

ORIGINAL ARTICLE

The efficacy and safety outcomes of cardiac resynchronization therapy in patients with heart failure in Thailand: Phramongkutklao experience

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Abstract

Background: Cardiac resynchronization therapy (CRT) is one of the crucial treatments in patients with symptomatic heart failure reduced ejection fraction. This study aimed to report the efficacy and safety of CRT implantation in treating patients with heart failure. The responders and related outcomes were also analyzed.

Methods: Medical records of all patients with CRT implantation, because of heart failure treatment indication, in Phramongkutklao Hospital between 2008 and 2019 were reviewed. Free from death and heart failure hospitalization were analyzed as composited efficacy outcomes with survival analysis. Follow-up echocardiography was used to define a responder. The safety outcomes were reported using descriptive data. Cox-proportional hazard model analysis was used for the responder as a predictor of outcomes.

Results: A total of 152 patients underwent CRT implantation because of heart failure. 77.63% were male, the mean age of 65.9 ± 13.19 years, 59.85% were diagnosed with ischemic cardiomyopathy, mean LVEF of $22.69 \pm 7.51\%$, and QRS duration of 147 ± 21 ms. Mean Follow-up was 41 months. The composited efficacy outcomes were 91.7%, 54.8%, and 35.4% at 1, 5, and 10 years, respectively. CRT-related complications were found in 12 patients (7.89%). 71.30% of patients who were responders had lower death or heart failure hospitalization when compared to non-responders (HR: 0.43, 95% CI: 0.24–0.78).

Conclusion: The efficacy and safety in CRT treating patients in our center were consistent with the previous randomized and observational studies. The responder rate remained the same as in previous trials but was a strong predictor for better outcomes.

KEYWORDS

cardiac resynchronization therapy, heart failure

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1 | INTRODUCTION

Heart failure is one of the common cardiovascular diseases and being the main problem in public health. It is one of the causes of morbidity and mortality. The prevalence of heart failure is estimated to be 64.3 million people worldwide.¹ In the United States, the prevalence is 5.7 million people and was expected to increase by 25% in 2030.² The prevalence also increases with patients' ages. There are 11.8% of people older than 60 years with heart failure.³ Even though there is no report of the prevalence of heart failure in Thailand, but more prevalence of heart failure in Southeast Asia was reported with the prevalence of 4.5–6.7 compared to other regions with a prevalence of 0.50–2.0.⁴

Heart failure is also one of the most common causes of death in the overall population. The estimated mortality was 55% five years after the onset of heart failure.⁵ This estimation was irrespective of the left ventricular ejection fraction (LVEF). Even there were scarce statements of mortality because of heart failure in the Thai population. Thai ADHERE study demonstrated the mortality of 5.4% in patients admitted because of acute heart failure.⁶ Moreover, the long-term mortality increased over time. The mortality was 28%, 58.2%, and 73.3 at 1-year, 5-year, and 10-year after the onset of heart failure, respectively.⁷

The goals of treating patients with heart failure are not merely to relieve their symptoms, improve functional capacity, and increase the quality of life but also preventing for heart failure rehospitalization and death. Even several medications have met the benefits of these treatment goals, but medical devices also have a crucial role in these patients. One of the most critical medical devices for patients with heart failure is cardiac resynchronization therapy (CRT) devices. Some patients achieved various benefits after device implantation. CRT implantation is recommended in patients with symptomatic heart failure who are in sinus rhythm with a QRS duration of 130 ms or more and LVEF less than or equal to 35%.⁸ The primary purpose of this therapy is to improve patients' symptoms, reduce morbidity, and reduce mortality.⁸ This treatment can improve the quality of life in two-thirds of the patients and reduce mortality in one-third of the patients.⁹

Even though the CRT implantation procedure has a high success rate of up to 95.9%, there is a slight chance of complications. The common complications comprise coronary sinus dissection, pneumothorax that need intercostal chest drain insertion, and dislodgement of the left ventricular (LV) pacing lead, which occurred in 2.1%, 1.3%, and 4.9%.¹⁰

