasks. This approach led to the development of the Early Childhood Behavior Questionnaire (ECBQ),[10] which was designed to assess temperament in children from 18-36 months old. The psychometric properties have demonstrated good internal consistency and reliability.[7] There are three versions of the ECBQ - the standard ECBQ (consisting of 201 items), the short-form ECBQ (107 items), and the very short-form ECBQ (36 items).[11]

The ECBQ has been widely used in English and in more than 18 languages, such as Chinese, Japanese, and French. The very short-form version has been widely implemented in English and ten non-English-speaking countries.[11]

To the best of our knowledge, there is no temperament questionnaire for Thai toddlers. As a result, research on temperament in the Thai population has been very limited. The aim of this study was to translate the original English very short form of ECBQ into Thai and to evaluate the reliability of the Thai version. We also aimed to study Thai toddlers' temperament by using this form. The English version of the very short-form ECBQ was selected for this research study because the number of the question items is feasible for implementation in busy clinical settings in Thailand.

MATERIALS AND METHODS

The details of the original questionnaire

The very short version of the Early Childhood Behavior Questionnaire (ECBQ) is used to evaluate the temperament of 18-36-month-old children. The questionnaire includes 36 items regarding children's behaviors, which are specific to each temperament type. There are 12 items for surgency, 12 for effortful control, and another 12 for negative affectivity. Parents or caregivers give a Likert scale score regarding the frequency of their child's behaviors. The scores range from 1 (never) to 7 (always), and "Does not apply" (if the question is not relevant to the child). The mean score of each temperament type is calculated, and the highest mean scores define the child's temperament type. If there is more than one equally highest mean score, the child is classified as more than one - i.e. a mixed-temperament type. Internal consistency was evaluated by using Cronbach's alpha coefficient. The internal consistency of negative affectivity, surgency, and effortful-control temperament were 0.70, 0.72, 0.72, respectively. The longitudinal stability over six months was 0.65.[12]

The translation process

The Thai version of the very short-form ECBQ was translated with the permission of the pioneer of the original English version. The content validity was measured by three Thai developmental and behavioral pediatricians. The acceptable content validity index was 0.67. Each item's content validity was initially ranged from 0.33 to 0.67. The items which had low content validity were retranslated. After substantial agreement from those three specialists, reflected by a content validity index of 1, the translation back into English was done to confirm that the Thai version adhered with the original English version.

Population and procedure

This cross-sectional, questionnaire-based research included caregivers of 18-to-36-month-old children who attended the well child clinic and daycare at Siriraj Hospital, or who were in pre-kindergarten and daycare in Bangkok and the surrounding metropolitan area. The recruitment period was from April, 2018 to June, 2019. The exclusion criteria were those whose children had a diagnosis of developmental delay or chronic diseases. Caregivers who could not read Thai were also excluded. This study was approved by the Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University.

After signing an informed consent, 360 caregivers were asked to fill out the 20-minute Thai very short-form ECBQ. Of these, 20 were randomized for two-week (short-term) test-retest reliability; another 20 were allocated for six-month (long term) test-retest reliability. Eighty-three pairs of primary and secondary caregivers were recruited for inter-rater reliability testing. The number of the participants in each group randomized for test-retest and inter-rater reliabilities were based on the reliabilities from the original English version (0.6 and 0.31, respectively), estimated type I error of 0.05, and the power of 80%. The scores obtained from the questionnaire were calculated so as to interpret the children's temperament. At the end of the study, all caregivers received the information about their child's temperament, as well as the developmental and behavioral pediatrician's guidance in child-rearing practices specific to each child's temperament.

Statistical analysis

The data were prepared and analyzed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe the participants' characteristics. Number and percentage were used to describe qualitative data, while mean and standard deviation (SD) were used to describe normally distributed quantitative data. A median (25^{th}, 75^{th} percentile) was used to report non-normally distributed data. The Chi-Square test was used to evaluate statistical significance.

Cronbach's alpha coefficient was used to evaluate the internal consistency of the questionnaire. The coefficient, which was < 0.5, 0.5-0.6, 0.6-0.7, and > 0.7, was defined as unacceptable, poor, questionable, and good internal consistency, respectively.[13,14] Test-retest reliability was interpreted by using the intraclass correlation coefficient (ICC). Inter-rater reliability was evaluated using the two-way random-effects model, while intra-rater reliability was evaluated by using the two-way mixed-effects model. In this study, an ICC which was < 0.5, 0.5-0.75, and 0.75-0.9 was classified as of poor, moderate, and good reliability, consecutively.[15]

RESULTS

The demographic data are shown in Table 1. Of the 360 caregivers, 323 (89.7%) answered the questionnaire regarding the child's gender. The majority of these caregivers were mothers. The short-term (two weeks) test-retest reliability was performed involving 20 fathers or mothers of the children, which included nine (45%) boys and 11 (55%) girls. Long-term (six months) test-retest reliability was performed involving 20 participants whose children were 11 (55%) boys and nine (45%) girls. Sixteen out of 20 caregivers, who were randomized for long- term test-retest reliability, were fathers or mothers. Another 4 out of 20 were other family members. Of the 83 pairs of primary and secondary caregivers recruited for inter-rater reliability, 46 (55.4%) were the caregivers of boys, and 37 (45.6%) were the caregivers of girls. All the children were Thai and lived in Bangkok and the surrounding metropolitan area. The mean age (SD) was 27.9 (6.2) months old.

Table 2 demonstrates Cronbach's alpha coefficient for each temperament and the range of Cronbach's alpha coefficient when one item was deleted. The overall Cronbach's alpha coefficients were 0.682, 0.627, and 0.692 for surgency, negative affectivity, and effortful-control temperament, respectively. The maximum of the coefficient when one item was deleted was 0.707.

Regarding the inter-rater reliability, the ICCs were 0.638, 0.670, and 0.463 for surgency, negative affectivity, and effortful-control temperament, respectively. The ICCs for short-term intra-rater reliability were 0.614, 0.750, and 0.602 for surgency, negative affectivity, and effortful-control temperament, respectively. For long-term one, the ICCs decreased to 0.602, 0.459, and 0.476, respectively. (Table 3)

TABLE 1. Demographic data of the children and the caregivers

Characteristics	Number (%)
Child's gender	
Boy	174 (53.9)
Girl	149 (46.1)
Missing data	37
Child's Age (N=357)	
18-23 months	98 (27.5)
24-30 months	110 (30.8)
31-36 months	149 (41.7)
Missing data	3
Caregivers	
Parents	346 (96.1)
Grandparents	12 (3.3)
Others	2 (0.5)
Caregivers' marital Status	
Single	32 (8.9)
Married	317 (88.1)
Divorced	11 (3.1)
Caregivers' education	
Under Bachelor degree	42 (11.7)
Bachelor degree	194 (53.9)
Above Bachelor degree	124 (34.4)
Family's monthly income	
≤30,000 Bahts	111 (31.7)
30,001-50,000 Bahts	107 (30.6)
50,001-100,000 Bahts	82 (23.4)
≥100,001 Bahts	50 (14.3)
Missing	10

TABLE 2. Cronbach's alpha coefficient for each temperament.

Temperament	Cronbach's alpha coefficient	Cronbach's alpha coefficient when item is deleted
Surgency	0.682	0.645 to 0.692
Negative Affectivity	0.627	0.576 to 0.636
Effortful Control	0.692	0.649 to 0.707

TABLE 3. Inter-rater reliability, short-term and long-term intra-rater reliabilities.

Temperament	ICC[a] (95% CI)	ICC[b] (95% CI)	ICC[c] (95% CI)
Surgency	0.638 (0.495-0.747)	0.614 (0.228-0.832)	0.602 (0.244-0.819)
Negative Affectivity	0.670 (0.536-0.772)	0.750 (0.461-0.896)	0.459 (0.021-0.746)
Effortful Control	0.463 (0.280-0.614)	0.602 (0.231-0.824)	0.476 (0.040-0.756)

ICC: Intraclass correlation coefficient
[a] Intraclass correlation coefficient between primary and secondary caregivers
[b] Intraclass correlation coefficient, two weeks apart (short-term)
[c] Intraclass correlation coefficient, six months apart (long-term)

The temperament classifications of 360 Thai children in this study were 205 (56.9%) for surgency, 135 (37.5%) for effortful control, and 3 (0.8%) for negative affectivity. There were 16 (4.4%) children whose caregivers rated their temperaments as surgency and effortful control equally; one (0.3%) child was classified as manifesting surgency and negative affectivity. Boys significantly had more surgency temperament and a higher mean surgency scores than girls. Girls exhibited more effortful-control than boys. There was no statistical significance of gender difference in terms of negative affectivity and mixed temperament. (Table 4)

TABLE 4. Descriptive statistics for the scale scores of each temperament in boys and girls.

Temperament	Boys	Girls	*p*-value
Surgency			
N (%)	107 (61.5)	72 (48.3)	0.019*
Mean scores ± SD	5.36 ± 0.62	5.16 ± 0.69	0.008*
Negative Affectivity			
N (%)	0	3 (2)	0.097
Mean scores ± SD	2.86 ± 0.67	3.00 ± 0.73	0.056
Effortful Control			
N (%)	57 (32.8)	68 (45.6)	0.022*
Mean scores ± SD	5.11 ± 0.65	5.09 ± 0.68	0.740
Surgency-Effortful Control equally			
N (%)	10 (5.7)	5 (3.4)	0.428
Mean scores ± SD	N/A	N/A	N/A
Surgency-Negative Affectivity equally			
N (%)	0	1 (0.3)	0.461
Mean scores ± SD	N/A	N/A	N/A

p-value < 0.05 is considered statistically significant
* *p*-value < 0.05

DISCUSSION

This is the first study in Thailand that has used the translated very short form of Early Childhood Behavior Questionnaire (ECBQ), which is the clinically practical evaluative tool for assessing Thai toddlers' temperament. This study is also the first preliminary report on Thai toddlers' temperament. The majority of Thai toddlers in this study demonstrated surgency temperament. Boys exhibited more surgency, while girls manifested more effortful control.

The very short form of ECBQ, Thai version demonstrated an internal consistency coefficient at 0.682 for surgency temperament, 0.627 for negative-affectivity temperament, and 0.692 for effortful-control temperament. Although these coefficients suggested questionable internal consistency, they were slightly lower than those of the original English version (0.72 for surgency, 0.7 for negative affectivity, and 0.72 for effortful control).[12] The maximum of the Cronbach's alpha coefficient of the Thai version of the questionnaire, when any item was deleted, was 0.707, which was slightly higher than the overall Cronbach's alpha coefficient. This suggests that no item disproportionately affected the overall internal consistency (i.e. No specific item should be removed from the Thai version of the very short-form ECBQ). A recent study translating the very short-form ECBQ into Czech, which recruited 709 children ages 18-36 months, also revealed an internal consistency by Cronbach's alpha coefficients of 0.65, 0.70, and 0.71 for surgency, negative affectivity, and effortful control, consecutively. However, there was no report regarding the inter-rater and test-retest reliabilities.[16]

The intraclass correlation coefficients exhibited moderate to good short-term intra-rater reliability (0.614, 0.602, and 0.750 for surgency, effortful control, and negative affectivity, respectively). In contrast, the long-term one had poor to moderate reliability (0.602 for surgency, 0.476 for effortful control, and 0.459 for negative-affectivity temperament). We postulated that the decline in the reliability might be due to chronological fading. However, the long-term ICCs almost reached those of the original English version, which was ranged from 0.55-0.83.[12] The inter-rater reliability was classified as being of poor to moderate reliability - i.e. 0.463, 0.638, and 0.670 for effortful control, surgency, and negative affectivity, respectively, which were slightly more favorable than in the original English version, which reported an overall inter-rater reliability of 0.31 (0.32, 0.24, and 0.36 for effortful control, surgency, and negative affectivity, respectively).[12] All of the properties demonstrated that very short-form ECBQ, Thai version can be fruitfully used in research on temperament among Thai children.

Our study found that the majority of our participants were reported as having a surgency temperament. Although no previous studies reported the most common temperament type in their populations, there has been plentiful evidence that culture affects temperament. American children get higher scores for surgency and lower scores for negative affectivity than Japanese children.[17] One possible explanation is that self-reliance, autonomy, and creativity are highly valued and promoted in the Western cultures, whereas such characteristics tend not to be in the Asian ones. However, the American children got higher scores for negative affectivity,[18] and tended to demonstrate more effortful control than Chilean and Italian toddlers, respectively.[19] Therefore, how Thai children's temperament differs from that of children's from other regions should be the subject of future research. Our findings regarding gender differences are comparable to those of previous international studies.[16,20] Possible explanations involve how boys and girls are raised to behave differently.

There were some limitations to this study. The data collection about parental temperament scoring did not be specified that the parent was a father or a mother. This lack of information hindered the comparisons between fathers' and mothers' perspectives that may lead to low inter-rater reliability, especially regarding effortful-control temperament. Although our sample size was adequate for evaluating the reliability of the questionnaire, it was obviously too low to represent all Thai toddlers. Future research should be done using a considerably larger sample size and should include the participants from every region of Thailand.

CONCLUSION

The very short form Early Childhood Behavior Questionnaire, Thai version demonstrated acceptable internal consistency and reliability. The majority of the Thai toddlers revealed a surgency temperament. Boys exhibited more surgency, while girls manifested more effortful control.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Professor Samuel P. Putnam for giving us permission to translate the Early Childhood Behavior Questionnaire, very short form into Thai, and to Dr. Sasima Tongsai and Ms. Kanokwan Sommai from the Division of Research, Faculty of Medicine Siriraj Hospital, Mahidol University for help with the statistical analysis.

Conflict of interest declaration

The authors declare no conflicts of interest relating to any aspect of this study.

Funding disclosure

There was no funding for this study.

APPENDIX

The ECBQ assesses the following 18 scales of temperament:

Activity Level/Energy: Level (rate and intensity) of gross motor activity, including rate and extent of locomotion

Attentional Focusing: Sustained duration of orienting on an object of attention; resisting distraction

Attentional Shifting: The ability to transfer attentional focus from one activity/task to another

Cuddliness: A child's expression of enjoyment in and molding of the body to being held by a caregiver

Discomfort: Amount of negative affect related to sensory qualities of stimulation, including intensity, rate, or complexity of light, sound, texture.

Fear: Negative affect, including unease, worry, or nervousness related to anticipated pain or distress and/or potentially threatening situations; being startled by sudden events

Frustration: Negative affect related to interruption of ongoing tasks or goal blocking

High-intensity Pleasure: Pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty and incongruity

Impulsivity: Speed of response initiation

Inhibitory Control: The capacity to stop, moderate, or refrain from a behavior under instruction

Low-intensity Pleasure: Pleasure or enjoyment related to situations involving low stimulus intensity, rate, complexity, novelty and incongruity

Motor Activation: Repetitive small-motor movements; fidgeting

Perceptual Sensitivity: Detection of slight, low-intensity stimuli from the external environment

Positive Anticipation: Excitement about expected pleasurable activities

Sadness: Tearfulness or lowered mood related to exposure to personal suffering, disappointment, object loss, loss of approval, or response to other's suffering

Shyness: Slow or inhibited approach and/or discomfort in social situations involving novelty or uncertainty

Sociability: Seeking and taking pleasure in interactions with others

Soothability: Rate of recovery from peak distress, excitement, or general arousal

Children's temperament divided into three factors:

Surgency/Extraversion is characterized by high positive loadings for Activity Level, High-Intensity Pleasure, and the Impulsivity scale and strong negative loadings on the Shyness scales.

Negative Affectivity is characterized by high positive loadings for Anger/Frustration, Sadness, Fear, and Discomfort and negative loading for the Soothability scales.

Effortful Control is characterized by high positive loadings for Inhibitory Control, Attention Control, and the Perceptual Sensitivity scales.

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Predictive Value of Right Ventricular Pressure Measurement for Residual Pulmonary Stenosis in Tetralogy Repair

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ABSTRACT

Objective: The long-term outcome of tetralogy of Fallot repair depends on an adequate relief of right ventricular outflow tract obstruction and preservation of the pulmonary valve function. Since intraoperative transesophageal echocardiography is not routinely performed in small patients, we postulated that the post-bypass right ventricular pressure measured intraoperatively could predict residual pulmonary stenosis when evaluated by transthoracic echocardiography.

Materials and Methods: Of the 187 patients who underwent tetralogy repair between 2012 and 2019 at Siriraj Hospital, Thailand, 95 with right ventricular pressure measurements and pre-discharge echocardiography were included in the study. Their intraoperative parameters, and postoperative outcomes were analyzed. The tolerable pressure cutoff was determined.

Results: The median patient age was 3.9 years old (interquartile range 2.75–6). Fifty-three patients (54.6%) required the use of the transannular patch. Ten patients (10.3%) had significant residual pulmonary stenosis with a mean right ventricular systolic pressure of 64.0±10.6 mmHg compared with 48.7±14.4 mmHg for the other patients. There was an association between the pressure figure and the degree of residual pulmonary stenosis (rho=0.391, p=0.01). A systolic pressure above 49 mmHg predicted pulmonary stenosis with a likelihood ratio of 2.18 (1.94-2.80, 95%CI). The likelihood rose to 2.93 (2.44-4.01, 95%CI) if the pressure resulted in a right to left ventricular pressure ratio above 0.62. The patients whose figures did not exceed 49 mmHg experienced no significant residual obstruction, regardless of the pressure ratio.

Conclusion: Intraoperative measurement of the right ventricular pressure can predict residual pulmonary stenosis after tetralogy repair with a reassuring cutoff of 49 mmHg.

Keywords: Tetralogy of Fallot repair; right ventricular pressure; residual pulmonary stenosis; intraoperative assessment (Siriraj Med J 2022; 74: 225-232)

INTRODUCTION

Tetralogy of Fallot is the most common cyanotic congenital heart disease worldwide. The first corrective surgery was performed in the 1950s and the treatment has been evolving ever since.[1] The current strategies involve adequate relief of right ventricular outflow tract obstruction and optimal preservation of the right ventricular and pulmonary valve function, guided predominantly by intraoperative transesophageal echocardiography.[2,3]

Residual pulmonary stenosis or regurgitation after the repair is not infrequent and, to some extent, it can lead to progressive right ventricular dysfunction requiring

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http://dx.doi.org/10.33192/Smj.2022.28

subsequent reoperation to prevent sudden cardiac death.[4-6] In the light of a paradigm shift from complete relief of the right ventricular outflow tract obstruction to preserving the pulmonary valve and infundibulum during tetralogy repair, the adequacy of resection has gained elevated importance as some reports have revealed a high incidence of residual right ventricular outflow tract obstruction following valve-sparing surgery. even during short-term follow-up.[7]

Intraoperative echocardiography is not routinely performed in small children at many institutes, including at our institute, and instead, many surgeons measure the right ventricular pressure intraoperatively to predict the degree of residual pulmonary stenosis and to identify whether the problematic outflow justifies immediate revision.[8] Unfortunately, the maximum tolerable pressure is arbitrary and depends on the individual threshold of acceptance. Besides, the left to the right systolic ventricular pressure ratio alone is subject to errors as it depends on the systemic vascular resistance, which may vary across patients in response to the cardiopulmonary bypass.

We postulate that, in the absence of intraoperative echocardiography, the right ventricular systolic pressure can predict residual right ventricular outflow tract obstruction. Further, in this study, we tried to identify the pressure criteria for outflow tract revision.

MATERIALS AND METHODS

Patients

Between 2012 to 2019, 187 consecutive tetralogy of Fallot patients underwent total correction at Siriraj Hospital, Thailand. After exclusion of the patients without documented post-bypass right ventricular systolic pressure measurements and pre-discharge transthoracic echocardiography, 95 patients were included in the study analysis. The decision to measure the ventricular pressure primarily depended on the surgeon's routine. Table 1 shows the baseline characteristic and operative variables of the study population. The preoperative pulmonary valve z-value and McGoon ratio were obtained from the cardiac catheterization measurements. The clinical outcomes between the 95 included patients were similar to those of the rest patients (who were excluded because of no documented intraoperative right ventricular pressure measurement) concerning significant residual pulmonary stenosis and in-hospital care duration (the results not shown).

The study was approved by Siriraj Institutional Review Board (COA no. Si 003/2020). The patient consent is waived as it contained minimal risk to the subject.

TABLE 1. Patient characteristics.