The prevalence of heart failure and its mortality in Thailand are not reported. A trend shows that CRT implantation in patients with heart failure in Thailand has recently increased in the last few years. The CRT implantation rate was rose from around 100 patients per year between 2010 and 2016 to almost 400 patients per year since 2017.¹¹ Even with this continuation in CRT implantation, there is no systematic study conducted in Thailand. Hence, the evaluation of the effects of this treatment in such a population is needed. Phramongkutklao hospital is the largest army hospital in Thailand

and has also been one of the high-volume centers of CRT implantations in the past decade. Therefore, we performed a retrospective study to assess the efficacy and safety of CRT in treating patients with heart failure.

2 | METHODS

2.1 | Study population

We reviewed all medical records of all patients with CRT implantation in Phramongkutklao Hospital between 2008 and 2019. Only patients who had CRT implanted because of heart failure treatment indication were included in this analysis. This indication comprised symptomatic heart failure with LVEF equal to or less than 35%, sinus rhythm or intended to be restored to sinus rhythm, and QRS duration of 120 ms or more. We decided to include patients with a QRS duration of 120 ms or more, which indicated CRT implantation according to the guidelines published before 2016. These guidelines comprised of 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities and 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy.^{12,13} The patients who have no documented data after implantation were excluded from this analysis.

2.2 | Baseline assessment

The patients' baseline characteristics included age, gender, weight, weight, New York Heart Association Functional Class (NYHA FC), and significant underlying diseases, including permanent atrial fibrillation, diabetes, and hypertension. A treating cardiologist determined the patients' heart failure etiology by assessing the patients' investigations before CRT implantation, including coronary angiography, coronary computer tomography angiography (CCTA), cardiac magnetic resonance (CMR) imaging, and myocardial perfusion scan. In addition, the patients with pre-existing pacemaker implantation with a high percentage of ventricular pacing were also stated. Pharmacological treatment data were collected, including the use and the dosage of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), angiotensin Receptor Blocker/Nepriylisin Inhibitor (ARNI), beta-blockers, aldosterone antagonists (MRAs), digoxin, amiodarone, and loop diuretics. In addition, we collected the patients' recent investigations before CRT implantation, which comprised QRS duration, type of bundle branch block, blood pressure, pulse rate, calculated glomerular infiltration rate (GFR). We collected vital signs at the starting time of implantation. Some meaningful echocardiographic findings which affect the patients' outcomes comprised LVEF, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter (LVEDs), and left atrial diameter

(LAd) were also collected. The LVEF was measured by the standard modified Simpson's method.

2.3 | Device implantation

Patients who meet the inclusion criteria underwent the procedure according to the published guidelines mentioned above. Systems from three manufacturers were used including Medtronic, Boston Scientific, and Abbott. The type of pulse generators and leads were used as available at the time of implantation. The implantation procedure and the coronary venous branch selection were performed according to three physicians' techniques and preferences.

2.4 | Follow-up and outcomes

We tried to collect data at least one-year follow-up from the last patient. Hence, the follow-up data included until the end of December 2020. The efficacy outcome is the combination of free from heart failure hospitalization and death from any cause. The safety outcome was freedom from complications related to the implantation procedures including skin erosion, coronary venous dissection, LV lead dislodgement, phrenic nerve stimulation, device infection, and pneumothorax. To assess the responder rate according to LV reverse remodeling measured by echocardiography, the follow-up echocardiography data comprised of LVEF and LVESV were also reviewed. The response to CRT was defined as a decrease in LVESV of $\geq 15\%$ and/or an absolute increase of $>5\%$ of LVEF. In addition, in those with defibrillation implantation, the occurrence of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and its therapy was also collected.