Variables		Study patients (n = 95)
Age, y	mean±SD	6.0±6.7
median [IQR]		3.9 [2.75–6]
Weight, kg	mean±SD	15.7±8.7
median [IQR]		13 [10.5–17.8]
Preoperative PV z-score		-2.14±1.52
McGoon ratio		2.21±0.47
Bypass time, min		165.5±58.7
Cross-clamping time, min		121.2±39.2
Transannular patch, n (%)		52 (54.7)
Direct RVSP, mmHg		50.3±14.8
Direct Prv/Plv ratio		0.60±0.18
PostOp TTE RVOT PPG, mmHg		25.2±14.3
missing, n (%)		15 (15.8)
PostOp TTE PS grade, n (%)		
none		16 (16.8)
mild		69 (72.6)
moderate		10 (10.5)
severe		0
Significant residual PS, n (%)		10 (10.5)
ICU stay, d	mean±SD	3.2±6.6
median [IQR]		2 [1, 3]
Hospital stay, d	mean±SD	9.8±7.4
median [IQR]		8 [7–11]

Abbreviations: ICU; intensive care unit, Plv; left ventricular pressure, Prv; right ventricular pressure, PostOp; postoperative, PPG; peak pressure gradient, PS; pulmonary stenosis, PV; pulmonary valve, RVOT; right ventricular outflow tract, RVSP; right ventricular systolic pressure, TTE; transthoracic echocardiography.

Surgical technique and right ventricular pressure measurement

All repairs were conducted through median sternotomy with cardiopulmonary bypass under mild systemic hypothermia. Intermittent, antegrade cold blood cardioplegia was given for myocardial protection. The surgical approach was transatrial and transpulmonary and/or transventricular in all the patients depending on the degree of infundibular hypoplasia and on the anatomy of the ventricular septal defect. The right

ventricular outflow was managed with either annular-preserving repair or standard transannular patch repair with monocusp creation using a 0.1 mm-thick expanded polytetrafluoroethylene membrane according to the intraoperative annular measurement. The patch size was tailored for a normal pulmonary valve size for the age and height of the patient. After the patients had come off the bypass, all the transducers were calibrated, and the right ventricular pressure was obtained by direct puncture to the right ventricular free wall using a 25 mm-long, 22-gauge needle connected to the pressure transducer system. The left ventricular pressure was simultaneously estimated by the peripheral arterial line and an arterial outlet pressure monitoring device.

Postoperative course and transthoracic echocardiography

In the intensive care unit, the hemodynamic support and ventilator management were adjusted according to the clinical progress by the attending physicians. Postoperative echocardiography was performed by pediatric cardiologists before hospital discharge or otherwise as clinically indicated. The pressure gradient across the right ventricular outflow tract, degree of pulmonary stenosis, and regurgitation were noted.

Definitions

The degree of residual pulmonary stenosis was estimated using transthoracic echocardiography by a combination of the morphologic appearance, and the measured peak velocity and peak pressure gradient across the pulmonary valve.

- Mild: peak velocity < 3 m/s, peak gradient < 36 mmHg
- Moderate: peak velocity = 3–4 m/s, peak gradient = 36–64 mmHg
- Severe: peak velocity > 4 m/s, peak gradient > 64 mmHg

Significant residual pulmonary stenosis is defined as a moderate or greater degree of pulmonary stenosis.

Statistical analysis

Based on the expected correlation coefficient of 0.3, a minimum sample size of 85 was required to estimate Spearman's rank correlation with a power of 0.8 and a significance level of 0.05. Descriptive statistics were used to present the baseline characteristics of the patients. Continuous variables were presented as the mean with the standard deviation or the median with the interquartile range. The differences were evaluated using the Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as number and percentage, and differences were evaluated using the chi-square test or Fischer's exact test, as appropriate. A p-value < 0.05 was set as the threshold for statistical significance. Receiver operating characteristic (ROC) curves were generated to determine the optimal cutoff values for the variables in the prediction of significant residual outflow tract obstruction. All the data were analyzed using the SPSS™ software version 20.0 (SPSS Inc., IBM Company, Chicago, Illinois, USA).

RESULTS

No operative mortality was observed. The pre-discharge transthoracic echocardiography was performed at the median post-operative day 5 (interquartile range 1-6). The mean intraoperative right ventricular systolic pressure after the repair was 50.3±14.8 mmHg (range 17–83 mmHg). The mean intraoperative right to left systolic ventricular pressure ratio was 0.60±0.18 (range 0.21–1.08). Concerning the degrees of postoperative tricuspid regurgitation, only 5 patients experienced moderate tricuspid regurgitation while the rest had no or mild regurgitation. Table 2 shows comparisons between the two surgical approaches: the transannular and non-transannular techniques. The transannular patch repair group was associated with less residual outflow obstruction, more pulmonary regurgitation, and a longer ICU stay and hospital stay.

Ten patients (10.5%) were documented to have significant residual right ventricular outflow tract obstruction with a higher systolic right ventricular pressure and pressure ratio. None of them underwent surgical revision at the index admission. Comparisons between the patients with and without significant residual pulmonary stenosis are shown in Table 3. The patients with residual subpulmonary obstruction required less transannular patching and subsequently a shorter in-hospital care duration. The characteristics of the patients with significant residual pulmonary stenosis are shown in Table 4.

Through Spearman's rank correlation analysis, we found a correlation between the systolic right ventricular pressure and the degree of postoperative residual pulmonary stenosis (rho = 0.391; p = 0.01). The right to left systolic ventricular pressure ratio was also correlated with the degree of postoperative residual pulmonary stenosis (rho = 0.369; p = 0.01). Through ROC curve analysis, we analyzed each intraoperative pressure parameter and the combination of both to identify the diagnostic cutoff for significant residual pulmonary stenosis identified by pre-discharge transthoracic echocardiography. The results are depicted in Fig 1. A systolic right ventricular

TABLE 2. Comparison of two outflow reconstruction techniques among the study patients.

Variables		Transannular approach (n = 52)	Transatrial/Pulmonary (n = 43)	P-value
Age, y	mean±SD	5.1±4.9	7.1±8.3	0.15
median [IQR]		3.4 [2.8–6.2]	4.8 [2.8–6.0]	0.43
Weight, kg	mean±SD	14.5±6.9	17.1±10.5	0.16
median [IQR]		12.2 [10.4–16.3]	14 [10.5–18.5]	0.27
Preoperative PV z-score		-2.82±1.47	-1.30±1.14	**<0.001**
McGoon ratio		2.21±0.47	2.27±0.59	0.58
Bypass time, min		176.1±68.5	148.7±40.1	**0.022**
Cross-clamping, min		129.5±42.3	108.4±32	**0.007**
Direct RVSP, mmHg		52±15	48.5±14.7	0.26
Direct Prv/Plv ratio		0.62±0.19	0.58±0.18	0.26
PostOp TTE PS grade, n (%)				0.46
none		8 (15.4)	7 (16.3)	
mild		41 (76.9)	27 (62.8)	
moderate		2 (3.8)	8 (18.6)	
severe		0	0	
Significant residual PS, n (%)		2 (3.8)	8 (18.6)	**0.039**
PostOp TTE PR grade, n (%)				**<0.001**
none		0	7 (16.3)	
mild		4 (7.7)	10 (23.3)	
moderate		20 (38.5)	21 (48.8)	
severe		27 (51.9)	4 (9.3)	
PostOp TTE RVOT PPG, mmHg		24.4±13.9	25.6±13.5	0.72
missing, n (%)		9 (17.3)	7 (16.3)	
IS at ICU arrival	mean±SD	11.3±12.7	8.2±6.2	0.15
median [IQR]		7.5 [5–15]	7 [4–13]	0.38
ICU stay, d	mean±SD	4.3±8.8	2±1.5	0.09
median [IQR]		2.5 [1–4]	1 [1–2]	**0.006**
Hospital stay, d	mean±SD	11.5±10	8.1±2.7	**0.032**
median [IQR]		10 [7–11.8]	8 [6–10]	**0.007**

Abbreviations: ICU; intensive care unit, IS; inotropic score, Plv; left ventricular pressure, Prv; right ventricular pressure, PostOp; postoperative, PPG; peak pressure gradient, PR; pulmonary regurgitation, PS; pulmonary stenosis, PV; pulmonary valve, RVOT; right ventricular outflow tract, RVSP; right ventricular systolic pressure, TTE; transthoracic echocardiography.

TABLE 3. Comparison of two outflow reconstruction techniques among the study patients.

Variables		Patients with significant residual PS (n = 10)	Patients without significant residual PS (n = 85)	P-value
Age, y	mean±SD	3.8±2.0	6.3±7.0	**0.019**
median [IQR]		3.3 [2.3–5.3]	4.3 [2.8–6.3]	0.31
Weight, kg	mean±SD	14.2±5.0	15.9±9.1	0.39
median [IQR]		13.3 [10–17.6]	13 [10.6–17.8]	0.85
Preoperative PV z-score		-1.59±0.74	-2.21±1.58	0.22
McGoon ratio		2.58±0.57	2.17±0.44	0.05
Bypass time, min		144±24.9	168±61	**0.028**
Cross-clamping time, min		109.6±29.5	122.6±40.1	0.23
Transannular patch, n (%)		2 (20)	49 (57.6)	**0.039**
Direct RVSP, mmHg		64±10.6	48.7±14.5	**0.001**
Direct Prv/Plv ratio		0.76±0.13	0.58±0.18	**0.002**
PostOp TTE RVOT PPG, mmHg		46.7±10.2	21.8±10.9	**<0.001**
missing, n (%)		0	14 (16.5)	
IS at ICU arrival	mean±SD	8.6±6.9	9.9±10.7	0.60
median [IQR]		7 [4–11.3]	6.8 [4.4–15]	0.89
ICU stay, d	mean±SD	1.7±1.9	3.5±6.9	0.07
median [IQR]		1 [1–1.3]	2 [1–3]	**0.018**
Hospital stay, d	mean±SD	7.7±1.8	9.3±3.6	**0.042**
median [IQR]		7 [6.8–8.5]	8 [7–11]	0.27

Abbreviations: ICU; intensive care unit, IS; inotropic score, Plv; left ventricular pressure, Prv; right ventricular pressure, PostOp; postoperative, PPG; peak pressure gradient, PS; pulmonary stenosis, PV; pulmonary valve, RVOT; right ventricular outflow tract, RVSP; right ventricular systolic pressure, TTE; transthoracic echocardiography.

pressure above 49 mmHg predicted postoperative residual pulmonary stenosis with a likelihood ratio of 2.18 (95%CI 1.94–2.80). A systolic right to left ventricular pressure ratio above 0.62 predicted postoperative residual pulmonary stenosis with a likelihood ratio of 2.57 (95%CI 2.21–3.42). The combination of both pressure criteria raised the likelihood of residual outflow obstruction to 2.93 (95%CI 2.44–4.01). Fig 2 shows the outflow tract decision flowchart according to our results. None of the study patients whose ventricular pressure did not meet both criteria experienced significant residual outflow obstruction.

DISCUSSION

We found an association between right ventricular systolic pressure and the degree of pulmonary stenosis. As a predictor for residual right ventricular outflow tract obstruction, the absolute figure of the intraoperative pressure performed comparably to the pressure ratio (an almost identical area under the ROC curve). When we combined both parameters, the predictive value from the likelihood ratio increased considerably. Apart from the pressure ratio, this information implies how high the right ventricular pressure is also matters, especially when the right to left systolic pressure ratio approaches the

TABLE 4. Characteristics of the patients with significant residual pulmonary stenosis.

Patient	Gender	Preoperative PV z-score	McGoon ratio	Technique	RVSP, mmHg	Prv/lv ratio	PostOp TTE RVOT PPG, mmHg	IS at ICU arrival	ICU stay, day	Hospital stay, day
1	M	-2.06	2.73	Subannular, valvulotomy	52	0.66	39	4	1	6
2	F	-1.5	2.3	Subannular, valvulotomy	50	0.63	49	15	2	6
3	M	-1.18	3.5	Supravalve, valvulotomy	69	0.69	47	11.7	8	12
4	F	-2.6	3	**Transannular, monocusp**	67	0.76	55	20	4	10
5	M	-1.9	2.5	Supravalve, valvulotomy	64	0.75	42	7	1	8
6	M	-1.63	1.5	Sub/supravalve patch, valvulotomy	50	0.70	38	5	1	8
7	M	-2.4	2	Supravalve, valvulotomy	81	0.70	55	10	1	7
8	F	-1.79	3.12	**Transannular, monocusp**	75	0.90	66	7.5	1	7
9	M	-0.4	2.53	Supravalve, valvulotomy	70	1.08	41	5	1	8
10	M	-0.4	2.6	Transatrial	62	0.73	44	10	1	7

Abbreviations: ICU; intensive care unit, IS; inotropic score, Plv; left ventricular pressure, Prv; right ventricular pressure, PostOp; postoperative, PPG; peak pressure gradient, PV; pulmonary valve, RVOT; right ventricular outflow tract, RVSP; right ventricular systolic pressure, TTE; transthoracic Echocardiography.

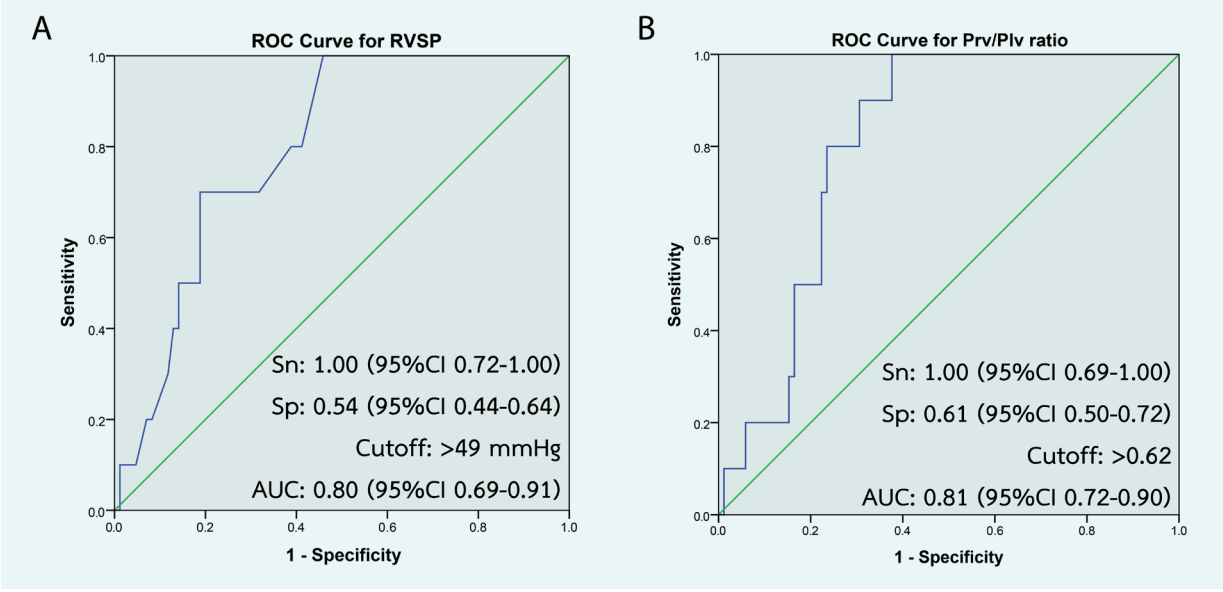

Fig 1. Receiver operating characteristic (ROC) curves of the predictors of right ventricular outflow tract obstruction. **(A)** Right ventricular systolic pressure (RVSP). **(B)** Right to left ventricular pressure ratio (Prv/Plv ratio).
Abbreviations: AUC; area under the curve, Sn; sensitivity, Sp; specificity.

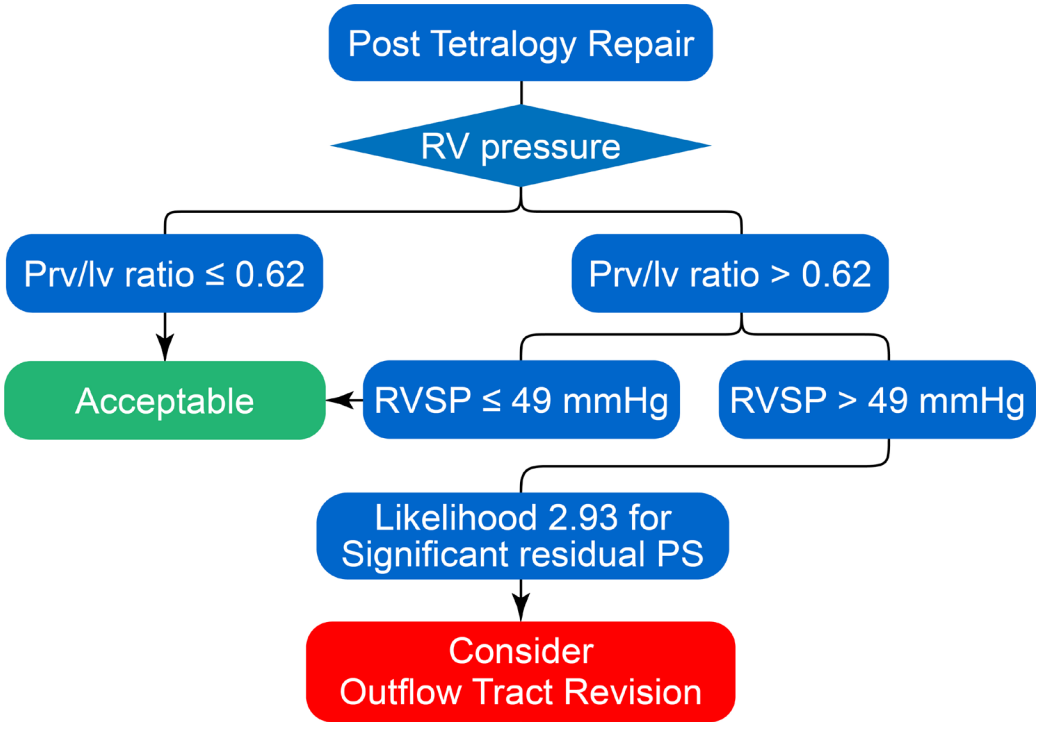

Fig 2. Outflow tract assessment decision flowchart
Abbreviations: Prv/lv; right ventricular to left ventricular systolic pressure ratio, PS; pulmonary stenosis, RV; right ventricle, RVSP; right ventricular systolic pressure.

published revision criteria. Although in the majority of the cases both the pressure and pressure ratio went in the same direction and magnitude, in some patients with a relatively low systolic blood pressure initially off the pump, use of the pressure ratio alone tended to overestimate the residual outflow obstruction. Only one of the sixteen patients (specifically, patient #9) with an initial systolic blood pressure below 70 mmHg experienced significant residual pulmonary stenosis despite a mean pressure ratio of 0.75±0.29 in the group with hypotension. Adding the absolute right ventricular pressure to the consideration could prevent unnecessary intervention in this context. To the best of our knowledge, this piece of information has not been reported before in the literature.

Regarding the pressure ratio cutoff value of 0.62, which is quite low compared with other reports[2,9], this figure was selected as a reassuring cutoff, not the revision one. As the specificity of the test suggested, some patients whose measurement exceeded these criteria eventually fell into the insignificant residual outflow stenosis at the sonographic follow-up. This implies that even if both proposed criteria are met, the surgeon should logically identify the culprit location and consider the possibility of further resection without scarifying the pulmonary valve integrity before commencing the second pump run. The reason behind this is possibly due to the heterogeneous nature of postoperative Fallot's outflow tract restriction (i.e., fixed or dynamic)[10], which, unfortunately, might need intraoperative echocardiography to differentiate.[3]

Unsurprisingly, the patients who needed the pulmonary valve ring enlarged performed worse than those with an intact pulmonary valve ring in terms of the pulmonary valve integrity and in-hospital care duration (Table 2). In contrast to a previous report[8], our study demonstrated better in-hospital outcomes among the patients with significant residual outflow tract obstruction (shorter ICU and hospital stay). This result could probably be attributed to the effect of the transannular approach and the resultant pulmonary insufficiency rather than the gradient itself (the transannular patching requirement of the patients with insignificant residual stenosis was almost triple that of the significant counterpart, Table 3).

It is to be noted that our study had limitations due to its retrospective nature and short period of follow-up. Also, changes in the outflow tract gradient over time were monitored only in selected patients. Furthermore, as we did not have a patient with critical residual outflow tract obstruction in our series, the diagnostic cutoff of such a condition was, therefore, unattainable. Longer-term follow-up of such a 'significant' patient is needed to elucidate the clinical significance of such findings.

CONCLUSION

In the setting without intraoperative transesophageal echocardiography, the direct measurement of right ventricular pressure can predict the adequacy of outflow tract reconstruction during the repair of tetralogy patients. Adding an absolute pressure criterion of 49 mmHg to the pressure ratio could prevent unnecessary surgical revision and protect pulmonary valve integrity.

ACKNOWLEDGEMENTS

We acknowledge the contribution of Dr. Sasima Tongsai from the Clinical Epidemiology Unit, who performed the statistical analysis for this study.

Funding statement: This research received no specific grant from any funding agency.

Conflict of interest statement: None declared.

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The Efficacy of Inside-Out Transversus Abdominis Plane Block vs Local Infiltration before Wound Closure in Pain Management after Kidney Transplantation: A Double-blind, Randomized Trial

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ABSTRACT

Objective: Transversus abdominis plane (TAP) block is a form of multimodal pain management in open abdominal surgery. Among patients who undergo kidney transplantation, their choice of painkillers is limited. This study aims to determine the efficacy of TAP block vs local infiltration in pain management after kidney transplantation.