2.5 | Statistical analysis

The baseline characteristics of the patients are presented using descriptive statistics. Categorical data are expressed as percentages and continuous data as mean \pm standard deviation. The primary efficacy outcome was demonstrated as time-to-event using Kaplan-Meier analysis in all patients. Cox-proportional hazard model analysis was used to evaluate the correlation between the cause of cardiomyopathy and outcomes. The safety outcome was described as percentages. Cox-proportion hazard model analysis was also applied for the calculation of univariate and multivariate predictors of the efficacy outcomes. The interested predictors included responder, age, gender, etiology of heart failure, whether the implanted device with the defibrillator, permanent atrial fibrillation (AF) or atrial flutter (AFL), diabetes, hypertension, renal function calculated with estimated glomerular filtration rate (eGFR), mean arterial pressure (MAP), pharmacological treatment and dosage, LV dilatation, left atrial dilatation, severe mitral regurgitation, and branch of the coronary sinus (CS) for LV lead placement.

3 | RESULTS

3.1 | Patient enrollment

Between July 2008 and December 2019, 207 patients underwent CRT implantation procedures in Pharmongkutklao hospital. Nine patients were excluded because of a lack of follow-up data after implantation. One patient was excluded because of an unsuccessful procedure when the operator tried to place the LV lead into all coronary sinus branches and ventricular capture could not achieve even with the highest pacing output. Forty-eight patients were excluded because of the indication of implantations was not for symptomatic heart failure. The most common indication in these patients was the failure of medical treatment for controlling ventricular rate in patients with permanent atrial fibrillation. Hence, these patients had either LVEF more than 35% or QRS duration less than 120 ms. The remaining 152 patients' data were analyzed in this study.

3.2 | Baseline characteristics of the patients

The baseline characteristic of the patients who underwent CRT implantation is shown in Table 1. Most patients were men (77.63%) and had an average age of 65.9 ± 13.19 years. There were 22 (14.57%), 82 (54.30%), 46 (30.46%), and 1 (0.66%) who had NYHA FC I, II, III, and V, respectively. Mean follow-up was 41 months (41.45 ± 31.47 months, ranging from 8 days to 4051 days). A total of 129 patients had one year or more of follow-up, and 23 patients had less than one year of follow-up. There were 10 patients who died within one year of implantation. Ninety-one patients (59.87%) were diagnosed with ischemic cardiomyopathy. The LVEF was $22.69 \pm 7.51\%$. The QRS duration was 147 ± 21 ms, and 86.13% were left bundle branch block (LBBB) morphology. Twenty-four patients (15.79%) had permanent atrial fibrillation. The rate of pharmacological treatment for heart failure was relatively low. There were 99 (65.13%), 104 (68.42%), and 65 (42.76%) patients treated with ACEIs/ARBs/ARNI, beta-blockers, and MRAs, respectively. The dose of these drugs is also low. There were only 29 (19.08%), 33 (21.71%), and 35 (23.68%) patients who reached at least 50% of the maximal recommended dose of heart failure medication of ACEIs/ARBs/ARNI, beta-blockers, and MRAs, respectively. The number of patients and the dosage of these medications were summarized in Table 2. The average time of pulse generator replacement was 59.23 ± 15.65 months.

3.3 | Efficacy outcomes

Fifty-eight (38.16%) patients reached the efficacy outcomes. The composited efficacy outcomes, which were free from heart failure hospitalization and death from any cause, were 91.7%, 54.8%, and 35.4% at 1, 5, and 10 years, respectively. We found death in 33 patients. Overall survival was 92.3%, 73.1%, and 52.7% at 1, 5, and 10 years, respectively. Forty-one patients were admitted because of

TABLE 1 Baseline characteristic

Characteristics	All patients (n = 152)
Age (years)	65.9 ± 13.19
Male, n (%)	118 (77.63)
NYHA FC, n (%)	
I	22 (14.57)
II	82 (54.30)
III	46 (30.46)
IV	1 (0.66)
Follow-up (months)	41.45 ± 31.47
BMI (kg/m ²)	23.88 ± 4.25
QRS duration (ms)	147 ± 21
LBBB, n (%)	131 (86.18)
Ventricular rate (bpm)	71 ± 16
MAP (mmHg)	96.81 ± 15.84
Permanent AF, n (%)	24 (15.79)
CRT-D, n (%)	137 (90.73)
LV lead type, n (%)	
Bipolar	77 (51.33)
Quadripolar,	73 (48.67)
CS branch placement, n (%)	
Basal lateral vein	83 (55.33)
Mid lateral vein	46 (30.67)
Apical lateral vein	21 (14.00)
Echocardiographic parameters	
LVEF (%)	22.69 ± 7.51
LVESV (ml)	133.79 ± 51.76
LA diameter (mm)	45.29 ± 12.47
LVEDd (mm)	62.06 ± 9.10
LVESd (mm)	54.28 ± 11.3
Mitral regurgitation, n (%)	
Mild	70 (55.56)
Moderate	23 (18.25)
Severe	4 (3.17)
GFR (ml/min/m ²)	59.05 ± 25.62
Ischemic cardiomyopathy, n (%)	91 (59.87)
Preexisting PPM with high percentage of RV pacing, n (%)	18 (11.84)
Diabetes	56 (36.84)
Hypertension	101 (66.45)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CRT-D, cardiac resynchronization therapy defibrillator; CS, coronary sinus; GFR, glomerular filtration rate; LA, left atrial; LBBB, left bundle branch block; LV, left ventricular; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVSDd, left ventricular end systolic diameter; MAP, mean arterial pressure; NYHA FC, New York Heart Association Functional Class; PPM, permanent pacemaker; RV, right ventricular.

heart failure throughout the study. Overall heart failure hospitalization was 95.0%, 66.6%, and 47.1% at 1, 5, and 10 years, respectively. In the aspect of the cause of death, cardiovascular death was not

TABLE 2 Heart failure medication and dosage

Medication, n (%)	All patients (n = 152)
ACEI/ARB/ARNI	99 (65.13)
≥50% of targeted dose	29 (19.08)
Beta-blocker	104 (68.42)
≥50% of targeted dose	33 (21.71)
MRA	65 (42.76)
≥50% of targeted dose	36 (23.68)
Digoxin	27 (17.76)
Loop diuretic	97 (63.82)
Amiodarone	16 (10.53)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker/neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

a majority. There were only nine patients (5.92%) who had cardiovascular death. The most common cause of death was an infection. Sixteen patients had severe sepsis resulting in death. Heart failure was the contributing cause of all cardiovascular death. The event-free form cardiovascular death was 97.2%, 94.4%, and 76.1% at 1, 5, and 10 years, respectively. The Kaplan-Meier curve for the composited efficacy outcomes, heart failure hospitalization, death from any cause, and cardiovascular death was depicted in Figure 1. Patients with ischemic cardiomyopathy had significantly worse outcomes in terms of death from any cause, with a hazard ratio of 2.03 (95% CI 1.06–3.88, *p*-value .03), but not with a composite of death or heart failure hospitalization, heart failure hospitalization, and cardiovascular death with a hazard ratio of 1.40 (95% CI 0.87–2.23, *p*-value .166), 1.24 (95% CI 0.67–2.20, *p*-value .464), and 2.24 (95% CI 0.70–7.17, *p*-value .17), respectively.

3.4 | Left ventricular reverse remodeling as responders

One hundred eight patients (71.05%) had follow-up echocardiography at the mean of 36 months (36.6 ± 29.71 months, range from 57 days to 3496 days) after CRT implantation. Seventy-seven (71.30%) patients were responders that met either criterion of a decrease in LVESV of ≥15% and/or an absolute increase of >5% of LVEF. The change in echocardiographic parameters was summarized in Figure 2. The LVEF was increased 16.17 ± 13.46% in responders but decreased 4.35 ± 5.67% in non-responders. The LVESV was decreased 38.44 ± 29.92% in responders but increased 12.62 ± 24.30% in non-responders. Death or heart failure hospitalization occurred in 26 of 77 patients in responders (24.07%) and 21 in 31 patients in non-responders (67.74%) [HR: 0.43, 95% CI: 0.24–0.78]. These outcomes included 12 deaths from any cause (15.58%) and 21 heart failure hospitalizations (22.27%) in responders, but 14 deaths from any cause (45.16%) and 17 heart failure hospitalizations (54.84%) in non-responders. The hazard ratio of 0.29 indicates that