Materials and Methods: In this prospective, randomized, double-blinded clinical trial, 46 patients with end-stage kidney disease who had undergone kidney transplantation were randomly divided into two groups: a local anesthetic infiltration (LA) group receiving 0.25% Bupivacaine 20 ml around the surgical wound before wound closure and a TAP block group receiving 0.25% Bupivacaine 20 ml by the inside-out technique. Their postoperative pain scores and morphine consumption were recorded at 2, 6, 12, 18, 24, and 48 hours.

Results: There was no statistically significant difference in the baseline characteristics between the groups. The postoperative pain score at two hours in the TAP block group was significantly lower than in the LA group (P value = 0.037), but without other differences in their pain scores after two hours. There was no statistical difference in the morphine consumption between the two groups. The total morphine consumption in the TAP block group was less than in the LA group, but this was not statistically significant. No patients suffered from complications of the TAP block.

Conclusion: Transversus abdominis plane block can reduce postoperative pain at two hours after kidney transplantation, without significant complications.

Keywords: Transversus abdominis plane block; kidney transplantation; pain management; postoperative pain (Siriraj Med J 2022; 74: 233-238)

Abbreviations

TAP	Transversus abdominis plane
NRS	Numerical rating scale
BMI	Body mass index
LA	Local anesthesia
QL	Quadratus lumborum

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http://dx.doi.org/10.33192/Smj.2022.29

INTRODUCTION

Kidney transplantation is the treatment of choice in patients with end-stage kidney disease. A kidney transplant is a major operation requiring a classical incision at the lower abdomen, extending from laterally to the pubic symphysis to the anterior superior iliac crest called Gibson incision. Many patients require a painkiller after the operation, and postoperative pain control is crucial to improving one's surgical outcome. Multimodal analgesia aims to decrease opioid consumption and its side effects. Especially among patients who undergo kidney transplantation, their choice of painkiller is limited, due to any such drugs' interaction with immunosuppressive drugs and nephrotoxicity.[1] Local anesthesia infiltration around the incision is one of the traditional methods of local pain control. Two decades ago, transversus abdominis plane (TAP) block was introduced as a new technique to reduce postoperative pain. This was originally reported by Rafi in 2001.[2] TAP block is a regional anesthesia, targeting sensory nerves running between the internal oblique muscle and the transversus abdominis muscle layer, these nerves receiving signal from anterior abdominal wall between level of T9 and T12 via a blinded technique or ultrasound guidance.[3,4] A TAP block can be performed by a surgeon or anesthesiologist using the outside-in technique after the induction of anesthesia or through the inside-out technique before the wound is closed. A TAP block has been used to control postoperative pain involving many kinds of abdominal surgery. The results from many trials have produced variable outcomes, some showing no significant difference in post-operative pain management, while others have resulted in significant pain scores and/or opioid consumption.[5-11] According to meta-analyses, the TAP block seems to benefit postoperative pain control in kidney transplantation patients.[12] Until now, there has been no report comparing traditional, local anesthetic infiltration with the TAP block by the inside-out technique in kidney transplantation patients. This study aims to determine the efficacy of the TAP block vs local infiltration in pain management after kidney transplantation.

MATERIALS AND METHODS

This prospective, randomized, double-blinded clinical trial was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, protocol number 826/2019(IRB4). After informed consent, 46 patients with end-stage kidney disease who had undergone kidney transplantation from both living-donor and cadaveric kidney transplant at Siriraj Hospital were recruited. Patients were excluded if they had a history of painkiller allergy, if they could not define a pain score in the numerical rating scale (NRS), were suspected of having a painkiller addiction or an abnormal coagulopathy, or had incomplete data.

Patients' demographic data (sex, age, BMI, and previous abdominal surgery); intraoperative data (operative time and length of wound); and postoperative data covering 48 hours (pain score and opioid usage) were collected. Patients were randomly divided into two groups: a local anesthetic infiltration (LA) group and a TAP block group. The group allocations were concealed in opaque envelops which were randomly picked up and opened just before each wound was closed. After standard monitoring, all patients received general anesthesia. The kidney transplantation was then done routinely. In the LA group, patients received 0.25% Bupivacaine 20 ml around the surgical wound before the wound was closed. In the TAP block group, the TAP block was performed by a surgeon with the ultrasound- guided inside-out technique. A curvilinear ultrasound probe was placed just lateral to the quadratus lumborum muscle above the iliac crest as high as possible via a standard Gibson incision. After the layer between the internal oblique muscle and the transversus abdominis muscle was found, 0.25% Bupivacaine 20 ml was injected into the space via needle 25-gauge 1.5 inch with the appearance of a Goose egg sign before the wound was closed (Fig 1). All patients were received postoperative care and pain control at postanesthesia care unit following Siriraj protocol[13] including Acetaminophen 500 mg 1 tab per oral every 6 hours for 3 days. After the operation, patients were assessed on a pain score with a numerical rating scale

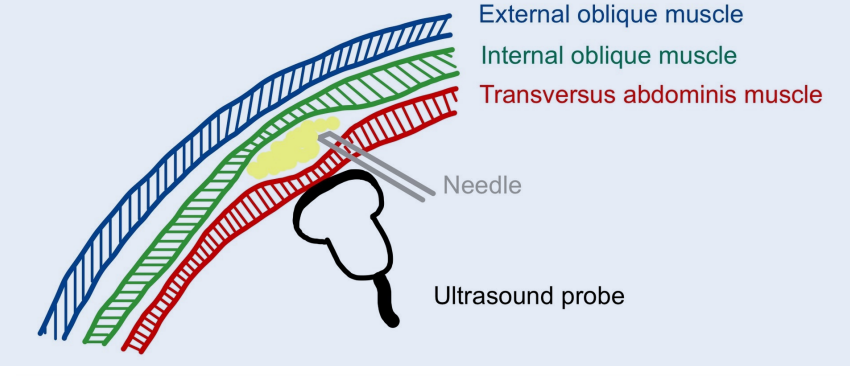

Fig 1. TAP block procedure
0.25% Bupivacaine 20 ml was injected into the space between the internal oblique muscle and the transversus abdominis muscle via needle 25-gauge 1.5 inch with ultrasound guided.

(NRS) (0=no pain, 10=worst possible pain) at 2, 6, 12, 18, 24, and 48 hours. If the pain score was more than 3 or analgesics were required, 1 mg of morphine was intravenously administered, and then the pain score was rechecked after five minutes. The amount of morphine consumption was recorded. All pain scores and morphine consumption were recorded by investigators who were blinded to the group allocations.

The goal was to compare the pain score and morphine consumption after the TAP block and LA technique. The sample size was calculated from previous study on TAP-block efficacy.[9-11] Statistical analysis was conducted using SPSS version 21 software. Demographic data and intraoperative data were present as mean ± SD. In a normal distribution of data, the Student's t-test and Pearson's chi-square were used to compare the results between the two groups. The postoperative pain scores and morphine consumption were present as a median with IQR, and compared between the groups by using the Mann-Whitney U test. A P value less than 0.05 was determined as having statistical significance.

RESULTS

From January, 2020 to November, 2020, 46 patients were enrolled in this study and were randomized into two groups, with 23 people in each group. One patient in the TAP block group was excluded due to the need for reoperation within 24 hours because of bleeding from tissue around the kidney graft (Fig 2). 62.2% of the study population was male, and the mean age was 46.7 years old (range: 26 – 62). The mean body mass index was 21.39 kg/m^2 (range: 15.6 – 27.9). 28.9% of the patients had previous abdominal surgery. The mean operative time was 177 minutes (range: 110 – 360) and the mean length of the wound was 16.6 centimeters (range: 12 – 23). There was no statistically significant difference in the baseline characteristics between the groups, as is indicated in Table 1.

The pain scores (NRS) were compared in two groups, (as seen in Fig 3), at 2, 6, 12, 18, 24, and 48 hours postoperatively. The median and IQR of pain scores at 2, 6, 12, 18, 24, and 48 hours in LA group are 3 (3-4), 2 (1-3), 2 (0-3), 1 (0-2), 0 (0-1) and 0 (0) respectively.

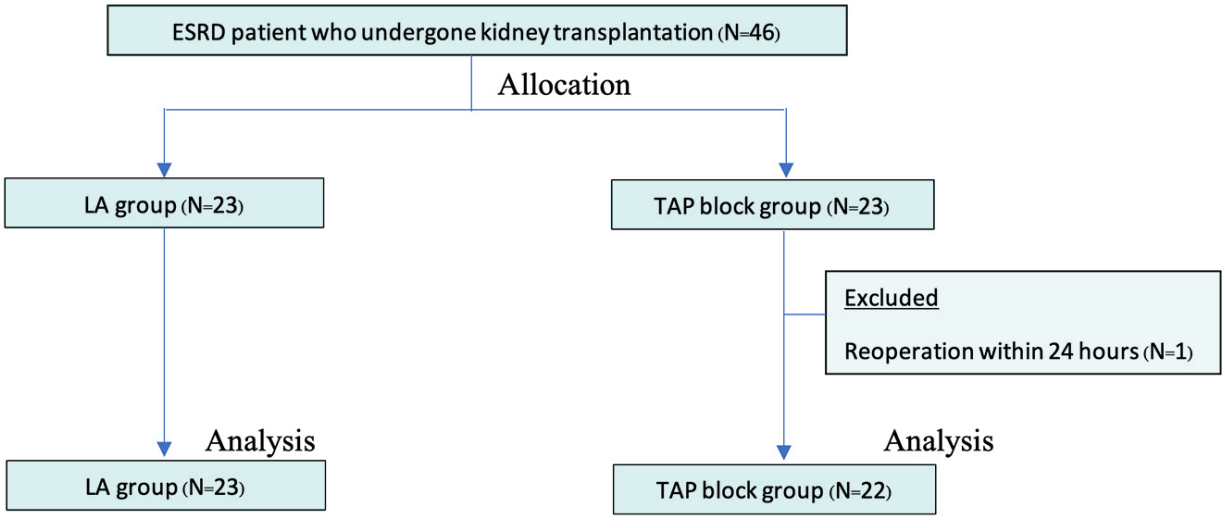

Fig 2. Patients flow chart.

TABLE 1. Comparison of two outflow reconstruction techniques among the study patients.

	LA group	TAP block group	P value
Sex			0.848
Male	60.9%	63.6%	
Female	39.1%	36.4%	
Age (years)	48.4 ± 9.7	44.9 ± 10.2	0.247
Body mass index	21.8 ± 3.1	20.9 ± 2.8	0.339
Previous abdominal surgery	30.4%	27.3%	0.815
Operative time (minute)	181.8 ± 50.1	172.5 ± 36.9	0.484
Length of wound (cm)	16.5 ± 2.2	16.7 ± 2.3	0.771

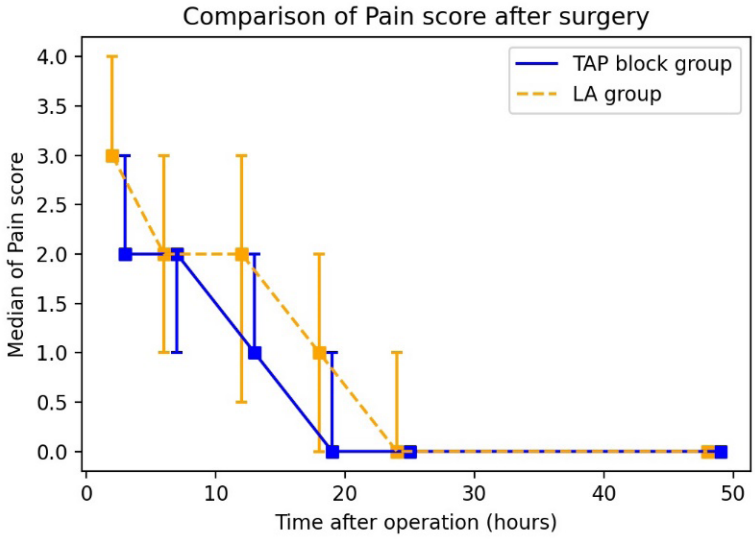

Fig 3. Postoperative pain score (NRS) at 2, 6, 12, 18, 24, and 48 hours postoperatively (median with IQR).

The median and IQR of pain scores at 2, 6, 12, 18, 24, and 48 hours in TAP block group are 2 (2-3), 2 (1-2), 2 (1-2), 0 (0-1), 0 (0-0.25) and 0 (0). The postoperative pain score at two hours in the LA group was higher than in the TAP block group (P value = 0.037), though there were no other differences in the pain scores after two hours and throughout a 48-hour period.

There was no statistical difference in morphine consumption between the groups, in terms of total usage, and any recorded time point, as shown in Fig 4. The median total morphine consumption in the LA group was 2 mg (IQR 1-4); in the TAP block group, it was 1 mg (IQR 1-3), with a p value of 0.105. No patients suffered from complications of the TAP block.

DISCUSSION

The most effective options for postoperative pain control after kidney transplantation are not always easily determined, due to the many limitations arising from patients' status. In post-kidney transplant patients, many kinds of painkillers have a risk of causing nephrotoxicity and can alter renal clearance. An epidural block is an option for postoperative pain control in abdominal surgery, but there is risk of epidural hematoma formation in kidney transplantation patients because of platelet dysfunction.[14] Regional nerve block has become a promising choice for postoperative pain control in kidney transplant patients. Regional nerve block or TAP block is target on specific sensory nerve but local anesthesia can be variable due to

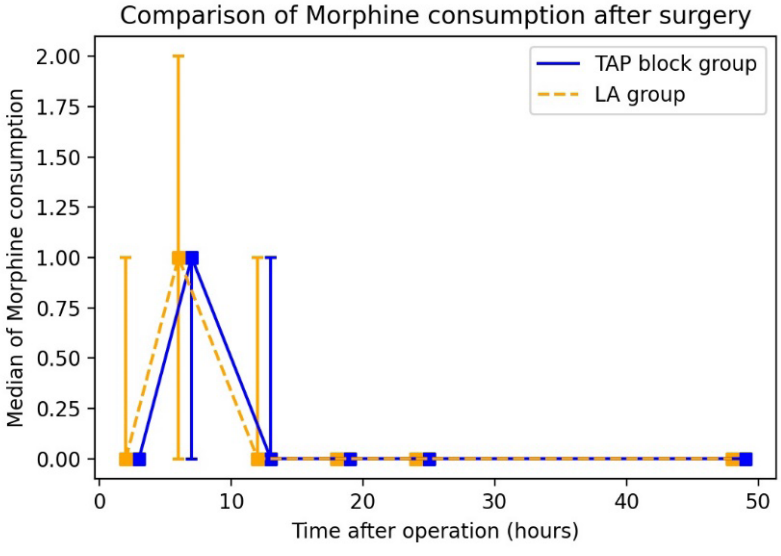

Fig 4. Morphine consumption at 2, 6, 12, 18, 24, and 48 hours postoperatively (median with IQR).

operator dependent and variations of anatomy.[3] From a meta-analysis[15], we see that a TAP block can reduce total opioid consumption (morphine consumption to 6 mg per day) as well as a patient's pain score within 24 hours after the operation. Our study shows that the pain scores two hours after the operation in the TAP block group were lower than in the LA group, but, again, there was no significant difference between the groups after that. Our LA group were given 0.25% Bupivacaine 20 ml around the surgical wound, which can also reduce the postoperative pain scores and morphine consumption. Even though our study had local pain control in the LA group, the results still reveal that the TAP block was better than the LA, as regards post-operative pain control after kidney transplantation. TAP block is recommended if ultrasound is available and patients do not have an abnormal coagulopathy.

Concerning the duration of pain control after the TAP block, our meta-analysis[15] showed that 0.375%, 0.5% and 0.75% Ropivacaine TAP block reduced the pain score at two hours after surgery, but only 0.75% Ropivacaine was effective 12 to 24 hours after surgery. We used 0.25% Bupivacaine 20 ml for the TAP block. Onset of action of 0.25% Bupivacaine is about 19 ± 41 seconds and duration of action is about 7.02 ± 1.46 hours after injection.[16] This may be one of the reasons why there were significantly reduced pain scores only at two hours after the operation. In some studies, specialists added drug regimens to the TAP block in order to prolong the pain-control effect. Yang et al.[17] have shown that the addition of dexmedetomidine can provide a more effective analgesic effect for the TAP block. Systematic review and meta-analysis from Choi et al.[18] have indicated that adding dexamethasone to the local nerve block can prolong the effect of nerve block more than by just doing a local nerve block alone.

In a meta-analysis[14], some of researchers used the blinded technique of the TAP block, but many used the ultrasound-guided approach. The efficacy of the latter has been shown to be superior. Today, the ultrasound-guided technique is considered the gold standard for the TAP block.[4] Regarding the other technique of TAP block in our study, we used the ultrasound-guided method with the inside-out technique. The typical outside-in TAP block technique may cause visceral organ damage, even if the procedure is ultrasound-guided.[19,20] The inside-out technique can reduce the possibility of visceral organ damage due to performers' visualization while performing the TAP block. Additionally, the TAP block, which is performed by a surgeon intra-operatively, requires less time than the conventional TAP block by an anesthesiologist, and there is with no difference in the postoperative pain-control outcomes.[21]

There is an important question involving the timing of the administration of the TAP block. In our study, the TAP block was applied before the wound was closed, though some performers do this before starting to operate. Dahl et al.[22] have demonstrated that postoperative pain scores were not significantly different between the pre- and post-incisional nerve block. Another technique that may help in pain management for kidney transplant patients is the quadratus lumborum (QL) block 2. According to Kolacz et al.[23], this kind of block can reduce fentanyl consumption within 24 hours after kidney transplantation, without a difference in the pain score, compared to the TAP block. Given the inside-out technique used in our study, we may also perform a QL block via a kidney-transplantation incision.

There were a number of limitations in this study. First, we could not assess the patients' sensory-distribution level because the TAP block was performed before the wound was closed and while patients were still under general anesthesia. Secondly, our inside-out technique is different from original TAP technique. The double pop sensation described in original technique cannot be felt during needle passage, so ultrasound guided is necessary to determine the depth of the needle. The third limitation is no use of intravenous patient control analgesia to access accurate dose of morphine requirement. Lastly, our sample size was too small to broadly assess the safety of the TAP block technique. Further studies are required to compare the safety of the inside-out method with the outside-in technique of the TAP block, and to determine the optimum dose or volume to use for the TAP block.

CONCLUSION

The transversus abdominis plane block can reduce postoperative pain after kidney transplantation, without significant complications. We conclude that the TAP block can be used as a part of multimodal pain management for post-kidney transplantation patients.

Conflicts of interest statement: The authors declare that there are no financial or other conflicts of interest involved in this project.

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The Analgesic Effect of Transcutaneous Electrical Nerve Stimulation (TENS) on the Opposite Side for Phantom Limb Pain

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ABSTRACT

Objective: To observe the effects of TENS on the contralateral limb and PLP reduction.

Materials and Methods: This was a single center retrospective study of 20 amputee participants with phantom limb pain. The inclusion criteria were participants aged above 18, average pain of at least 4/10 on the numerical rating scale (NRS), duration of pain longer than one week and treatment with TENS on the opposite side. We recorded pain intensity before and after TENS application, response time to treatment, satisfaction, and adverse effects.

Results: Of the 20 amputee participants, all patients suffered from PLP and three also suffered from residual limb pain. The average pain score before use of TENS was 4.85/10 and after was 1.15/10. The mean pain intensity score was reduced by 3.7/10 (95% CI 2.95-4.45/10) or 76.28% (95% confidence interval 63.61-89.47%). The average overall satisfaction was 81.65%, and no adverse effects from application of TENS was reported.

Conclusion: The study shows that the application of TENS on the opposite side is a safe and effective treatment method for intractable pain from PLP.

Keywords: Transcutaneous electrical nerve stimulation; amputee; phantom limb pain; contralateral; neuromodulation; neuropathic pain (Siriraj Med J 2022; 74: 239-244)

INTRODUCTION

Up to 80% of amputees experience pain sensation to a limb after amputation (phantom limb pain: PLP) and/or pain at the stump (residual limb pain; RLP) that negatively impacts their quality of life.[1-5] Although chronic PLP is common, evidence evaluating the efficacy of treatments remains scarce, and there is still no consensus for a standard treatment in standard guidelines.[5,6] The most common treatments are pharmacological. However, strong evidence supporting the short and long-term efficacy of pharmacological treatments for PLP is still lacking.[6,7]

In an effort to identify additional effective treatment options for PLP, clinicians and investigators have examined a variety of non-pharmacological treatments such as application of mirror visual feedback[8,9] and transcutaneous electrical nerve stimulation (TENS)[10-13], especially for the patients who had limited success from pharmacological treatment. TENS delivers pulsed electrical currents across the intact surface of the skin to stimulate the peripheral

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http://dx.doi.org/10.33192/Smj.2022.30

nerves and spinal cord, resulting in segmental and extra-segmental analgesia.[14] Research indicates that the application of TENS at the site of residual limb pain or projected site of phantom pain is associated with decreases in pain intensity, both at rest and during movement.[10] However, residual limb application of TENS can be challenging in certain situations because it may aggravate discomfort in patients with pre-existing pain or cause skin irritation that reduces stump integrity in recent amputees.

Contralateral TENS, by inhibiting the contralateral segmental in the dorsal horn from another side[14], potentially alleviates PLP and can address the problems associated with the stump. A number of reports and small case series have reported successful outcomes of contralateral TENS for PLP[11-13], and we already apply this treatment in our daily practice. As there is no data collection of large series for such treatment, we conducted this study to examine the effects in the Thai population.

We hypothesized that patients with PLP who received TENS on the contralateral limb would report significant pain reduction after treatment. The primary objective of this study was to observe the effects of TENS on the contralateral limb and PLP reduction. The secondary objectives included observing for adverse effects, satisfaction, and the duration of contralateral TENS treatment for PLP.

MATERIALS AND METHODS

In this retrospective observational study, in order to compare the analgesic effect before and after treatment, we performed sample size calculations with the aim to detect a 30% reduction in pain scores after treatment, which is a meaningful change. Using data from a pilot study, the mean pain score of patient suffering from phantom limb pain in our center was 5.2/10 (SD=2). By using PASW Statistics version 18 (Chicago, IL, USA), a sample size of 16 patients was enough to detect a difference, with an alpha error of 0.05 and power of 90%. As the estimate of incomplete data was 20%, the final number of patients needed for this study was adjusted to 20 patients.

After approval by the Mahidol University-IRB, the research team identified the medical records of patients who suffered from phantom limb pain at the Siriraj Pain Clinic and received contralateral TENS treatment for pain relief at Siriraj Hospital from January 1, 2018 to December 31, 2018. The research team collected the following data points:

1. General demographic and medical history, including age, sex, and cause of amputation
2. Pain history, including pain diagnosis, past medications and previous treatment(s) for PLP, and pain-related interference assessed by a validated Thai version of a brief pain inventory questionnaire[15]
3. NRS before and after treatment
4. Side effects and patient satisfaction of treatment

In routine practice, we offer the treatment to adult patients who have moderate to severe pain (average pain intensity from numeric rating scale more than 3 out of 10) despite appropriate pharmacological treatment (the patients had taken at least two analgesics). TENS was not offered in contraindicated conditions such as pregnancy, epilepsy, active malignancy, deep vein thrombosis, frail or damaged skin or to patients with cardiac pacemakers or implantable cardioverter defibrillators.

We used commercially available TENS units in our daily practice (Fig 1) due to their low cost and ease of use. First, we applied TENS' electrodes on the contralateral limb, mimicking the pain area on the opposite side. As the commercial TENS units were obtained from a variety of brands and did not have measurable parameter settings (frequency, pulse width, amplitude), we used clinical response as our end point. We turned on the stimulation and increased the intensity until the patient felt pain-free paresthesia.

We recorded an initial pain score, then applied the stimulation for at least 30 minutes and recorded their subsequent pain score. If the patient did not report any change, the session was extended to 45 minutes or 60 minutes. At the end of the session, we assessed the patient satisfaction scale (0-100) and the presence of any adverse effects. There was no long-term follow-up after the session.

Fig 1. Commercially available TENS unit.

RESULTS

We collected data from a total of 21 patients who received treatment. However, one patient was excluded because of amputation on both legs. There is no exclusion due to unreliable reporting of pain score because of psychological or physical morbidities. Finally, the data of 20 patients were included in this analysis. All patients had been suffering from PLP, and three of them also suffered from residual limb pain (RLP). The demographic data of all patients is shown in Table 1. The average pain score was 4.85 out of 10 despite the use of at least two analgesics such as gabapentin, tricyclic antidepressant, or opioids (Table 2). The pain-related interferences were evaluated by a brief pain inventory questionnaire.[15] The average total score of pain-related interference (impact of pain on general activity, mood, work, relationships, sleep, and enjoyment of life) was 16.35 out of 60. The average time elapsed since amputation before this treatment was 1.9 years.

TABLE 1. Patient's demographic data. PLP (phantom limb pain), RLP (residual limb pain).

Demographic data (n=20)	
Sex	
Male	10(50%)
Female	10(50%)
Age: mean (SD) years	57.1 (15.63)
Pain	
PLP	20(100%)
PLP+RLP	3(15%)
Level of amputation	
Transhumeral	5(25%)
Transfemoral	9(45%)
Transtibial	6(30%)
Cause	
Vascular	8(40%)
Trauma	5(25%)
Tumor	7(35%)

Pain intensity

Pain intensity was rated by the average numeric rating pain score (NRS). The average NRS before application of TENS was 4.85/10 ±1.18, and it decreased to 1.15/10±1.38 after the treatment. The difference in average pain intensity was 3.7±1.59 with a p-value of <0.001 for the paired T-test (95% confidence interval was 2.95-4.45). The NRS ranged from 3-8 out of 10 before application of TENS and decreased to 0-5 post-treatment.

Nineteen out of 20 patients reported clinically significant pain relief (pain score decreased by more than 30%). The mean percentage of pain reduction was 76.54 ± 6.18% (95% confidence interval was 63.61-89.47%).

The individual responses to treatment are shown in Fig 2. Only one patient who had PLP after a right elbow amputation due to recurrent fibrosarcoma (number 12) did not respond to treatment. This patient also did not respond well to other treatments, including gabapentin and tricyclic antidepressants.

Duration of treatment

In this study, we applied TENS on the contralateral limb until the pain score decreased or for 60 minutes, if pain did not improve. Sixteen participants responded to treatment in the first 30 minutes, and another three responded after it was extended to 45 minutes. Only one participant (patient 12) reported no significant change in NRS after 60 minutes. The median time required for TENS to decrease pain was 30 minutes. The cumulative number of responders over time is shown in Fig 3.

TABLE 2. Medication used for treatment of phantom limb pain.

Medication	Number of patients (Percentage)	Dose range (mg/day)
Gabapentin	20 (100%)	600-3000
Tricyclic antidepressants (amitriptyline, nortriptyline)	15 (75%)	10-25
Weak opioids (tramadol, codeine)	11 (55%)	Tramadol 50-400 mg/day
Strong opioids (morphine)	1 (5%)	20 mg/day

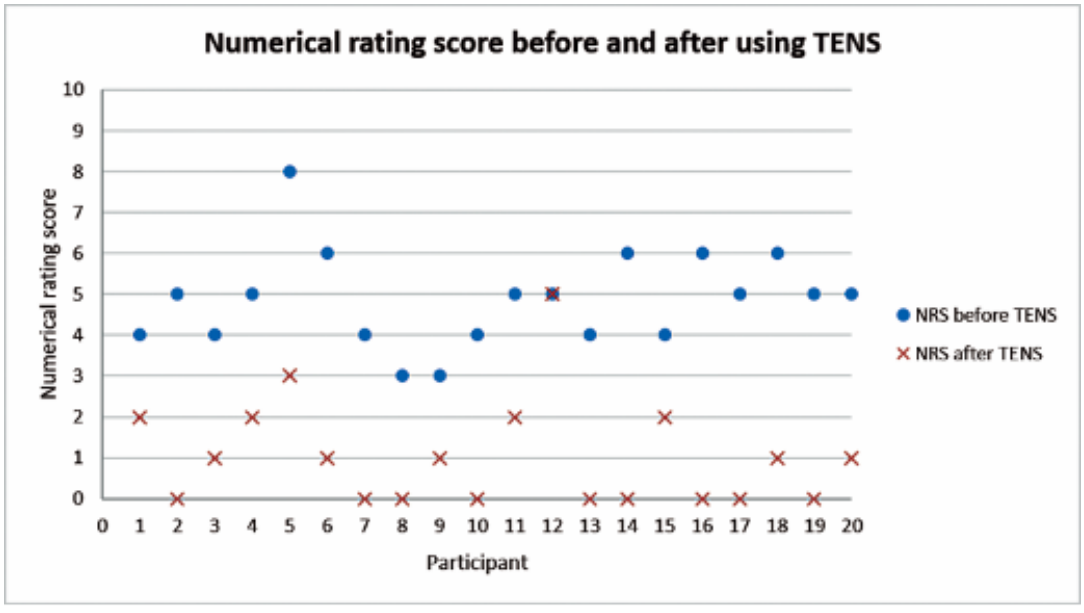

Fig 2. Individual response to contralateral TENS stimulation.

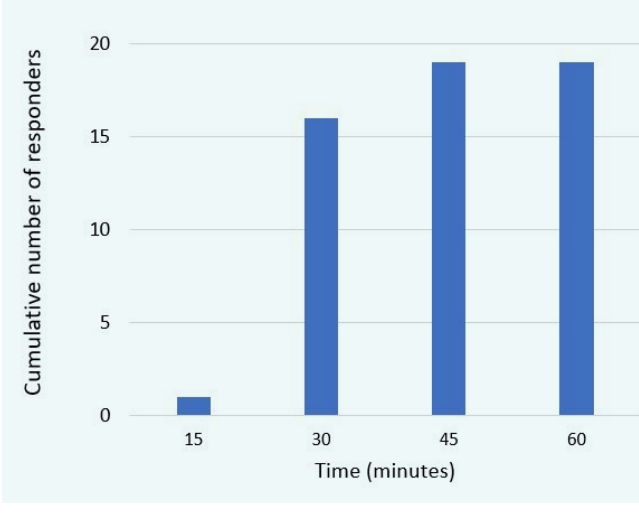

Fig 3. Cumulative number of patient reporting pain relief over time.

Adverse effect and satisfaction

The application of transcutaneous electrical nerve stimulation on the contralateral side was tolerated by all participants without any adverse events during the session. Participants reported no difficulty in using TENS and titrating the amplitude. The average overall satisfaction was 81.65% (0-100% and 0% for patient 12).

DISCUSSION

This study aimed to determine if the application of TENS on the opposite limb could reduce pain intensity in patients suffering from PLP. Our findings suggest a significant reduction of NRS immediately after treatment. Additionally, the treatment led to high satisfaction rates and no report of adverse events.

Following amputation, up to 80% of patients reported pain, either in the part that was amputated (phantom pain) or at the site of amputation (residual limb pain), or both.[1-4] This pain can affect their quality of life and prevent proper rehabilitation and prosthetic usage. PLP is poorly understood and one of the most difficult type of pain to treat.[16] The underlying pathophysiology of PLP is unclear, although it is generally accepted that nociceptive and neuropathic processes are involved and that neuropathic changes include reorganization and adaptation within the peripheral and central nervous systems.[17] Additionally, evidence evaluating the efficacy of treatments for chronic PLP remains scarce.[6] Currently, multimodal treatment strategies are used, including pharmacological treatments (gabapentinoids, tricyclic antidepressants, and opioids), pain intervention (sympathetic blocks, sympathectomies), mirror box therapy, and TENS.[17] However, there is no strong evidence that supports the long-term efficacy of each treatment for PLP.[17,18]

TENS delivers pulsed electric currents across the intact surface of the skin to stimulate peripheral nerves and the spinal cord, resulting in segmental and extra-segmental analgesia.[14] Additionally, physiological and clinical research suggest that TENS inhibits second-order nociceptive neurons, may increase blood flow, reduces muscle spasms, and selectively activates large diameter afferent fibers, which reduces nociceptor cell activity and sensitization in the central nervous system,[17,19,20] all of which are potential analgesic mechanisms for phantom pain and/or residual limb pain. Mulvey et al, indicates that TENS application at the site of residual limb pain or on the site of phantom pain is associated with decreases in

pain intensity, both at rest and with movement (frequency 100 hertz, pulse width 80 microseconds and the current increased until the patient achieved strong non-painful sensations).[10] However, residual limb application of TENS can be challenging in certain situations because this stimulation may aggravate pain in patients with preexisting pain or allodynia. The application of TENS on the residual limb can also cause skin irritation that reduces stump integrity in recent amputees.

Contralateral TENS can address problems associated with residual limb TENS. Moreover, a number of case reports and small case series have reported successful outcomes of contralateral TENS for PLP/ RLP and phantom limb sensation.[11-13] Additionally, Carabelli[13] described a better response when TENS was applied to the contralateral limb compared to residual limb stimulation. The beneficial effects may be the result of stimulation on contralateral segmental inhibition in the dorsal horn.[14]

The case series of contralateral TENS were done by Kawumara (10 cases), Katz (2 cases), and Carabelli (3 cases).[11-13] The settings of TENS applications in these studies varied from frequency 4-80 hertz, pulse width 90-225 microseconds and range of amplitude 50-80 MA depending on patients' tolerance. Compared to these previous studies, we use commercially available machines without standard settings, but adjusted the treatment by clinical response. Nevertheless, the results from our larger series still confirmed that contralateral TENS application successfully reduced pain significantly in 95% of patients. The NRS pain score decreased by an average of 3.7/10 (from 4.85 to 1.15/10) or 76.28%. Since almost all patients in this study experienced moderate to severe pain despite the use of at least two analgesics and suffered a negative impact on their quality of life, the population in this study were considered patients with difficult to treat or intractable PLP. To the best of our knowledge, this is the largest application of contralateral TENS for intractable PLP. Moreover, the treatment is associated with a high satisfaction rate as no adverse events were reported and the method is inexpensive and easy to use. This data demonstrates that TENS is one of the logical options for treatment of phantom limb pain.

An additional interesting finding was the duration of treatment in this study. Many studies of the application of TENS for phantom limb pain treatment do not have an exact duration to reduce pain.[17,18] Our study showed that 80% of patients responded after 30 minutes of treatment and 95% responded after 45 minutes, with no additional response after 45 minutes. The data suggests that the duration for application of TENS on the contralateral limb for treating phantom limb pain should be at least 30 minutes, which can be extended to 45 minutes. For treatments longer than 45 minutes, there is probably no additional benefit.

There were several limitations to this study. First, the design was an observational study and not a randomized control trial, so it is possible that factors such as the placebo effect or natural regression may have an effect. Second, as we used commercially available TENS machines, there was no standard treatment protocol. However, commercially available machines were more practical in clinical practice due to low cost and accessibility by the patients. Although this research suggests short term analgesic effect of the application of TENS in contralateral limb for PLP, a randomized control trial is needed to confirm this finding. Finally, as we only collected short term data immediately after treatment in this study, long-term follow up regarding duration of the treatment and its impact on quality of life and medication use after treatment is needed. Nevertheless, this study provides useful information such as the effect of treatment on a sample size and duration of application of treatment for protocol design for a future prospective randomized study.

CONCLUSION

This cohort study shows that the application of TENS in the contralateral limb can lead to meaningful reduction of pain in patients suffering from difficult to treat phantom limb pain. This treatment has a high success rate and is associated with high satisfaction rates and no reported adverse events. The suggested duration of treatment is at least 30 minutes and may be extended up to 45 minutes.

ACKNOWLEDGEMENTS

We would like to thank Ms. Nattaya Bunwatsana for assistance with document preparation for the IRB approval process. The authors have no conflict of interest to declare.

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Propensity Score Matched Study of Tri-Weekly vs. Weekly Platinum-Based Chemotherapy Concurrent with Radiotherapy in the Treatment of Locally Advanced Cervical Cancer

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ABSTRACT

Objective: To compare tumor control and toxicity between tri-weekly chemotherapy and weekly platinum-based chemotherapy in locally advanced cervical cancer using the propensity score matching method.

Materials and Methods: DESIGN: Retrospective cohort with propensity score matched population. SETTING: Four university hospitals. PARTICIPANTS: 781 advanced local cervical cancer patients. INTERVENTION: tri-weekly platinum-based chemoradiotherapy versus weekly chemoradiotherapy OUTCOMES: Overall survival (OS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), and toxicity, including hematological and renal toxicity.

Results: Overall median follow-up time was 59.5 months. After the propensity score matching process was completed, 326 patients were analyzed (163 in each group). The five-year OS was 66% and 64% (p 0.630); five-year LRFS was 85% and 81% (p 0.209); five-year RRFS was 89% and 94% (p 0.307); and five-year DMFS was 75% and 79% (p 0.420) in the tri-weekly and weekly groups, respectively. The patients in the tri-weekly and the weekly group had grade 2 -3 neutropenia (10.5% vs 2.5%). The other toxicities appeared to be similar in both groups in terms of white blood count, platelet and creatinine.

Conclusion: There was a potential small benefit of local control (4%) and overall survival (2%) with the tri-weekly regimen but we could not demonstrate statistical significance. However, this came at the price of an increase of 7% to 8% in grade 2-3 neutropenia.

Keywords: Cervical cancer; chemotherapy; radiotherapy; weekly regimen; tri-weekly regimen (Siriraj Med J 2022; 74: 245-255)

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http://dx.doi.org/10.33192/Smj.2022.31

INTRODUCTION

A 1999 US National Cancer Institute announcement defined concurrent platinum-based chemotherapy with radiotherapy as the standard of care for women with locally advanced cervical cancer due to approximately 10% added survival benefit after five years without a significant increase in late toxicities.[1] This was based on the results of five randomized controlled trials.[2-4,5,6]

Despite this, the frequency of the platinum-based regimen remains heterogeneous and routine chemotherapy is different among hospitals. For example, some hospitals administer weekly chemotherapy sessions whereas others give tri-weekly chemotherapy. To compare these treatment methods, many randomized controlled have been carried out.[7-14] Interestingly, most of the evidence remains conflicting in terms of both tumor control and toxicity. For example, a randomized controlled trial from the University of Ulsan, Korea in 2008[13] showed that the weekly regimen not only improved compliance but was comparable with the tri-weekly regimen in response and survival rate. On the other hand, a collaborative randomized controlled trial by the Korea Institute of Radiological and Medical Sciences, Dongnam Institute of Radiological and Medical Sciences and National Cancer Institute, Korea[12] showed that the tri-weekly regimen was 20% more effective in terms of overall survival and had less grade 3-4 neutropenia than the weekly regimen.

Moreover, evidence from meta-analyses looking at the same question is also conflicting. Zhu J et al,[15] carried out a meta-analysis based on six randomized controlled trials and two retrospective studies. It showed that the tri-weekly regimen was superior to the weekly regimen only in local recurrence but not overall survival. The same results were reported in a recent meta-analysis[16] based on eight randomized controlled trials. Meanwhile, a meta-analysis was also carried out by Petrelli et al,[17] based on four randomized controlled trials and four retrospective studies. Its results showed that the platinum-based combined therapy should be the preferred treatment over weekly regimen due to benefits in overall survival.

As a result, there are different policies for the weekly and tri-weekly regimen. The routine regimen at the Radiation Oncology Division at Siriraj Hospital is weekly cisplatin (40 mg/m^2) or carboplatin (AUC2), but some hospitals have a routine tri-weekly regimen of cisplatin (75-100 mg/m^2) (or carboplatin AUC5) with or without 5FU. We are still waiting for high-quality evidence, notably results of the Tri-weekly Cisplatin Based Chemoradiation in Locally Advanced Cervical Cancer (TACO) trial (Clinical Trials. gov Identifier: NCT01561586). In the meantime, we still require evidence for solving this issue. Hence, we collected data from a multicenter in Thailand where locally advanced cervical cancer patients underwent concurrent chemoradiotherapy. This could help provide a suitable answer to a controversial issue with the help of advanced statistical analysis, such as propensity score matching that can simulate pseudo randomization by matching pre-treatment variable factors.

MATERIALS AND METHODS

We used retrospective cohort data from a multicenter in Thailand (Siriraj Hospital (SI), Ramathibodi Hospital (RA), King Chulalongkorn Memorial Hospital (CU) and Songklanagarind Hospital (PSU). We recruited patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of locally advanced cervical cancer who were definitively treated with concurrent chemoradiotherapy between Jan 2007 to Dec 2015. For staging purposes, all patients underwent a CT scan with contrast media of the whole abdomen, chest X-ray and cystoscopy. Diagnostic radiologists in each hospital newly reviewed the lymphadenopathy status according to the pelvic lymphatic pathway.[18,19] Depending on the policy of each hospital, a weekly or tri-weekly regimen of cisplatin or carboplatin concurrently with radiotherapy was given to the patient. Generally, 46-50 Gy of external beam radiotherapy and 4 fractions of each 6.5 to 7.0 Gy high dose rate brachytherapy were routinely prescribed. For chemotherapy, usually, the clinical policy of SI, CU and PSU is to give cisplatin weekly whereas RA gives cisplatin tri-weekly. Additionally, Siriraj Hospital may also adhere to the weekly carboplatin regimen as it is the preference of some radiation oncologists regardless of the patient's performance status. The main outcome of this study was overall survival. The secondary outcomes were local-recurrence free survival, regional-recurrence free survival and distant metastasis-free survival, which were defined as first day of radiotherapy to the date of first failure at cervical area, regional pelvic or paraaortic lymph node and visceral distant metastases or lymph node metastases above the diaphragm respectively. Hematological toxicity (hemoglobin, white blood cell count, neutrophil count and platelet) and renal toxicity in the maximum grade of each patient were also reported.