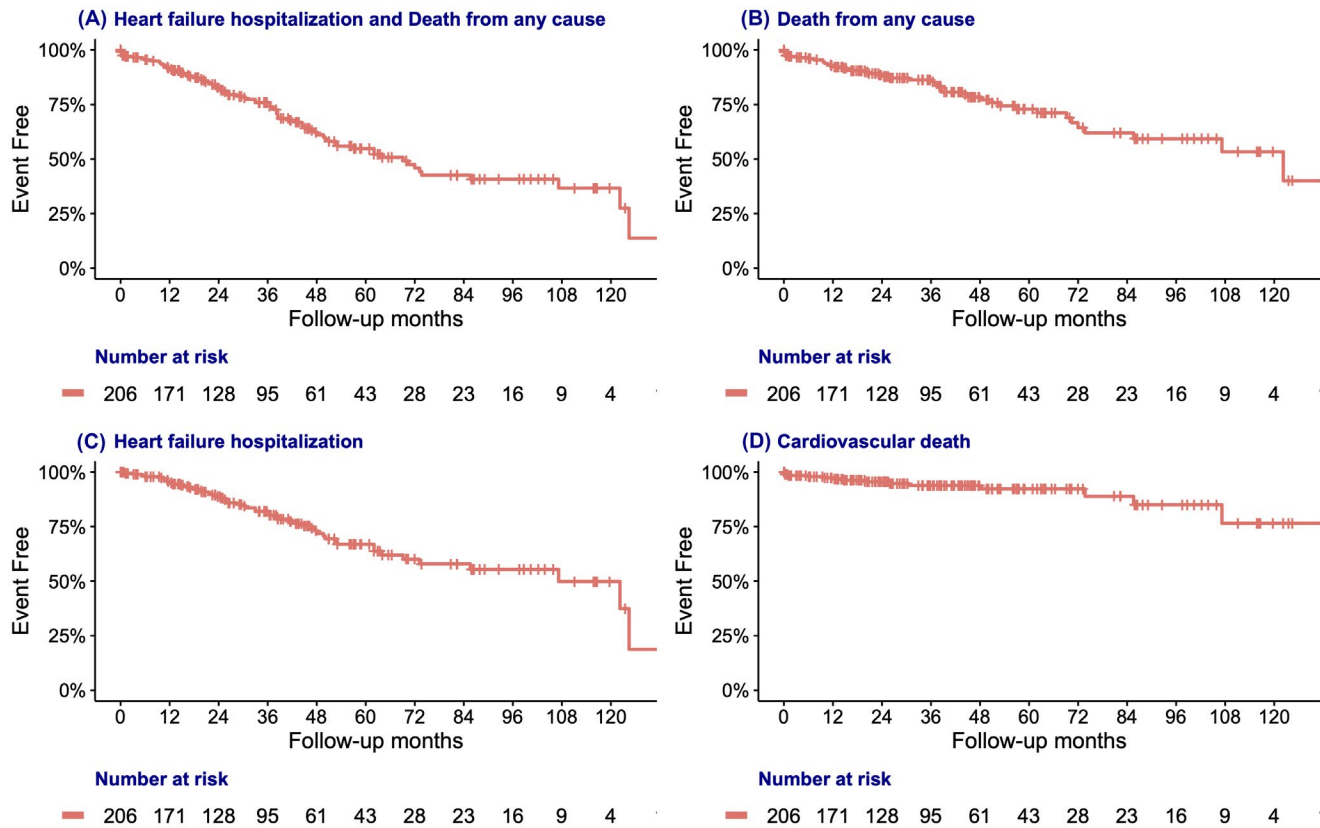


FIGURE 1 The Kaplan-Meier curves for survival free of the (A) primary outcomes, (B) death from any cause, (C) heart failure hospitalization, and (D) cardiovascular death in all patients