Sample size

A randomized controlled trial from Korea[12] showed that the tri-weekly regimen was more effective in overall survival. This study reported a hazard ratio of 0.375. When using this hazard ratio, 0.05 type I error and 80% statistical power, the sample size contained only 38

patients in each arm. However, we planned to include more patients as per our data availability.

Statistical analysis

In order to eliminate the selection bias of weekly or tri-weekly chemotherapy regimen, we performed a propensity score-matching analysis. This method is based on balancing baseline characteristics of patients to simulate randomization. Theoretically, the best propensity score came from factors that clinicians unfairly selected in the weekly or tri-weekly regimen, such as patient or tumor characteristics before treatment, especially pelvic or para-aortic lymph nodes. In this study, we used the new 2018 FIGO stage, which included pelvic and para-aortic lymphadenopathy status, histology, tumor grade, tumor size, age, initial hemoglobin and hydronephrosis status. For this purpose, we used MatchIt package version 3.02 in R software version 4.05. Logistic regression with the factors above was used to predict the linearized propensity score. We then used this score in the MatchIt function with the nearest method with varying caliper distances. We further proved whether this procedure worked by comparing baseline characteristics before and after the propensity score-matched procedure.

After we got the matched population, we also explored whether the factors after the start of the treatment were well-balanced, especially the chemotherapy regimen (cisplatin or carboplatin). We aimed to control this additional confounder in non-parametric analysis. For time-to-event analysis, we used the Kaplan Meier method and log-rank test to determine the hypothesis. Non-parametric analysis was performed to show a difference with 95% confidence interval. For toxicity comparison, we used the Fisher exact test to test the hypothesis.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Faculty of Medicine Siriraj Hospital, Mahidol University (Si 312/2016).

RESULTS

The patient characteristics before and after the propensity score matching process is shown in Table 1. Missing data were in only histopathological grade, which was available 80%. Before the matching process, a total of 781 patients (618 in the weekly group and 163 patients in the tri-weekly group) were compared. The patients in the tri-weekly group seemed to have a better prognosis in terms of 2018 FIGO stage. For example, less pelvic lymph node metastases (stage IIIc1, 20.2%) were observed in the tri-weekly group, compared with the weekly group (stage IIIc1, 34.3%). After the propensity score matching process was completed (163 patients in the weekly group and 163 patients in the tri-weekly group), there was a similar prognosis, especially in terms of FIGO staging. The pelvic lymph node metastases were only 20.2% in both the weekly and tri-weekly groups. Also, the proportion of histology was very similar in terms of adenocarcinoma (22.1% in the weekly group and 22.7% in the tri-weekly group). Furthermore, age, tumor type, tumor size, tumor grade, initial hemoglobin and also any side effects of hydronephrosis were better balanced in both groups (Table 1). Despite the balance in these prognostic factors, the chemotherapy regimens (cisplatin or carboplatin) were different in both groups. Cisplatin was given to half of the patients (56%) in the weekly group, but almost all the (96%) patients in the tri-weekly group. This difference was then further adjusted in a statistical analysis.

The overall median follow-up time was 59.5 months. The follow-up rate for disease recurrence status and for death status was 87% and 100% respectively. For tumor control outcome, the tri-weekly group showed an unadjusted non-statistically small benefit in overall survival (Fig 1A). This small benefit was only 2%-3% as per the follow-up time (Supplementary Fig S1). After chemotherapy regimen (cisplatin or carboplatin) adjustment, this small difference disappeared and the survival curve seemed to cross each other (Fig 1B). Interestingly, the tri-weekly group showed better local recurrence-free survival (Fig 2A). This difference was about 6%-7% in the first two years of follow-up and about 3%-4% in the third to fifth year (Supplementary Fig S2). Unfortunately, with our limited sample size, a statistical difference could not be detected. Again, after chemotherapy regimen adjustment, this difference disappeared (Fig 2B). For regional recurrence-free survival (Fig 3A) and distant metastasis-free survival (Fig 4A), the difference between the weekly group and tri-weekly group was small and not consistent with the follow-up time (Fig 3B and Fig 4B). Also, the adjustment of chemotherapy regimen (Supplementary Fig S3 and Fig S4) showed no significant change from unadjusted analysis.

Toxicity outcome was available for 96% of study population. For grade 2 or greater toxicity (Table 2), the patients in the tri-weekly group had more absolute neutrophil count toxicity (10.5%), when compared to patients in the weekly group (2.5%). On the other hand, patients in the tri-weekly group seemed to have less hemoglobin toxicity (29.4%) when compared to patients in the weekly group (33.8%). These results are

TABLE 1. Patient characteristics before and after propensity score matching.

Patient Characteristics	Before Propensity score Matching			After Propensity score Matching		
	Weekly n=618	Tri-weekly n=163	p-value	Weekly n=163	Tri-weekly n=163	p-value
Age	53.8 (11.7)	54.1 (10.6)	0.80	54.7 (11.7)	54.1 (10.6)	0.59
Stage: I-II	132 (21.4%)	51 (31.3%)	0.004	51 (31.3%)	51 (31.3%)	0.92
IIIa-b	180 (29.1%)	55 (33.7%)		53 (32.5%)	55 (33.7%)	
IIIc1	212 (34.3%)	33 (20.2%)		33 (20.2%)	33 (20.2%)	
IIIc2	82 (13.3%)	20 (12.3%)		24 (14.7%)	20 (12.3%)	
IVa	12 (1.9%)	4 (2.5%)		2 (1.2%)	4 (2.5%)	
Type: Exophytic type	428 (69.3%)	129 (79.1%)	0.015	120 (73.6%)	129 (79.1%)	0.30
Ulcerative type	190 (30.7%)	34 (20.9%)		43 (26.4%)	34 (20.9%)	
Tumor size	4.43 (1.54)	4.15 (1.37)	0.036	4.21 (1.41)	4.15 (1.37)	0.72
Histology: SCC	475 (76.9%)	121 (74.2%)	0.50	122 (74.8%)	121 (74.2%)	1.00
Adenocarcinoma	117 (18.9%)	37 (22.7%)		36 (22.1%)	37 (22.7%)	
Adenosquamous carcinoma	(4.2%)	5 (3.1%)		5 (3.1%)	5 (3.1%)	
Differentiation: Well	119 (19.3%)	37 (22.7%)	<0.001	38 (23.3%)	37 (22.7%)	0.96
Moderate	227 (36.7%)	30 (18.4%)		30 (18.4%)	30 (18.4%)	
Poorly	153 (24.8%)	61 (37.4%)		64 (39.3%)	61 (37.4%)	
Unknown	119 (19.3%)	35 (21.5%)		31 (19.0%)	35 (21.5%)	
Initial Hb	11.5 (1.8)	11.6 (1.6)	0.38	11.5 (1.9)	11.6 (1.6)	0.76
Hydronephrosis: No	550 (89.0%)	143 (87.7%)	0.68	143 (87.7%)	143 (87.7%)	1.00
Yes	68 (11.0%)	20 (12.3%)		20 (12.3%)	20 (12.3%)	

approximately the same when we categorized to cisplatin and carboplatin (Supplementary Table S1). The other toxicities appeared to be very similar in both groups in terms of white blood count, platelet and creatinine. The compliance towards chemotherapy in both groups was very good (79.14% in five cycles or more in the weekly group and 89.6% in two cycles or more in the tri-weekly group).

DISCUSSION

The standard treatment for locally advanced cervical cancer is concurrent platinum-based chemotherapy and radiotherapy.[1] The frequency of the chemotherapy regimen is either weekly or tri-weekly administration according to clinical practice guideline of some institution in Thailand.[20] The weekly regimen is easy to manage in terms of no requirements for patient admission and possibly fewer side effects, however, there is still the concern that the weekly regimen might not be enough in terms of tumor control. Therefore, any additional evidence may potentially provide a benefit in routine management of chemotherapy in this setting.

Our results show that the tri-weekly group experienced 8% more neutrophil count grade 2 or greater toxicity than the weekly group. This effect led to no significant reduction in compliance. Interestingly, our results also showed a potential 6%-7% benefit in local control and possibly a small benefit (2%-3%) in overall

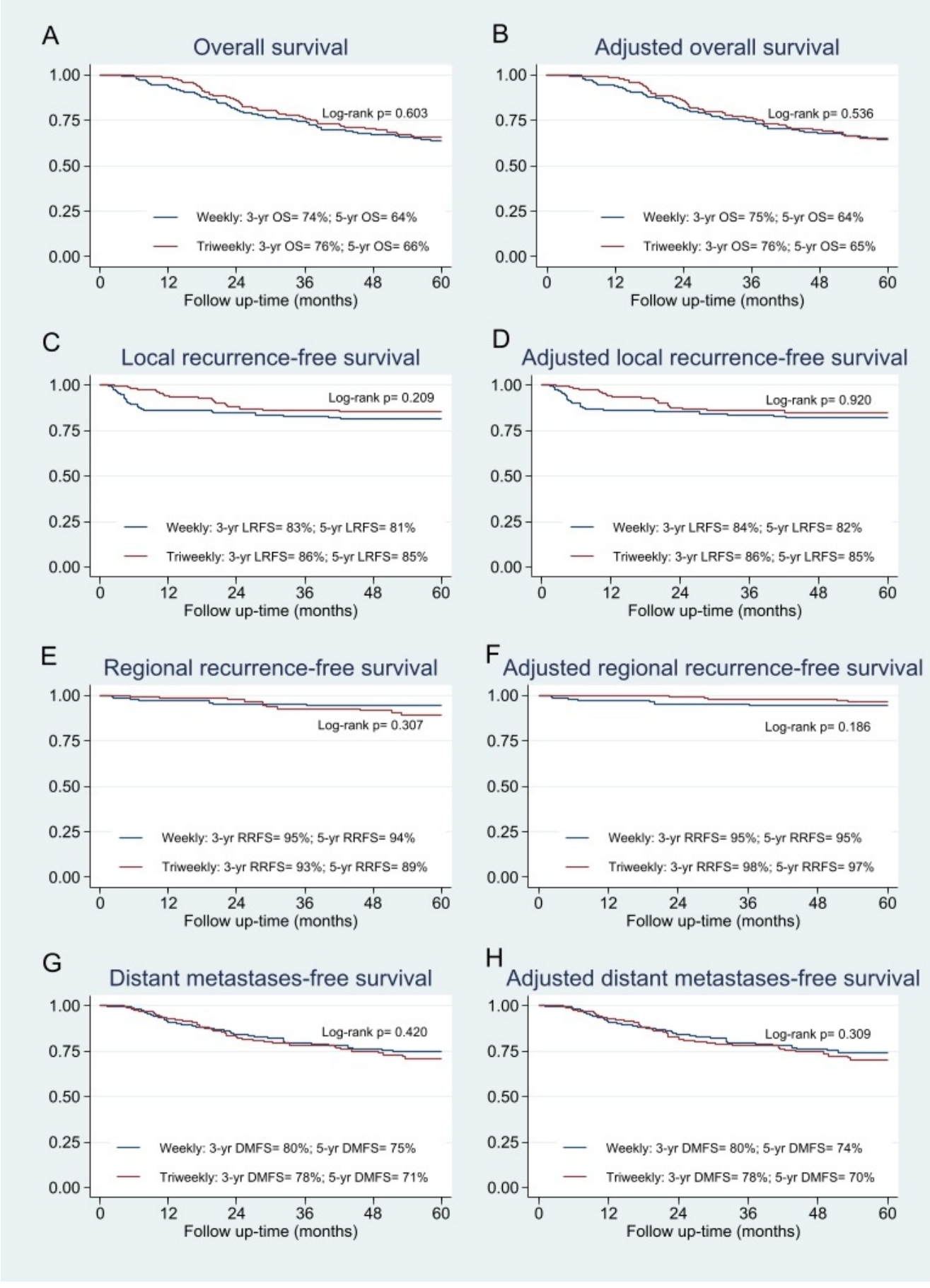
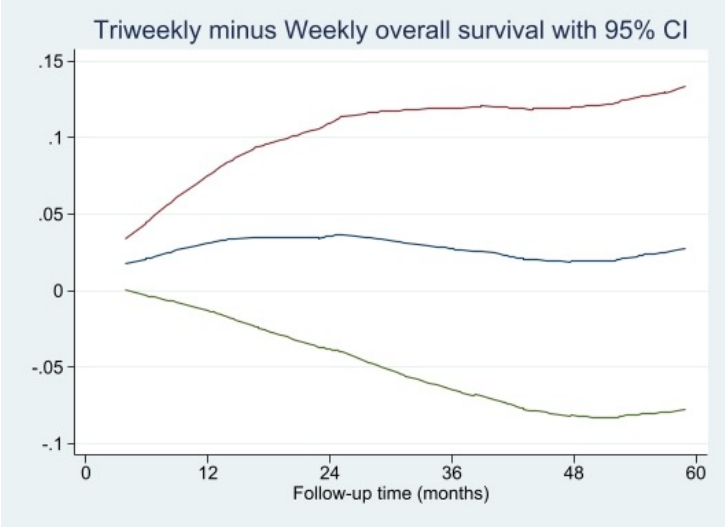
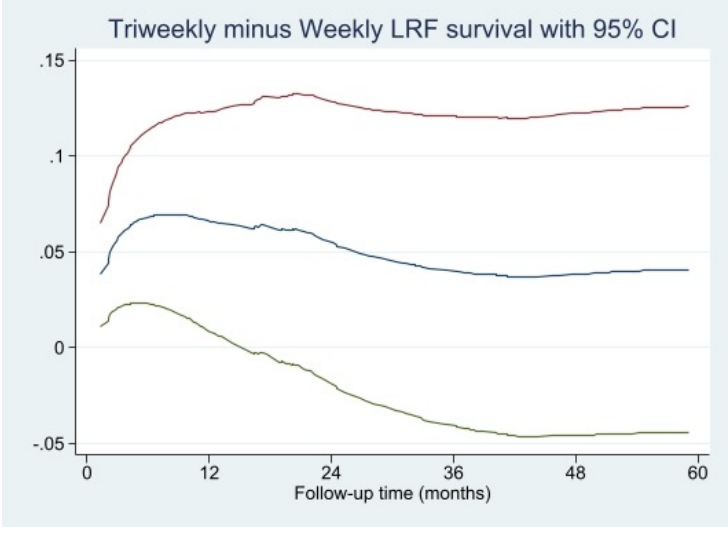


Fig 1. Kaplan-Meier survival estimate comparison between weekly and tri-weekly chemotherapy, unadjusted curve (left) and adjusted by chemotherapy regimen (carboplatin or cisplatin) (right).



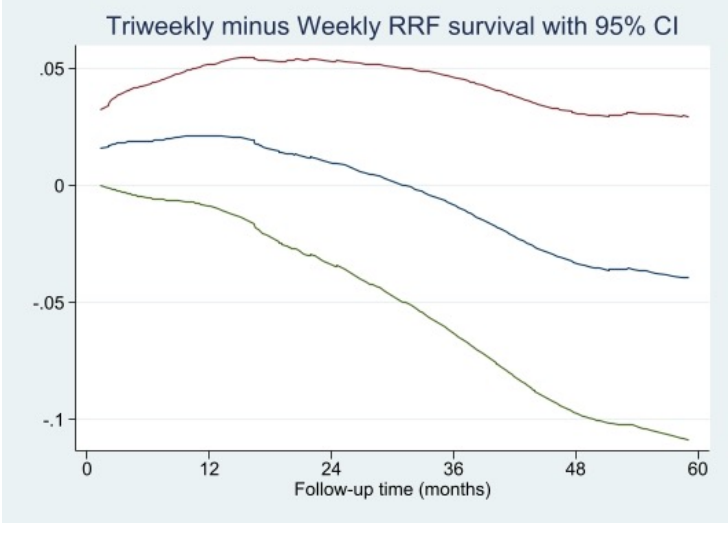
	Absolute difference
3-yr OS	0.03% (-0.7% to 1.2%)
5-yr OS	0.03% (-0.8% to 1.3%)

Supplementary Fig S1. Absolute difference of overall survival with 95% confidence interval.



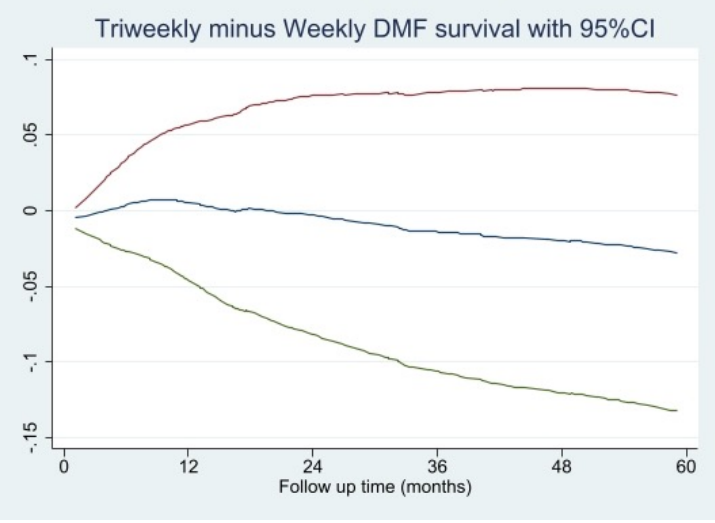
	Absolute difference
3-yr OS	0.04% (-0.04% to 0.12%)
5-yr OS	0.04% (-0.04% to 0.13%)

Supplementary Fig S2. Absolute difference of local recurrence-free survival with 95% confidence interval.



	Absolute difference
3-yr OS	-0.01% (-0.06% to 0.05%)
5-yr OS	-0.04% (-0.11% to 0.03%)

Supplementary Fig S3. Absolute difference of regional recurrence-free survival with 95% confidence interval.



	Absolute difference
3-yr OS	-0.01% (-0.11% to 0.08%)
5-yr OS	-0.03% (-0.13% to 0.08%)

Supplementary Fig S4. Absolute difference of distant metastasis-free survival with 95% confidence interval.

TABLE 2. Toxicity and compliance between weekly and triweekly chemotherapy.

		Weekly n=163	Tri-weekly n=163	p-value
Compliance				
No of cycle	1	2 (1%)	14 (9%)	Not applicable
	2	8 (5%)	132 (81%)	
	3	2 (1%)	14 (9%)	
	4	20 (12%)	-	
	5	91 (56%)	-	
	6	38 (23%)	-	
	7	1 (1%)	-	
	Missing data	1 (1%)	3 (1%)	
Toxicity				
Hemoglobin	0	44 (27.0%)	25 (15.3%)	0.011
	1	60 (36.8%)	81 (49.7%)	
	2	51 (31.3%)	40 (24.5%)	
	3	4 (2.5%)	8 (4.9%)	
	Missing data	4 (2.5%)	9 (5.5%)	
White blood cell	0	51 (31.3%)	45 (27.6%)	0.43
	1	77 (47.2%)	73 (44.8%)	
	2	28 (17.2%)	29 (17.8%)	
	3	3 (1.8%)	7 (4.3%)	
	Missing data	4 (2.5%)	9 (5.5%)	
ANC	0	123 (75.5%)	102 (62.6%)	0.009
	1	32 (19.6%)	35 (21.5%)	
	2	4 (2.5%)	12 (7.4%)	
	3	0	5 (3.1%)	
	Missing data	4 (2.5%)	9 (5.5%)	
Platelet	0	109 (66.9%)	145 (89.0%)	<0.001
	1	50 (30.7%)	14 (8.6%)	
	2	1 (0.6%)	1 (0.6%)	
	3	0	0	
	Missing data	3 (1.8%)	3 (1.8%)	
Creatinine	0	139 (85.3%)	141 (86.5%)	0.80
	1	19 (11.7%)	14 (8.6%)	
	2	1 (0.6%)	2 (1.2%)	
	3	0 (0.0%)	1 (0.6%)	
	Missing data	4 (2.5%)	5 (3.1%)	

SUPPLEMENTARY TABLE S1. Toxicity and compliance between weekly and triweekly cisplatin and carboplatin.