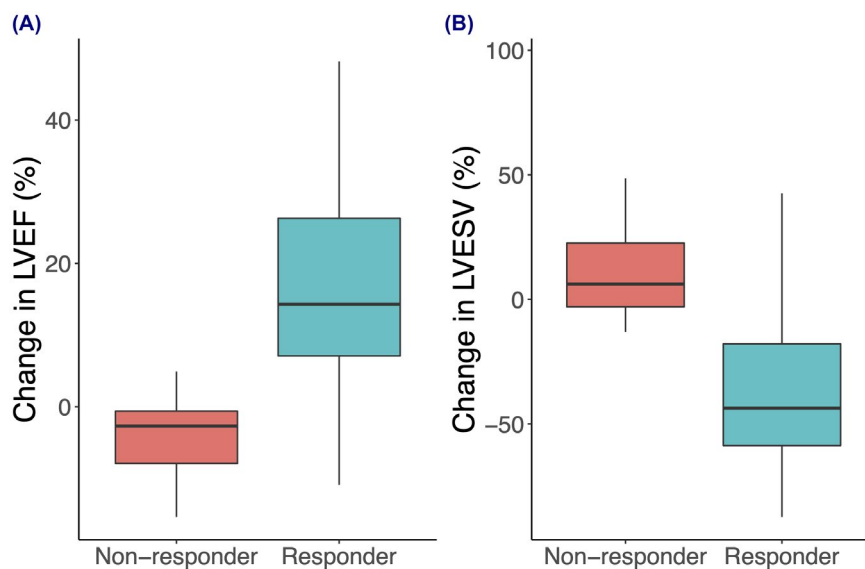


FIGURE 2 Echocardiographic change in LVEF and LVESV in responders and non-responders

there was a 71% reduction in the risk of death from any cause (95% CI 0.13–0.64, p -value .002), and the hazard ratio of 0.42 also indicates that there was a 58% reduction in the risk of heart failure hospitalization (95% CI 0.22–0.81, p -value .01) among responders. The risk of death from cardiovascular causes in responders is likewise lower, demonstrated by the hazard ratio of 0.09 (95% CI 0.02–0.47, p -value .004). Kaplan-Meier estimates of event-free outcomes

comparing between responders and non-responders are shown in Figure 3. The response rate in patients with ischemic cardiomyopathy showed a lower response trend. Nevertheless, it was not statistically significant compared to non-ischemic cardiomyopathy, with a hazard ratio of 0.66 (95% CI 0.42–1.05, p -value .08).

To define the predictor of responders, we analyzed data using univariate analysis. Digitalis use was the only statistically significant