		Cisplatin			Carboplatin		
		Weekly	Tri-weekly		Weekly	Tri-weekly	
		n=92	n=157	P value	n=71	n=6	p-value
Compliance							
No of cycle	1	0(0%)	13(8%)	NA	2(3%)	1(17%)	NA
	2	3(3%)	128(82%)		5(7%)	4(67%)	
	3	2(2%)	13(8%)		0(0%)	1(17%)	
	4	11(12%)	-		9(13%)	-	
	5	49(53%)	-		42(59%)	-	
	6	26(28%)	-		12(17%)	-	
	7	0(0%)	-		1(1%)	-	
	Missing data	1(1%)	3(2%)		0(0%)	0(0%)	
Toxicity							
Hemoglobin	0	28(30%)	24(15%)	0.003	16(23%)	1(17%)	0.553
	1	30(33%)	78(50%)		30(42%)	3(50%)	
	2	31(34%)	39(25%)		20(28%)	1(17%)	
	3	1(1%)	8(5%)		3(4%)	0(0%)	
	Missing data	2(2%)	8(5%)		2(3%)	1(17%)	
WBC	0	22(24%)	44(28%)	0.417	29(41%)	1(17%)	0.085
	1	43(47%)	71(45%)		34(48%)	2(33%)	
	2	23(25%)	27(17%)		5(7%)	2(33%)	
	3	2(2%)	7(4%)		1(1%)	0(0%)	
	Missing data	2(2%)	8(5%)		2(3%)	1(17%)	
ANC	0	66(72%)	99(63%)	0.285	57(80%)	3(50%)	0.025
	1	20(22%)	34(22%)		12(17%)	1(17%)	
	2	4(4%)	11(7%)		0(0%)	1(17%)	
	3	0(0%)	5(3%)		0(0%)	0(0%)	
	Missing data	2(2%)	8(5%)		2(3%)	1(17%)	
Platelet	0	61(66%)	141(90%)	<0.001	48(68%)	4(67%)	1.000
	1	29(32%)	12(8%)		21(30%)	2(33%)	
	2	1(1%)	1(1%)		0(0%)	0(0%)	
	3	0(0%)	0(0%)		0(0%)	0(0%)	
	Missing data	1(1%)	3(2%)		2(3%)	0(0%)	
Creatinine	0	81(88%)	137(87%)	0.842	58(82%)	4(67%)	0.413
	1	9(10%)	12(8%)		10(14%)	2(33%)	
	2	1(1%)	2(1%)		0(0%)	0(0%)	
	3	0(0%)	1(1%)		0(0%)	0(0%)	
	Missing data	1(1%)	5(3%)		3(4%)	0(0%)	

survival. These results could lead to potential benefits in individual clinical judgment, especially in the context of a university hospital in Thailand while we wait for stronger evidence.

Nowadays, strong evidence to clearly support weekly or tri-weekly platinum-based chemotherapy with radiotherapy in locally advanced cervical cancer is limited. Two famous randomized controlled trials from Korea provide conflicting results and different points (Table 3). The first study from Korea[13] showed a comparable tumor control effect and more compliance with weekly chemotherapy. The reasons behind this could be that the tri-weekly combined chemotherapy regimen with cisplatin and 5FU has poor compliance due to 15% grade 4 hematological toxicity, compared with only 2% in the weekly group. Therefore, the weekly group in this study might display a similar effect because of inadequate chemotherapy in the tri-weekly group due to toxicity. On the other hand, the second randomized controlled trial from Korea[12] showed that the tri-weekly regimen was 20% more effective in terms of overall survival and had less grade 3-4 neutropenia than the weekly regimen. Less toxicity can be explained by the fact that the regimen in this study was only cisplatin without 5FU. Interestingly, even with planned randomization, the baseline characteristics in this second study were not well-balanced. The patients in the weekly chemotherapy group had much poorer prognosis. For example, the patients in the weekly group had an advanced stage of disease (stage III and stage IVA 45.1%), compared with

TABLE 3. Comparison of two Korean randomized controlled trials and this study.

Study	Kim et al[13] (RCT)		Ryu et al[12] (RCT)		Our study (PS matched)	
	Weekly (Cis) (n=77)	Tri-weekly (Cis+5FU) (n=78)	Weekly (Cis) (n=51)	Tri-weekly (Cis) (n=53)	Weekly (Cis, carbo) (n=163)	Tri-weekly (Cis, carbo) (n=163)
Patient characteristics	Stage II =58(75%)	Stage II =52(67%)	Stage II =28(55%)	Stage II =34(64%)	Stage I-II =51(31.3%)	Stage I-II =51(31.3%)
	Stage III-Iva =19(25%)	Stage III-Iva =26(33%)	Stage III-Iva =23(45%)	Stage III-Iva =19(36%)	Stage III-Iva =112(68.7%)	Stage III-Iva =112(68.7%)
	Pelvic LN+ =31(40%)	Pelvic LN+ =32(41%)	Pelvic LN+ =29(57%)	Pelvic LN+ =27(51%)	Pelvic LN+ =33(20%)	Pelvic LN+ =33(20%)
			PAN + =7(14%)	PAN + =5(9%)	PAN + =24(15%)	PAN + =20(12%)
Chemotherapy compliance	>80% planned dose = 64(83%)	>80% planned dose = 47(60%)	>=5 cycles = 98%	>=2 cycles = 94%	>=5 cycles = 80%	>=2 cycles = 90%
Hematological toxicity	Grade 3-4 =19(25%)	Grade 3-4 =32(41%)	Neutropenia	Neutropenia	Neutropenia	Neutropenia
	Grade 4 =2(3%)	Grade 4 =15(19%)	Grade 3-4 =20(39%)	Grade 3-4 =12(23%)	Grade 3-4 =0(0%)	Grade 3-4 =5(3%)
			Thrombocytopenia	Thrombocytopenia	Thrombocytopenia	Thrombocytopenia
			Grade 3-4 =4(8%)	Grade 3-4 =3(6%)	Grade 3-4 =0(0%)	Grade 3-4 =0(0%)
Overall survival	4 year : 67%	4 year : 70%	5 year : 67%	5 year : 89%	5 year : 64%	5 year : 66%

the tri-weekly group (stage III and stage IVA 35.9%). Moreover, positive pelvic and paraaortic lymph nodes were more frequent in the weekly group (70.6%) than in patients in the tri-weekly group (61.3%). This also could be a reason why the weekly group had poorer tumor control.

Our study had some strengths. First, it included real-world data from a multi-centered study from university hospitals in Thailand, meaning it was more generalized than a single-institute study. Second, we used advanced statistical analysis to match patients who showed well-balanced baseline characteristics. Third, this study had adequately long-term follow-up time. However, there were several limitations of this study as well. First, our data came from the two-dimensional brachytherapy era. Nowadays, many hospitals use three-dimensional brachytherapy, which likely leads to more local control of the primary site. Therefore, the benefit of tri-weekly chemotherapy might be less than that seen in this study. Also, our sample size was not large enough to detect any actual difference.

CONCLUSION

In summary, the tri-weekly chemotherapy regimen showed a non-statistically potential benefit over the weekly regimen in terms of local control and overall survival but with more neutrophil toxicity. Further evidence with adequate sample size could validate this result. In the meantime, individual judgment using this data can be discussed with patients.

ACKNOWLEDGMENTS

Lalita Chunkoh as the main patient-data collector at SI, RA and CU Hospitals; Ladathip Suwan as the patient-data collector and supervisor of data collection at RA Hospital; Buntipa Netsawang as the supervisor of patient-data collection at CU Hospital; Siriporn Wong as an additional patient-data collector at CU Hospital; Dr. Poompis Pattaranutaporn as the supervisor of laboratory data collection at RA Hospital.

Conflict of interest: None to declare

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Validation of Several Formulas to Differentiate Thalassemia from Iron Deficiency Anemia and Proposal of a Thalassemia–Iron Deficiency Discrimination (TID) Predictive Score

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ABSTRACT

Objective: This study aimed to validate the sensitivity analysis of all the available formulas for their ability to differentiate between IDA and thalassemia and propose a novel formula to improve the sensitivity of all thalassemia subtypes screening.

Materials and Methods: We conducted a 5-year, single-center, Cohort study on 227 microcytic anemia patients diagnosed between June 2015 and September 2020 at Chaophraya Yommarat Hospital, Suphanburi, Thailand to validate the sensitivity of all the available formulas and invent the novel predictive score.

Results: Approximately three-quarters of our cases were all subtypes of thalassemia diseases while 26.9% were IDA. The sensitivity of almost all the previous formulas for thalassemia prediction ranged between 13.9%-44.0%, while the specificity varied between 0%–98.4%. Nevertheless, the sensitivity of the formulas that had favorable sensitivity was quite low. Here, a novel thalassemia–iron deficiency discrimination (TID) predictive score is proposed, which demonstrated a sensitivity of 90.4% the specificity of 78.7%, the positive predictive value of 92.0 %, the negative predictive value of 75.0%, and the accuracy of 87.2%.

Conclusion: The proposed TID predictive score is a novel uncomplicated formulation which offers high sensitivity for all thalassemia subtypes prediction.

Keywords: Iron deficiency anemia; microcytic anemia; predictive score; thalassemia (Siriraj Med J 2022; 74: 256-265)

INTRODUCTION

According to the World Health Organization, iron deficiency anemia (IDA) is the major cause of nutritional anemia worldwide.[1] The incidence of IDA in Thai women of reproductive age was reported to be 28.7%, 30.2%, and 31.8%, in 2013, 2014, and 2015, respectively.[1] Another study reported an anemia rate of 21% in educated young Thai women, with the two most prevalent causes among those cases being thalassemia (28%) and IDA (21%).[2]

Patients with IDA and thalassemia may both present with microcytic anemia (defined as a mean corpuscular volume (MCV) < 80 fL), which should be further investigated to distinguish between these two entities due to their different treatment approaches. Iron supplementation and the correction of occult blood loss remain the standard treatments for IDA. On the other hand, certain types of thalassemia diseases, such as hemoglobin (Hb) E/β-thalassemia and homozygous

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http://dx.doi.org/10.33192/Smj.2022.32

β-thalassemia, require regular blood transfusion and iron chelation to prevent iron deposition in various organs, which could lead to multiple organ dysfunction, i.e., liver cirrhosis, endocrinopathies, and heart failure.[3]

Detailed evaluation to confirm IDA involves an iron study test, consisting of measuring the levels of serum ferritin, serum iron, total iron-binding capacity (TIBC), and transferrin saturation (TSAT). If the serum ferritin value is ≤30 ng/mL or the TSAT value is <16%, IDA diagnosis can be confirmed with high sensitivity and high specificity.[4] Meanwhile, Hb typing is employed for the diagnosis of thalassemia.[5] However, in developing countries, some primary hospitals have limited resources to manage iron studies and Hb typing test. As a result, to make a diagnosis, blood samples have to be transferred to a comprehensive laboratory center, which can be a time-consuming process. As such, other available tools to initially discriminate these conditions could be of value. For thalassemia diagnosis, a range of associated factors can be assessed to develop a thalassemia predictive score.

According to the extensive literature review we performed, several formulas exist for thalassemia prediction among microcytic anemic patients, including the Red Blood Cell Count (RBC), Red Cell Distribution Width (RDW), Red Cell Distribution Width Index (RDWI), Green and King formula, Srivastava formula, Mentzer formula, Ehsani formula, Ricerca formula, England and Fraser formula, Sirdah formula, and Shine and Lal formula.[6-14] The reported sensitivity and specificity of these formulas range from 40% to 100%.[6-18] Another formula, the 11T score is an interesting formula that combines 11 other formulas to calculate its score, providing a higher discrimination ability.[15-18] In a previous study that attempted to validate this score among a Thai population, the 11T score showed a sensitivity of 82.1% and specificity of 91.7% for thalassemia prediction. However, it should be noted that only β-thalassemia subtype was included in previous studies. In addition, IDA in those trials was diagnosed when serum ferritin was <10 ng/mL.[18]

In the present study, we aimed to validate the sensitivity assessment of all the available formulas for their ability to differentiate between IDA and all thalassemia subtypes. In addition, we propose a novel formula to improve the sensitivity of thalassemia screening. In addition, to increase the diagnostic sensitivity in our study, the diagnosis of IDA could be established when ferritin was <30 ng/mL and TSAT was <16%.[4]

MATERIALS AND METHODS

Study design and population

We conducted a 5-year, retrospective, single-center, cohort study on microcytic anemia patients diagnosed between June 1, 2015, and September 30, 2020, at Chaophraya Yommarat Hospital, Suphanburi, Thailand. The inclusion criteria were: (1) patients aged 15 years old or older, and (2) patients with microcytic anemia. (3) patients who had the result of iron study in the IDA group and Hb typing and/or PCR in the thalassemia group. The exclusion criteria were patients receiving erythropoiesis-stimulating agents or receiving iron supplementation before blood testing. We categorized patients into 2 groups by different timeframes; a group for internal validation using patients during June 2015 - August 2017 and a group for calculation score using patients during September 2017 - September 2020. The study was approved for registration in the Thai Clinical Trial Registry with the identification number TCTR20210725003.

Instrument and evaluation parameters

All blood samples were collected by using 3-ml dipotassium ethylenediaminetetraacetic acid tubes (K_2EDTA) for a complete blood count (CBC) test and analyzed within 2 hours after taking the samples by Mindray BC-6200 automated blood counter (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China). This device used impedance technology to count and size RBC and platelet (PLT) together with cyanotic-free colorimetric method for Hb. MCV and % RDW were calculated based on the RBC histogram. In addition, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) was also calculated from RBC, Hb, and hematocrit parameters. The patient's demographic data and initial laboratory results were collected. Patients with microcytic anemia were classified into two groups: the IDA group and the thalassemia group. In the thalassemia group, three included thalassemia disease subtypes were as follows: α-thalassemia, β–thalassemia disease, and α- combined β-thalassemia disease.

Study size consideration

At least 200 microcytic anemia cases were required to validate the formulas and develop a novel predictive score. Furthermore, 150 patients (40 patients with IDA and 110 patients with thalassemia) were separately assigned for an internal validation of this score.

Handing of continuous predictors

The proposed predictive score was developed followed by the predictive model study Risk of Bias Assessment Tool (PROBAST). Four red blood cell parameters were incorporated for this predictive score calculation including MCH, RDW, RBC and PLT.

Terminology

Anemia is defined by a hemoglobin (Hb) level < 13/dL in males or Hb < 12 g/dL in females.[19] Anemia with small red blood cells (MCV < 80 fL) is termed microcytic anemia.[4] A diagnosis of IDA is established if a patient has microcytic anemia with serum ferritin < 30 ng/mL and transferrin saturation < 16%.[4] The 11T score is a summary score from 11 formulas, comprising RBC ($\times 10^{12}$/L), RDW, RDWI (RDW × MCV/RBC), Green and King formula (MCV2 × RDW/Hb × 100), Srivastava formula (MCH/RBC), Mentzer formula (MCV/RBC), Ehsani formula [MCV - (10 × RBC)], Ricerca formula (RDW/RBC), England and Fraser formula [MCV - RBC - (5 × Hb) - 3.4], Sirdah formula [MCV - RBC - (3 × Hb)], and Shine and Lal formula (MCV2 × MCH/100).[18]

Statistical analysis

PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was applied for the data analyses. The patients' demographic and clinical characteristics were summarized descriptively by causes of microcytic anemia. Continuous variables were reported as the mean±standard deviation for normally distributed continuous variables, and the median with interquartile ranges (Q1, Q3) for nonnormally distributed continuous variables. Categorical variables were reported as the frequency and percentage and were compared using Fisher's exact test or chi-square test. Continuous variables were compared using the Student's t-test or Mann–Whiney U test. The univariate and multivariate predictors of thalassemia were estimated using Cox proportional hazards analysis (backward stepwise method) and presented as an odds ratio (OR) and 95% confidence interval (CI). The receiver operating characteristic (ROC) curve for the cutoff score and for thalassemia diagnosis was presented as the area under the curve (AUC), accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For all the tests performed, a two-tailed p-value < 0.05 was considered to be statistically significant. The calibration belt model was used for model calibration. The model was attended by the Hosmer –Lemeshow χ^2 goodness-of-fit test.

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Research in Human Subjects at Chaophraya Yommarat Hospital, Suphanburi, Thailand. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was waived due to a retrospective study.

RESULTS

Baseline patient characteristics

In total, 227 microcytic anemic patients were included in this study. Approximately three-quarters (73.1%) were diagnosed with thalassemia disease, including Hb E/β-thalassemia, homozygous β-thalassemia, Hb H disease, Hb H/CS disease, AE Bart's disease, and EF Bart's disease, whereas 61 patients (26.9%) were IDA.

In the thalassemic group, the mean patient age was 42.1±20.5 years old. The mean Hb and MCV were 8±1.7 g/dL and 61.7±9.2 fL, respectively. The median PLT count was 308,000/μL (range, 189,000-413,000/μL). Among the IDA group, the mean patient age was 57.6±18.3 years old. The mean Hb was 6.1±1.7g/dL and the mean MCV was 62.9±8.3 fL. The median PLT count and serum ferritin were 384,000/μL (range, 263,000-478,000/μL) and 16.7 ng/mL (range, 4-22.2 ng/mL), respectively. Several factors were significantly different between the thalassemic and the IDA groups, such as age, body mass index, Hb level, MCH, MCHC, red blood cell distribution width (RDW), red blood cell counts, PLT count, and iron profiles. Table 1 displays the baseline patient features and initial laboratory results of the thalassemic and IDA patients.

Validation of the previous formulas predicting thalassemia

We analyzed the sensitivity, specificity, PPV, NPV, and accuracy of each previous formula to predict thalassemia, including RBC, % RDW, RDWI, Green and King, Srivastava, Mentzer, Ehsani, Ricerca, England, and Fraser, Shine and Lal, and 11T score, by using the included patient's data in this study. The sensitivity of almost all the formulas ranged between 13.9% - 44%. Only the RDW and Shine and Lal formulas yielded high sensitivity (97.6%), but with low specificity results, with figures of 0% and 3.3%, respectively. The specificity of each formula varied between 0%-98.4%. The high specificity of above 90% was found with several formulas, including RDWI, Green and King, England and Fraser, Sirdah, and 11T score; unfortunately, the sensitivity of these formulas was quite low. The PPV of almost all the formulas provided high results, which were above 90%. In contrast, the NPV of all the formulas was as low as approximately 30% (range, 0%-36.3%). The accuracy of each formula varied between 36.1%-72.3%. Table 2 demonstrates the sensitivity, specificity, PPV, NPV, and accuracy of each formula for predicting thalassemia.

Subgroup analysis of the formulas for predicting each type of thalassemia

We performed a subgroup analysis of each thalassemia subtype, including β-thalassemia disease, α-thalassemia

TABLE 1. Baseline patient features and initial laboratory results of the thalassemic and iron deficiency anemia patients.

Parameters	Total (N=227)	Thalassemia (All) (N=166) (73.1%)	β -thalassemia (1) (N=89) (39.2%)	α - thalassemia (2) (N=62) (27.3%)	α-thalassemia combined with β-thalassemia (3) (N=15) (6.6%)	Iron deficiency anemia (0) (N=61) (26.9%)	*P*-value for multiple comparisons			
							1 vs. 0	2 vs. 0	3 vs. 0	All vs. 0
Age(mean±SD) (years)	46.3±21	42.1±20.5	42.8±20.4	41.5±21.5	40.9±17.1	57.6±18.3	<0.001	<0.001	0.002	<0.001
Sex (Male)	74(32.6%)	54(32.5%)	33(37.1%)	18(29%)	3(20%)	20(32.8%)	0.589	0.652	0.531	0.971
BMI	21.4±4.1	20.8±3.6	20.8±3.9	20.3±3.1	22.5±3.3	23.2±4.9	0.001	<0.001	0.602	0.001
Hemoglobin typing	181 (79.7%)	166(100%)	89(100%)	62(100%)	15(100%)	15(24.6)	<0.001	<0.001	<0.001	<0.001
PCR for α-thalassemia	14(6.2%)	14(8.4%)	4(4.5%)	3(4.8%)	7(46.7%)	0(0%)	0.146	0.244	<0.001	0.024
Comorbidities	77(33.9%)	44(26.5%)	26(29.2%)	15(24.2%)	3(20%)	33(54.1%)	0.002	0.001	0.018	<0.001
Hypertension	34(15%)	16(9.6%)	12(13.5%)	3(4.8%)	1(6.7%)	18(29.5%)	0.016	<0.001	0.097	<0.001
Diabetes	22(9.7%)	12(7.2%)	10(11.2%)	1(1.6%)	1(6.7%)	10(16.4%)	0.361	0.004	0.682	0.039
Dyslipidemia	15(6.6%)	6(3.6%)	5(5.6%)	0(0%)	1(6.7%)	9(14.8%)	0.059	0.001	0.676	0.005
CAD	11(4.8%)	10(6%)	4(4.5%)	5(8.1%)	1(6.7%)	1(1.6%)	0.649	2.07	0.358	0.296
CKD	11(4.8%)	9(5.4%)	8(9%)	1(1.6%)	0(0%)	2(3.3%)	0.202	0.619	1.00	0.732
Liver disease	8(3.5%)	7(4.2%)	5(5.6%)	1(1.6%)	1(6.7%)	1(1.6%)	0.402	1.00	0.358	0.686
Arthritis	7(3.1%)	6(3.6%)	4(4.5%)	2(3.2%)	0(0%)	1(1.6%)	0.649	1.00	1.00	0.678
Others	19(8.4%)	7(4.2%)	2(2.2%)	5(8.1%)	0(0%)	12(19.7%)	<0.001	0.062	0.109	<0.001

TABLE 1. Baseline patient features and initial laboratory results of the thalassemic and iron deficiency anemia patients. (Continue)

Parameters	Total (N=227)	Thalassemia (All) (N=166) (73.1%)	β -thalassemia (1) (N=89) (39.2%)	α - thalassemia (2) (N=62) (27.3%)	α-thalassemia combined with β-thalassemia (3) (N=15) (6.6%)	Iron deficiency anemia (0) (N=61) (26.9%)	*P*-value for multiple comparisons			
							1 vs. 0	2 vs. 0	3 vs. 0	All vs. 0
Laboratory										
CBC										
Mean±SD										
Hemoglobin (g/dl)	7.5±1.9	8±1.7	7.9±1.9	8±1.5	8.5±1.7	6.1±1.7	<0.001	<0.001	<0.001	<0.001
Hematocrit (%)	25±14.3	26.4±16.2	26.2±21.7	26.9±4.4	25.9±6.3	21.2±5	0.082	<0.001	0.003	0.015
MCV (fL)	62±8.9	61.7±9.2	61.3±8.9	63.7±9.5	56.1±7.3	62.9±8.3	0.286	0.605	0.005	0.404
MCH (pg)	18.8±3	19.2±2.8	19.9±3	18.6±2.2	17.3±2.4	17.7±3.3	<0.001	0.066	0.674	0.001
MCHC (g/dl)	31.3±14.7	32.5±17	32.3±2.5	33.2±27.8	30.9±2.5	28.0±2.2	<0.001	0.148	<0.001	0.042
RDW (%)	23.6±5.4	24.7±5.7	24.5±6.3	25.2±5	23.8±4.7	20.4±3	<0.001	<0.001	0.016	<0.001
RBC (x10^{12}/L)	4±1	4.2±1	4±1	4.3±0.9	4.9±0.9	3.4±0.8	<0.001	<0.001	<0.001	<0.001
Median±IQR										
WBC (cells/μL)	7,410	7,595	7,860	6,900	7,750	6,320	0.009	0.495	0.096	0.031
Platelet(/μL)	316,000 (224,000-436,000)	308,000 (189,000-413,000)	307,000 (172,000-409,000)	298,000 (202,000-401,000)	353,000 (298,000-470,000)	384,000 (263,000-478,000)	0.015	0.006	0.759	0.006
Iron study										
Median±IQR										
serum ferritin (ng/ml)	249 (8.96-859)	590 (259-1,427)	882.5 (323-2387.5)	383.6 (184-759)	548 (268.7-1499)	16.7 (4-22.2)	<0.001	<0.001	<0.001	<0.001
serum iron (μg/dl)	17 (11-51)	69 (44-104)	66 (41-104)	70.5 (47.0-89)	79 (49.0-105)	12 (10-15)	<0.001	<0.001	0.004	<0.001
Transferrin saturation (%)	4.9 (3.2-24.2)	27.5 (19.1-44)	26.3 (16.6-46.8)	32.9 (23-44)	36 (23-38.6)	3.5 (2.5-4.6)	<0.001	<0.001	<0.001	<0.001
Mean±SD										
TIBC (μg/dl)	322.7±90.2	250.6±80.3	258.1±96.8	241.9±57.7	235.7±31.8	371.3±58.6	<0.001	<0.001	0.027	<0.001

Abbreviations: MCV = Mean corpuscular volume, MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration, RDW = Red blood cell distribution width, RBC = Red blood cell, WBC = White blood cell, TIBC = Total iron binding capacity (μg/dL), TSAT = Transferin saturation (%).