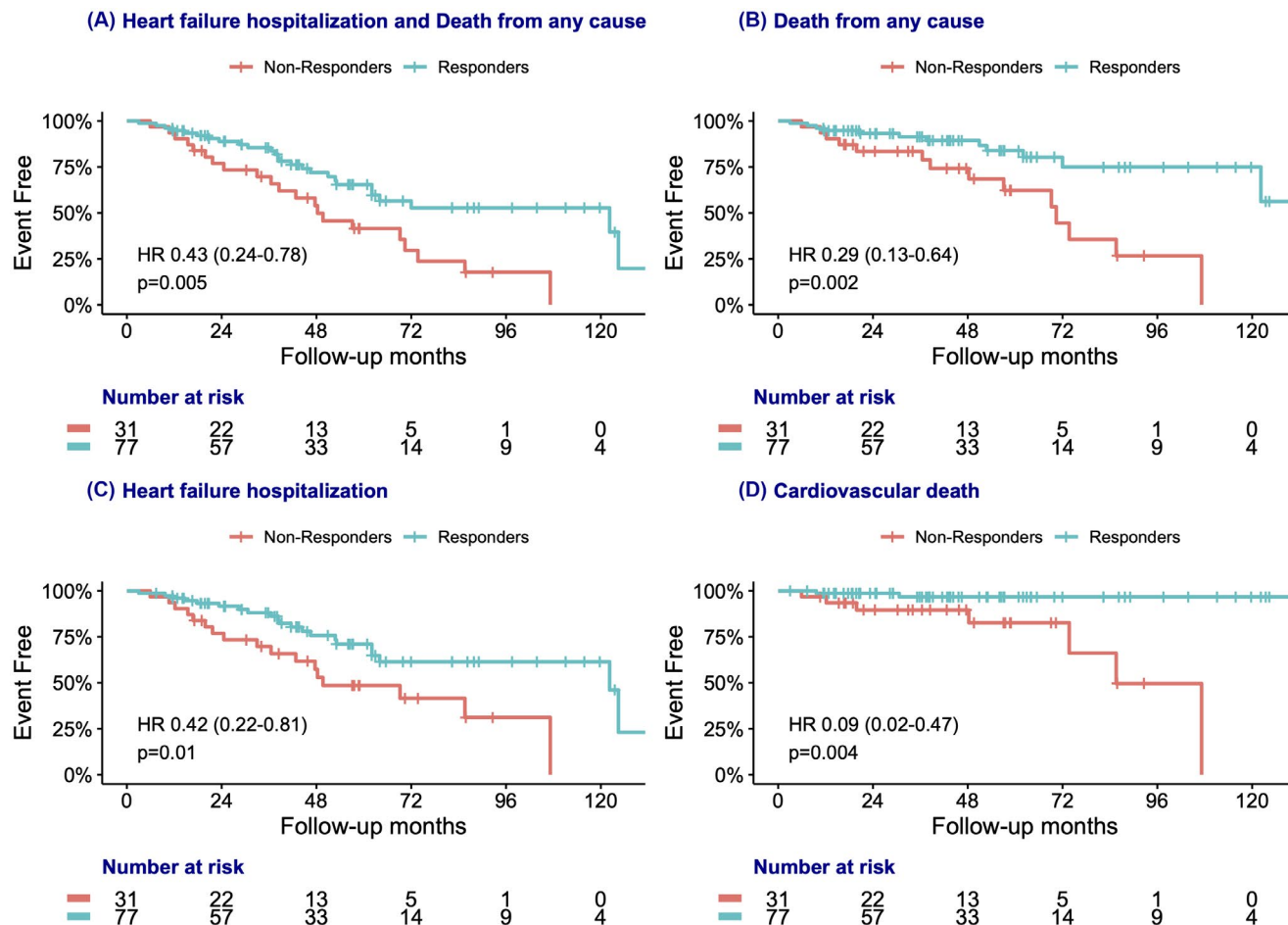


FIGURE 3 The Kaplan–Meier curves for survival free of the (A) primary outcomes, (B) death from any cause, (C) heart failure hospitalization, and (D) cardiovascular death among responders and non-responders

TABLE 3 CRT-related complications

Complication, n (%)	All patients (n = 152)
LV lead dislodgement	5 (3.29)
Phrenic nerve stimulation	2 (1.32)
Pocket infection	2 (1.32)
CS dissection	1 (0.66)
Pericardial effusion	1 (0.66)
Pneumothorax	1 (0.66)

Abbreviations: CS, coronary sinus; LV, left ventricular.

predictor for predicting a responder with a hazard ratio of 0.44 (95% CI 0.21–0.92, p -value .03). However, there was no significant predictor observed after multivariate analysis.

We found no outcome difference in patients who had no follow-up echocardiography. The composited efficacy outcomes, free from heart failure hospitalization and death from any cause, were 88.9% at one year and 49.0% at 5 years. Overall survival was 90.7% at 1 year and 62.8% at 5 years. Overall heart failure hospitalization was 96.2% at 1 year and 76.5% at 5 years. The event-free from cardiovascular death was 96.6% at 1 year and 96.6% at 5 years.

3.5 | Safety outcomes

CRT-related complications were found in 12 patients (7.89%). The most common complication was lead LV lead dislodgement which was found in 5 patients (3.29%). Table 3 demonstrates the overall complications of all patients.