TABLE 2. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each formula to predict thalassemia.

Formula	Cutoff	Thalassemia n (%)	Iron deficiency anemia n (%)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)
RBC (x10^{12}/L)	≥5	36(97.3)	1(2.7)	21.7%	98.4%	97.3%	31.6%	42.3%
	<5	130(68.4)	60(31.6)	(15.7-28.7)	(91.2-100)	(85.8-99.9)	(25-38.7)	(35.9-48.7)
RDW (%)	≥14	162(72.6)	61(27.4)	97.6%	0%	72.6%	0%	71.4%
	<14	4(100)	0(0)	(93.9-99.3)	(0-5.9)	(66.3-78.4)	(0-60.2)	(65.48-77.25)
RDWI [6]	<220	23(92)	2(8)	13.9%	96.7%	92%	29.2%	36.1%
	≥220	143(70.8)	59(29.2)	(9-20.1)	(88.7-99.6)	(74-99)	(23-36)	(29.9-42.4)
Green and King [7]	<72	27(96.4)	1(3.6)	16.3%	98.4%	96.4%	30.2%	38.3%
	≥72	139(69.8)	60(30.2)	(11-22.8)	(91.2-100)	(81.7-99.9)	(23.9-37)	(32-44.7)
Srivastava [8]	<3.8	56(84.8)	10(15.2)	33.7%	83.6%	84.8%	31.7%	47.1%
	≥3.8	110(68.3)	51(31.7)	(26.6-41.5)	(71.9-91.8)	(73.9-92.5)	(24.6-39.5)	(40.6-53.6)
Mentzer [9]	<13	65(90.3)	7(9.7)	39.2%	88.5%	90.3%	34.8%	52.4%
	≥13	101(65.2)	54(34.8)	(31.7-47)	(77.8-95.3)	(81-96)	(27.4-42.9)	(45.9-58.9)
Ehsani [10]	<15	73(90.1)	8(9.9)	44%	86.9%	90.1%	36.3%	55.5%
	≥15	93(63.7)	53(36.3)	(36.3-51.9)	(75.8-94.2)	(81.5-95.6)	(28.5-44.7)	(49-62)
Ricerca [11]	<4.4	35(81.4)	8(18.6)	21.1%	86.9%	81.4%	28.8%	38.8%
	≥4.4	131(71.2)	53(28.8)	(15.1-28.1)	(75.8-94.2)	(66.6-91.6)	(22.4-35.9)	(32.4-45.1)
England [12]	<0	24(96)	1(4)	14.5%	98.4%	96%	29.7%	37%
and Fraser	≥0	142(70.3)	60(29.7)	(9.5-20.7)	(91.2-100)	(79.6-99.9)	(23.5-36.5)	(30.7-43.3)
Sirdah [13]	< 27	63(94)	4(6)	38%	93.4%	94%	35.6%	52.9%
	≥ 27	103(64.4)	57(35.6)	(30.5-45.8)	(84.1-98.2)	(85.4-98.3)	(28.2-43.6)	(46.4-59.4)
Shine and Lal [14]	<1530	162(73.3)	59(26.7)	97.6%	3.3%	73.3%	33.3%	72.3%
	≥1530	4(66.7)	2(33.3)	(93.9-99.3)	(0.4-11.3)	(67-79)	(4.3-77.7)	(66.4-78.1)
11T score [16]	≥7	40(97.6)	1(2.4)	24.1%	98.4%	97.6%	32.3%	44.1%
	<7	126(67.7)	60(32.3)	(17.8-31.3)	(91.2-100)	(87.1-99.9)	(25.6-39.5)	(37.6-50.5)
11T score (cutoff 5)	≥5	64(88.9)	8(11.1)	38.6	86.9	88.9	34.2	51.5
	<5	102(65.8)	53(34.2)	(31.1-46.4)	(75.8-94.2)	(79.3-95.1)	(26.8-42.2)	(45.0-58.0)
11T score (cutoff 6)	≥6	58(95.1)	3(4.9)	34.9	95.1	95.1	34.9	51.1
	<6	108(65.1)	58(34.9)	(27.7-42.7)	(86.3-99.0)	(86.3-99.0)	(27.7-42.7)	(44.6-57.6)
11T score (cutoff 8)	≥8	30(96.8)	1(3.2)	18.1	98.4	96.8	30.6	36.7
	<8	136(69.4)	60(30.6)	(12.5-24.8)	(91.2-100.0)	(83.3-99.9)	(24.2-37.6)	(33.3-46.0)
11T score (cutoff 9)	≥9	20(95.2)	1(4.8)	12.0	98.4	95.2	29.1	35.2
	<9	146(70.9)	60(29.1)	(7.5-18.0)	(91.2-100.0)	(76.2-99.9)	(23.0-35.8)	(29.0-41.5)

Abbreviations: PPV = Positive predictive value, NPV = Negative predictive value, RBC = Red blood cell count interval, RDW = Red blood cell distribution width, RDWI = Red blood cell distribution width index.

disease, and β-thalassemia combined with α-thalassemia disease. In the subgroup of the β-thalassemia group, the results were not significantly different from in the full analysis. Similarly, the results remained similar to the full analysis in the α-thalassemia disease group. However, when we validated the formulas in the β-thalassemia combined with α-thalassemia disease patients, the NPV and the accuracy of almost all the formulas were better than in the full analysis, with figures ranging between 79.0%-93.0%, while the sensitivity and specificity were not different from in the full analysis.

Proposed novel thalassemia–iron deficiency discrimination (TID) predictive score

Because the validation of each previous formula was imperfect, we attempted to determine the significant factors to differentiate between thalassemic and IDA patients. We found that MCH, % RDW, RBC, and PLT were significant factors related to thalassemia. Therefore, the predictive score is calculated by using these factors as the following:

y = (-4.643) + (2.273 if MCH 17 to 20) + (3.888 if MCH > 20) + (2.025 if RDW 21 to 25) + (4.986 if RDW > 25) + (0.485 if RBC 3.5 to 4.5) + (4.787 if RBC > 4.5) + (0.785 if PLT < 265,000) + (1 if PLT 265,000 to 400,000)

Subsequently the TID predictive score was simplified by multiplying with 2 as the following:

y = (-9) + (5 if MCH 17 to 20) + (8 if MCH > 20) + (4 if RDW 21 to 25) + (10 if RDW > 25) + (1 if RBC 3.5 to 4.5) + (10 if RBC > 4.5) + (2 if PLT < 265,000) + (2 if PLT 265,000 to 400,000) (Fig 1)

We used the ROC analysis for the TID predictive score. The most appropriate cutoff level for predicting thalassemia was ≥2, in which the AUC was 0.93 (95% CI: 0.890 - 0.969; Fig 2). The sensitivity and specificity of the score were 90.4% and 78.7%, respectively (Table 3).

Internal validation of the TID predictive score

The split 150 sample profiles were utilized for the internal validation study of the TID predictive score. The AUC was 0.88 (95% CI: 0.815 - 0.947). The sensitivity to predict thalassemia from the internal validation was 96.4%, with the specificity and the accuracy of 50.0% and 84.0%, respectively. There was a non-statistically significant difference in AUCs between the predictive TID predictive score creation and the internal validation (*P*-value = 0.805).

DISCUSSION

The most common cause of microcytic anemia in developed countries is IDA. However, thalassemia should not be overlooked in patients with microcytic anemia, especially in Asian populations.[20-21] In Southeast Asian subjects, the prevalence of α-thalassemia among anemic patients is 20%–30%, and β-thalassemia is about 3%–9%.[20-21] A CBC is a worthwhile initial investigation that can be performed in every hospital. Although CBC is a simple test, it gives an instant result, but it cannot totally differentiate the cause of microcytic anemia. Hence, confirmation tests, such as iron study, Hb typing, and PCR for α-thalassemia, are still mandatory for a definitive diagnosis. However, such confirmation tests are invariably more sophisticated, quite expensive, and can take several days to several weeks to get the results back. So these are not always practical in developing countries with limited resources.

Several formulas have been developed to predict thalassemia and used as a screening tool for thalassemia diagnosis. For example, predictive formulas, such as Green and King, Srivastava, and Mentzer have shown a sensitivity of 87.7%–93.8% and specificity of 82.5%–95% according to the previous results.[7-9,15] The 11Tscore was developed to improve the sensitivity and specificity for improving thalassemia diagnosis.[15] It is composed of 11 predictive formulas.[15-18] A previous study from France found it had a sensitivity of 85.7% and specificity of 97.5%,[15] while the study from Thailand reported a sensitivity of 82.1% and specificity of 91.7%.[18] However, the 11Tscore has been applied for predicting only the β-thalassemia subtype.[15-18] Another study reported that the Jayabose RDW index, the Green and King formula, and the Janel 11T score are good formulas to differentiate thalassemia trait from IDA among their population.[22] Moreover, the serum ferritin cutoff value from previous studies for IDA diagnosis varied between <10 ng/ml and <16 ng/ml.[16-18] Currently, the definition for IDA diagnosis is serum ferritin < 30 ng/ml and TSAT < 16 %.[4] therefore, we defined IDA according to this recent suggestion in this study.

In our study, we validated all the previous formulas with all subtypes of thalassemia, including α-thalassemia disease, β-thalassemia disease, α-thalassemia combined with β-thalassemia disease, and IDA patients. In contrast to the previous results, the sensitivity and specificity to predict thalassemia disease among these included patients were not high. Therefore, we proposed a novel TID predictive score composed of 4 red blood cell indices, namely % RDW, RBC, and PLT count. The TID predictive score had a sensitivity of 90.4% and specificity of 78.7% to differentiate all thalassemia subtypes from IDA. Although, the specificity from the internal validation was insignificantly lower compared

TID predictive score = (-9) + (MCH points) + (RDW points) + (RBC points) + (Platelet points)

Parameter	Value	Points
MCH (pg)	<17	0
	17-20	5
	>20	8
RDW (%)	<21	0
	21-25	4
	>25	10
RBC ($x10^{12}$/L)	<3.5	0
	3.5-4.5	1
	>4.5	10
Platelet (/µL)	≤400,000	2
	>400,000	0

Fig 1. The thalassemia–iron deficiency discrimination (TID) predictive score and their values.

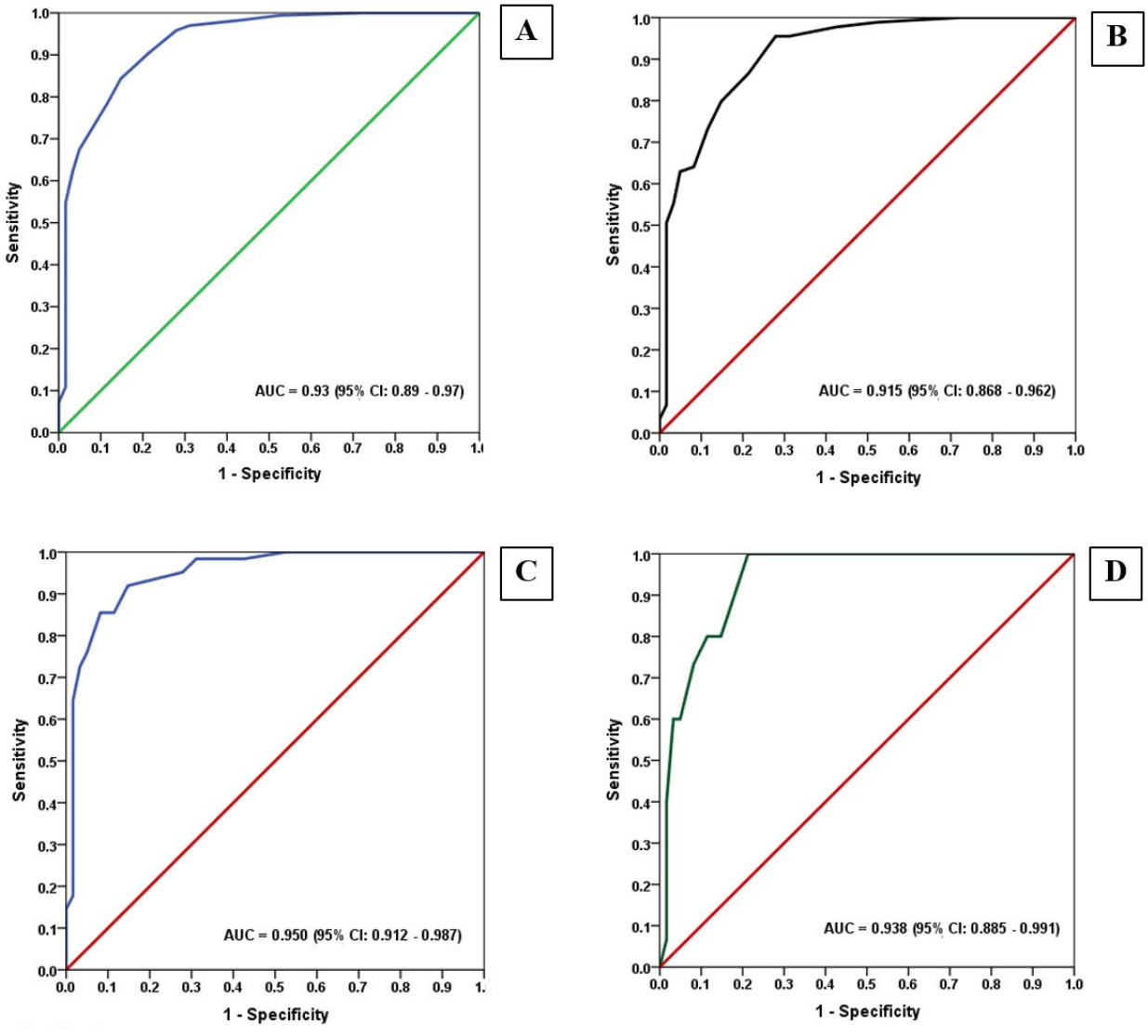

Fig 2. Receiver operating characteristic curve and the area under the curve for obtaining the cut off value for thalassemia prediction using the TID predictive score (A) all thalassemia subtypes (B) β-thalassemia disease (C) α-thalassemia disease (D) α-thalassemia combined with β-thalassemia

TABLE 3. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the TID predictive score.

Logistic model	Cutoff	Thalassemia n (%)	Iron deficiency anemia n (%)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)
Logistic model score	≥2	150(92)	13(8)	90.4%	78.7%	92.0%	75.0%	87.2%
	<2	16(25)	48(75)	(84.8-88.1)	(66.3-88.1)	(86.7-95.7)	(62.6-85.0)	(82.9-91.6)

Abbreviations: PPV = Positive predictive value, NPV = Negative predictive value.

to the figure from the predictive score generation, the sensitivity remained satisfying. The TID predictive score applies % RDW for calculation because in Thailand CBC report is practically presented with % RDW. However, a recent study showed that absolute RDW is more specific to differentiate thalassemia from IDA in microcytic anemia comparing with relative RDW.[23]

This score might be beneficial for thalassemia screening, whereby patients who have a score ≥2 can be selected for further investigation to confirm thalassemia disease. This could reduce unnecessary expenses from over investigation, which would be especially important in resource-limited countries. In other words, patients who have a lower likelihood of having thalassemia as assessed from the predictive score could be treated as IDA while waiting for their iron study.

There are some limitations of this study to note. First, because this was a retrospective study, some information may have been missing. Second, the TID predictive score demonstrated a specificity of 50.0% from the internal validation, some IDA patients who have high TID predictive scores might experience a treatment delay while awaiting for Hb typing result. Third, IDA patients from this cohort had significantly more severe anemia than the thalassemia subjects. This factor might influence the sensitivity/specificity of discriminant formulas. Lastly, in the subgroup analysis, the size of some subgroups is quite small which leads to imprecise formula validation.

CONCLUSION

Thalassemia and IDA are the most common causes of microcytic anemia. Here, a TID predictive score was proposed that demonstrated higher sensitivity for thalassemia prediction while remaining uncomplicated to be applied due to its few involved parameters.

ACKNOWLEDGEMENTS

The authors are grateful to the Department of Medicine, Chaophraya Yommarat Hospital, Suphanburi, Thailand and the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand for grant support. We also thank Assoc.Prof. Preechaya Wongkrajang and Dr. Ratikorn Anusorntanawat for their valuable consultation and advice and thank Ms. Pattaraporn Tunsing and Ms. Kemajira Karaketklang for the data collection and statistical analyses.

Conflicts of interest: The authors confirm that there are no known conflicts of interest associated with this publication.

Funding: This study was funded by grants from the Department of Medicine, Chaophraya Yommarat Hospital, Suphanburi, Thailand and the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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The Evolution of Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy

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ABSTRACT

Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy is a cutting-edge surgical technique for resection of hepatic malignancies that has piqued the interest of the international hepatobiliary community. Patients with insufficient future liver remnants, many of whom are considered unresectable via other methods, have the possibility of being cured with this treatment. The main issues; howbeit include, increased perioperative morbidity and mortality as well as both early and rapid disease recurrence. However, with continuous improving of patient selection, optimizing stage 2 operation times and refined operative techniques this has led to reduced morbidity and mortality rates. As for its usage, the most frequent indication is colorectal liver metastasis (CRLM); in which, the results in CRLM have shown higher resectability; however, it has a comparable complication rate to two-stage hepatectomy. Conversely, perihilar cholangiocarcinoma and hepatocellular carcinoma have terrible outcomes; although, with technical refinement and better patient selection good outcomes are achievable.

Herein, we summarized the current evidence based of the application of ALPPS in real-life practice, including the potential complications related to this procedure.

Keywords: ALPPS; Future liver remnant; hepatectomy (Siriraj Med J 2022; 74: 266-273)

INTRODUCTION

An insufficient future liver remnant is a factor excluding patients from curative intent liver resection, as the low hepatic functional reserve of the small, future liver remnant (FLR) can lead to post-hepatectomy liver failure (PHLF). Portal vein embolization (PVE) results in compensatory hypertrophy of FLR; however, the biggest drawback of PVE is insufficient FLR hypertrophy, or subsequent disease progression; which affects roughly 20% of patients.[1]

Recently, Two-stage hepatectomy (TSH) has been introduced for patients with bilateral multinodular colorectal liver metastases.[2] This can be used in conjunction with Portal vein occlusion (PVO); either portal vein ligation (PVL) or percutaneous PVE. The main idea being that the liver grows in the interval between sequential resection, and the risk of PHLF is presumably reduced due to this staged approach.[3,4] However, although TSH is well established, failure to proceed to stage 2 is reported as being a problem in up to one-third of patients.

Dr. Hans Schlitt discovered the Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS) by chance. He noticed a small liver remnant during an extended right hepatectomy for hilar cholangiocarcinoma. So, he decided to perform a hepaticojejunostomy and right PVL after parenchymal

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http://dx.doi.org/10.33192/Smj.2022.33

transection for enhancing exposure. Fortunately, computed tomography (CT) scanning revealed extensive hypertrophy of the remnant segments one week later. Hence, the right liver was subsequently removed.[5] ALPPS is based on the fast hypertrophy of remnant segments. It can enhance the remaining liver by up to 80% over an average duration of 1-2 weeks compared to 20-45% in 2-8 weeks in PVE patients.[6,7] The possible mechanism of rapid hypertrophy in ALPPS is based on the increase of portal flow in the disconnection of the interlobar perfusion, accompanied by the increased level of inflammatory cytokines that induce liver regeneration. The disadvantage is a high procedure-related morbidity and mortality rate of roughly 40% and 15%, respectively, mainly from liver failure and bile leakage.[8] As a result, the safety of ALPPS in comparison to standard techniques is still debatable.

Pathophysiology of liver regeneration in ALPPS

There are two proposed mechanisms for rapid hypertrophy after the first stage of ALPPS. Firstly, the parenchymal transection will not allow communication of interlobar collateral circulation. The portal flow can maximize the shearing force to the hepatocyte that causes the liver to regenerate. The later mechanism is based on the increased level of inflammatory mediators that drive liver regeneration.[9]

The disparity between the size and function of a remnant could explain the high risk of ALPPS complications. The regenerate hepatocyte shows edema and expansion, but is still partly immature within the first two weeks after the procedure, albeit from unknown causes.[10] Histologically, the hepatocyte has greater cell density, is smaller in size, brighter and has narrower sinusoidal compared to PVE.[11] In electron microscopy, the FLR area is frequently shown as being vacant in appearance. This is caused by hepatocytic cytoplasm filled with glycogen granules and fewer cytoplasmic organelles, lipofuscin granules. To date, all of these properties can be interpreted as immature cells.

Technical considerations (right trisectionectomy ALPPS)

The liver was examined with intraoperative ultrasonography to confirm the number and location of the tumor. The liver was fully mobilized, and the hepatoduodenal ligament was skeletonized. The right portal vein was ligated with non-absorbable suture material. The parenchymal transection was carried down along the falciform ligament (Fig 1). Most of the authors advocated for using a plastic bag for covering the deportalized liver, so as to control bile leakage. CT scanning was performed at 9 days on average, postoperatively. The right hepatic artery, right hepatic duct, right, and middle hepatic vein were then divided in the second stage operation.[5,12]

Modifications to the initial techniques

Bile duct ligation

Recent studies have suggested against routine bile duct ligation.[13,14] Many published reports have reported complications; such as, a higher rate of bile leakage, biloma formation and severe, dense adhesion at the porta hepatis during second stage operations. The previous hypothesis was that by increasing the biliary obstruction response in obstructed livers, right bile duct ligation could promote additional FLR hypertrophy.

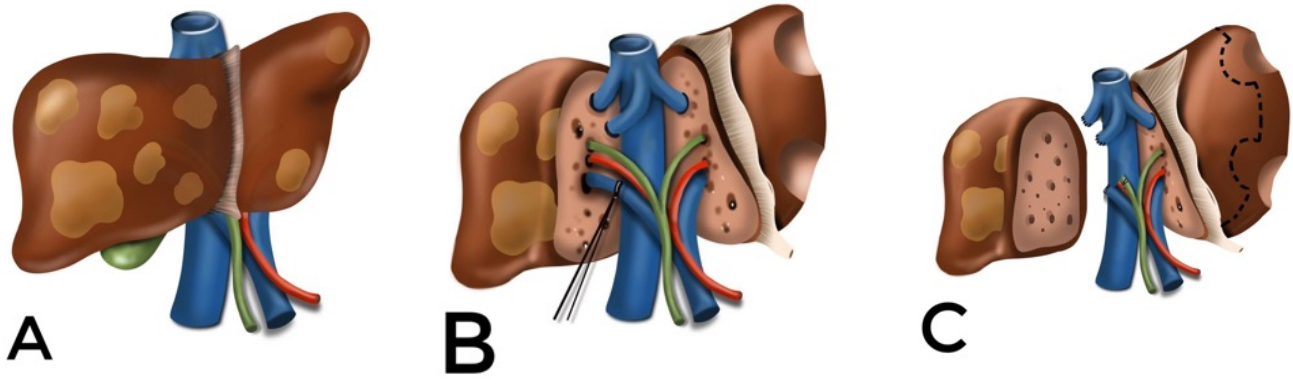

Fig 1. Schematic overview of Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (right trisectionectomy). (A) The liver was occupied with multiple tumors on both sides. The potential procedure is right trisectionectomy with the lateral section as the future remnant liver. (B) In the first stage, complete parenchymal transection was carried out along the falciform ligament, the tumors in the remnant liver were removed, and the right portal vein was ligated. (C) The future liver remnant shows significant hypertrophy, and then the deportalized lobe was removed.

Preservation of the middle hepatic vein

The first ALPPS series mentions ligation of the middle hepatic vein during the first stage of the procedure[5] however, a recent study[13] discovered its relation with congestion of liver segments IV, V, VIII. This may result in decreased outflow, followed by a higher risk of ischemia and hepatic necrosis as well as subsequent bile leakage. The middle hepatic vein is now preserved as the venous outflow of segment IV, rather than being removed as previously reported, without compromising parenchymal hypertrophy. Most hepatobiliary surgeons currently use this method.[6]

Hybrid ALPPS (Non touch technique)

This modification aims to avoid manipulating the right lobe of the liver in order to improve tumor tissue handling and prevent hematologic malignancy spread.[13,15,16] The parenchymal transection is performed using an anterior approach, without mobilization, and the hepatoduodenal ligament is left intact. In the days following the operation, interventional radiology performs right PVE. At the second stage, there is less inflammation around the liver; according to reports. Nevertheless, some of the authors are against this idea, due to the inability to achieve optimal vascular control during a technically complex procedure; especially via an anterior approach.[14,15]

Partial ALPPS

This modified technique solely differs in the degree of liver partition. In contrast to conventional ALPPS, where parenchymal transection was complete, partial ALPPS transected only 50% to 80% of the parenchyma in stage I.[14] Anatomic outflow structures (hepatic veins), and/or tumor(s) lying inside or near the future transection line, determine the degree of partial transection. The main advantage of this modification in technique is that it limits the deleterious congestion of the excluded segments and segment IV necrosis, by preserving their outflow via the middle hepatic vein.[17,18] Partial ALPPS generates equivalent FLR hypertrophy to complete ALPPS, but with decreased morbidity and near-zero mortality.[16] However, Chan et al. demonstrated that complete ALPPS can cause rapid FLR hypertrophy more so than partial ALPPS, while having no impact on perioperative risks in chronic liver disease.[19] In the meta-analysis by Wu et al, they compared partial and complete ALPPS and showed that FLR hypertrophy and time intervals between stages were not substantially different for both techniques.[20] Although, the post-operative complication rate was significantly lower in partial ALPPS.

Mini-ALPPS

Mini-ALPPS simplifies first stage hepatectomy, by using a partial parenchymal transection technique and intraoperative portal vein embolization, without hilar dissection or liver mobilization. This approach allows for an accelerated FLR hypertrophy to be obtained at a mean of 63% within 11 days.[19] This is similar to that reported for classic ALPPS; but without the high rate of mortality and morbidity.[5,6]

Associating Liver Tourniquet and Portal Ligation for Staged Hepatectomy

With this method, a tourniquet is used to replace the completion of the parenchymal transection, this reduces the complexity and time required in the first stage of the operation.[21] A thick suture material is applied around the liver in the deep sulcus of the parenchymal transection (an extra-glissonian approach). Then the tourniquet is subsequently tightened to completely obstruct all interlobar collateral circulation.

Radiofrequency assisted liver partition

This is an application of radiofrequency ablation to the parenchyma, after right PVL at the site of demarcation. The hypertrophic rate is increased by up to 62% over a mean interval of 22 days, according to the study, and that it also avoids the complications of liver partition.[22]

ALPPS outcome

Primary outcomes

The studies that investigated the efficacy of ALPPS have consistently revealed that ALPPS causes hypertrophy of 60-90%, with the average duration of the stage being 9-14 days (Table 1). Most of the cases (95-100%) that complete the first stage could be undergoing a later stage.[5,6,15,23,24] The international ALPPS registry consists of 141 (70%) colorectal liver metastasis (CRLM) patients among 202 patients.[25] Within 7 days, the median initial standardized future liver remnant of 21% grew by 80%, and ninety-day mortality was 9%. Severe complications occurred in 27% of patients. Red blood cell transfusion, an operative time of more than 300 minutes, patient ages being greater than 60 years, and non-CRLM were all independent risks for severe complications. Additionally, the registry shows that many factors directly affect the rate of liver hypertrophy; such as, age, intermittent Pringle maneuver, and abnormal parenchyma.[25]

According to meta-analysis,[26] ALPPS seems to be more effective than the two-stage approach in causing remnant hypertrophy, with significantly higher resection

TABLE 1. Success rate and outcome of Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy compare with two-staged hepatectomy.

Author (reference)	Year	Primary tumor (N)			FLR volume increment (%)		Drop-out rate after first stage (%)		Morbidity*/ mortality (%)
		CRLM	HCC	CCA	ALPPS	TSH	ALPPS	TSH	
Schnitzbauer[5]	2012	14	3	4	74	n/a	n/a	n/a	64/12
Shindoh J[8]	2013	14	3	4	70	62	n/a	28	40/12
Schadde E[25]	2014	141	17	19	80	n/a	2	n/a	27/9
Schadde E[6]	2015	228	32	27	90	n/a	2	n/a	14/9
Sandstrom[31]	2018	97	-	-	68	36	8	43	43/8
Wang Z[36]	2020	-	45	-	57	n/a	9	n/a	12/11
Chan A[37]	2021	-	46	-	49	38	2	32	21/6.5

Abbreviations: CRLM; Colorectal Liver Metastasis, HCC; Hepatocellular carcinoma, CCA; Cholangiocarcinoma, FLR; Future liver remnant, ALPPS; Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, TSH; two-stage hepatectomy
* Clavien-Dindo grade ≥ IIIB
n/a: non-available

rates of approximately 92-100%.[25–28] Additionally, there is a shorter time interval of 1-2 weeks vs. 20-45% in 2-8 weeks following PVE. Furthermore, prolonged periods between stages in TSH has caused up to 30% of patients to be ineligible for a final hepatectomy, due to disease progression.[10,29,30] At the same time, ALPPS faces the problem of most candidates having a higher risk for micrometastasis in FLR after a second stage operation. Additionally, there is an argument concerning the hypertrophic liver, in regards to cellular swelling or complete functioning regeneration, and that liver hypertrophy in such a short period of time may not ensure its functional capacity.[9] In conclusion, despite ALPPS having a greater resectability rate, there is no significant difference in disease free survival between ALPPS and TSH.

Morbidity and mortality

The major obstacle of the procedure is the significant rate of morbidity and mortality. The largest study, 202 patients, cited major morbidity of 28% and mortality of 9%.[6,15,25] Although, the reported mortality rate is variable, the high complication rate is may have occurred from the small sample size of the study. A German study revealed a 12 percent 90-day death rate, triggering a fierce debate among international experts;[5] surgical exploration, right portal vein ligation (PVL additionally, other small studies found significantly higher rates; ranging from 22-29%. Conversely, there have been no 90-day mortalities recorded across multiple centers.[13,15,25]

Comparison between ALPPS and Two-stage hepatectomy.

The retrospective comparative analysis of 140 patients undergoing PVE to the 25 patients undergoing ALPPS showed that the rates of hypertrophy were similar in both groups: 70% in the ALPPS group and 60% in the PVE group.[8] Overall, there was no significant difference in major morbidity between the two groups (40% ALPPS versus 30% PVE). However, for other complications ALPPS had significantly higher rates than PVE in all causes; bile leak (24% versus 6%), re-laparotomy (30% versus 3%) and sepsis (20% versus 0%); but was no significantly higher in liver-related mortality (12% versus 6%).

Data from the retrospective multicenter study showed a trend towards higher morbidity and mortality associated with ALPPS compared with PVE. The 90-day mortality was 15% versus 6%, and post-hepatectomy liver failure was 13% versus 9% for the ALPPS versus the PVE group, respectively. Moreover, patients in the

ALPPS group achieved more completion of resection (83% versus 66%); however, the recurrence at one year was comparable (54% versus 52%).[25]

In contrast to Aloia et al, the PVE group had just a 34% increase in FLR compared to a 77% gain in the ALPPS group.[28] The LIGRO was a landmark randomized controlled trial that compared the resection rate between ALPPS and TSH in CRLM patients. This study demonstrated that ALPPS could offer a higher resection rate compared to TSH, 92% to 57%, respectively, with comparable surgical margins, complications, and short-term mortality.[31]

A recent systematic review and meta-analysis of ALPPS versus traditional staged hepatectomy, in 2019,[7] found that ALPPS increased FLR more than PVE and TSH. However, the results of the study are limited due to the high heterogeneity among the studies. As for overall mortality and morbidity, the higher trend is on the side of ALPPS over PVE/TSH; morbidity 30% and 26%, respectively, without heterogeneity; mortality 10% and 4% consequently, without heterogeneity. The feasible rate of stage 2 after ALPPS and PVE were 94% versus 63%, respectively, which is the same as between ALPPS and TSH, 95% versus 72%, respectively.

ALPPS in CRLM

In the first international registry,[6] the 90-day postoperative mortality among all patients who underwent ALPPS was 9%. For patients with CRLM, the 2-year overall survival (OS) and disease-free survival (DFS) were 62% and 41%, respectively. Patients with CRLM who were younger than 60 years of age had a better chance of survival than patients with other malignancies. A separate analysis of the international ALPPS registry included 228 patients with CRLM, which comprised of 72% of the study population. In this report, the 90-day mortality was 5%. The leading cause of mortality was liver-related, for which it was recommended by the authors to evaluate the patients underlying condition, using the model of end-stage liver disease, and the international study group for liver surgery criteria, so as to discriminate against higher or lower risk.[27]

Some of the suggested approaches to improve ALPPS outcome include stratification of patients for developed liver failure following first stage hepatectomy, achieving expertise in the learning curve, refinement in patient selection, modifications to the original ALPPS procedure to reduce liver traumatization, interval chemotherapy, a shorter time off chemotherapy, and preservation of segment IV.[9] The objective of oncologic liver surgery is to achieve a tumor-free margin. In there meta-analysis, Margonis et al,[29] found that a margin of >1 mm was related with better overall survival, and a margin of >1 cm was even associated with better DFS. As a result, a better oncologic outcome may even justify the removal of significant volumes of parenchyma. Furthermore, regarding the numbers and sizes of metastases remaining in the FLR, full tumor clearance of the FLR during the first stage is crucial for any two-stage strategy. These traditional markers; numbers and sizes of metastases as well as intensity of oncologic pretreatment area are important prognostic factors. KRAS mutation, which has been linked to poor survival, and TP53 mutation have both been linked to a higher chance of tumor relapse in recent studies.[30]

Hence, analysis by Schnitzbauer et al,[32] assumed that there is a tendency for potential overuse of ALPPS. Additionally, the role of major hepatectomy in CRLM has become less, due to effective down-sizing of chemotherapy being available. In this case, ALPPS must be viewed as a last resort at the very end of the therapeutic spectrum for CRLM.

ALPPS in Hepatocellular carcinoma (HCC)

The ALPPS registry's initial report, which included 17 patients with HCC, and the second, which included 32 patients with HCC, reported 90-day mortality rates of 12% and 13%, respectively.[6,25] These results appeared to be the consequence of both an early learning curve and a typically increased mortality of liver resection in altered liver parenchyma. More devastating was when the first major analysis from the ALPPS registry, with 35 ALPPS for intermediate-stage tumor, revealed a 90-day mortality of 30%.[33] However, a thorough examination revealed that ALPPS had been employed with broad inclusion criteria and in an undifferentiated manner. Fortunately, after careful selection, using the ALPPS technique in a good patient candidate with HCC (Child A cirrhosis, FLR volume > 30%, an indocyanine green clearance rate at 15 minutes <20%, platelet count > 100,000/μL and no complete right portal vein thrombosis), led to a decrease in mortality of 7% and 0%.[23,34,35] A recent study, from Wang et al, investigated their outcomes of conventional ALPPS in 45 HCC patients.[36] The results showed that the patients who received ALPPS had similar effects to those who underwent one-stage hepatectomy,; with 1- and 3-year OS rates of 64% and 60% and 1- and 3-year DFS rates of 48% and 44%. Furthermore, the results were far superior to those who received transarterial chemoembolization. Recently, Chan et al. investigated the role of ALPPS for hepatitis-related HCC. The study shows ALPPS induced FLR volume increment by 48.8%, without difference in morbidity and mortality compared

to PVE. Although, over 56.5% of patients that complete stage 2 had cirrhosis.[37]

ALPPS in cholangiocarcinoma

From the beginning, ALPPS was firstly used in a case of hilar cholangiocarcinoma, even so, the latest data reveals the highest perioperative complication risks among all indicated diseases. The 90-day-mortality for intrahepatic cholangiocarcinoma from the ALPPS registry is about 13%.[6] The risk of perioperative complications is higher in perihilar cholangiocarcinoma (PHC), most likely from post first stage parenchymal necrosis, possibly infected bile, and biliary leakage. A matched case study that compared data from the ALPPS registry to data on PVE and right trisectionectomy for PHC found that perioperative mortality was as high as 48% in the ALPPS group versus 24% in the matched group.[38] These results led to unacceptable arguments over whether it is a homicidal choice of treatment or not. However, from a closer viewpoint, ALPPS in the research was performed with the intention to improve resectability, by rapidly increasing FLR; but at the same time some principles of surgery for PHC were neglected. For example; performing the 1st stage operation in the presence of infection and inflammation by conventional ALPPS; thereby causing a higher risk of biliary leakage. Conversely, new techniques; such as: "Mini-ALPPS" and "Hybrid ALPPS", were introduced. Both strategies aim to achieve appropriate FLR growth in the shortest period possible, and both prevent hilar dissection during the first stage. As a result, in PHC patients, ALPPS should not be deemed a categorical contraindication.

Authors opinions

After the initial outcome of ALPPS demonstrated the dramatic increment of FLR, this procedure became famous among the hepatobiliary surgery community. However, many patients have been through this procedure without proper indication, which has lead to avoidable complications. Even with the international ALPPS registry results, the 90-day mortality was much higher than conventional hepatectomy.[6]

The authors suggest that the following issue should be considered before selecting a patient for ALPPS.

1. For CRLM: the patient should receive episodes of systemic chemotherapy, with or without targeted therapy. Good response liver metastasis could omit the need for this risky procedure. ALPPS should only be used as a last measure in the treatment of CRLM.[32]
2. The CRLM patients who progress while on systemic therapy are poor candidates for ALPPS.
3. After stage 1, preoperative liver evaluation is crucial. Both quantitative and qualitative assessments are essential. The second stage should be terminated, or postponed for any patient that has good FLR increase but impaired function. There are some discrepancies between the increased volume and the remnant›s function because most of the regenerated hepatocyte is still partly immature.[10]
4. In chronic viral hepatitis or cirrhosis there is scant evidence of ALPPS; therefore, the surgeon should select the most suitable patients for ALPPS.
5. Patients with cholangiocarcinoma should avoid ALPPS. ALPPS in cholangiocarcinoma had the highest risk of perioperative complication among all indicated diseases. The 90-day-mortality for intrahepatic cholangiocarcinoma is high as 13%, and might be higher for perihilar cholangiocarcinoma.[6]

CONCLUSION

ALPPS is one of the strategies to overcome inadequate future liver remnants. Perioperative complications are the main concern for ALPPS, because the tremendous volume increment within 1-2 weeks is not well correlated with the function of the remnant liver. As early results from the ALPPS registry have shown, inappropriate patient selection resulted in a high risk of PHLF and postoperative mortality. Proper patient selection coupled with a satisfactory pre-and interstage liver assessment could improve outcomes; especially for CRLM, which has comparable results to TSH.

ACKNOWLEDGEMENT

The authors would like to thank Woralux Phusoongnern, M.D., FRCNST, for the illustrations.

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