3.6 | Defibrillator therapies

In all 137 patients with CRT defibrillator implantation, 17 patients (12.5%) experienced appropriate ventricular tachyarrhythmia therapies. Ten patients had sustained VT, which was terminated by anti-tachycardia pacing in eight patients and by defibrillation in two patients. Seven patients had VF, which all successfully terminated by defibrillation. Two patients received inappropriate defibrillation because of atrial tachyarrhythmias.

3.7 | Predictors of outcomes

The univariate and multivariate predictors of efficacy outcomes were summarized in Table 4. There was no difference in the

results according to patients' gender. The etiology of heart failure, using the defibrillator, diabetes, hypertension, and persistent AF/AFL appeared to be not associated with outcomes. Even patients' electrocardiographic characteristics, including QRS duration of 120–129 ms and non-LBBB pattern, were not associated with worsening effects. Older age (>60 years), impaired renal function (eGFR <60 ml/min/1.73 m²), and low MAP (<70 mmHg) were appeared to be associated with worse consequences. Unadjusted Kaplan-Meier curve for efficacy outcomes, stratified by these three predictors, was depicted in Figure 3. After a multivariate Cox-proportion hazard model analysis, there were only impaired renal function and low MAP were more likely to have worse outcomes. The hazard ratio was 1.82 with a 95% confidence interval of 1.04–3.20 for impaired

renal impairment and 5.99 with a 95% confidence interval of 1.36–26.33 for low MAP. The unadjusted Kaplan-Meier curves demonstrating the predictors for survival free from the efficacy outcomes are shown in Figure 4.

4 | DISCUSSION

CRT implantation is a beneficial adjunctive to pharmacological therapy in patients with heart failure. CRT is also one of the crucial treatments for improving patients' symptoms, reducing morbidity, and reducing mortality.⁸ Therefore, it was recommended in heart failure patients who met CRT implantation indications.

TABLE 4 Univariate and multivariate predictors of the primary outcomes

Variable	Univariate model		Multivariate model	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
CRT-D	1.26 (0.56–2.79)	0.58		
Male	1.65 (0.83–3.27)	0.15		
Age ≥60 years	2.01 (1.04–3.90)	0.03*	1.59 (0.80–3.17)	0.19
ICM	1.43 (0.82–2.51)	0.21		
Preexisting PPM	1.31 (0.62–2.77)	0.49		
QRSd ≥130 ms	0.87 (0.49–1.56)	0.64		
LBBB	0.65 (0.29–1.45)	0.29		
AF/AFL	1.53 (0.80–2.90)	0.20		
GFR <60 ml/min/1.73 m ²	1.91 (1.12–3.24)	0.02*	1.82 (1.04–3.20)	0.04*
MAP <70 mmHg	4.98 (1.19–20.82)	0.03*	5.99 (1.36–26.33)	0.02*
Diabetes	1.61 (0.95–2.72)	0.08		
Hypertension	0.66 (0.39–1.12)	0.12		
ACEI/ARB/ARNI use	0.78 (0.46–1.33)	0.37		
ACEI/ARB/ARNI ≥50% of targeted dose	0.49 (0.22–1.08)	0.08		
Beta-blocker use	0.86 (0.50–1.47)	0.58		
Beta-blocker ≥50% of targeted dose	0.7 (0.35–1.39)	0.31		
MRA use	1.12 (0.67–1.88)	0.67		
MRA ≥50% of targeted dose	1.26 (0.69–2.3)	0.46		
Digoxin use	1.02 (0.54–1.94)	0.94		
Loop diuretic use	1.17 (0.68–2.02)	0.57		
Amiodarone use	1.61 (0.69–3.79)	0.27		
LVESV >60 ml	2.04 (0.28–14.98)	0.48		
LA diameter >50 mm	1.74 (0.89–3.38)	0.10		
Severe MR	3.57 (0.46–27.52)	0.22		
Non-apical LV lead placement	1.09 (0.49–2.40)	0.83		

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker/neprilysin inhibitor; CRT-D, cardiac resynchronization therapy defibrillator; GFR, glomerular filtration rate; ICM, ischemic cardiomyopathy; LA, left atrial; LBBB, left bundle branch block; LV, left ventricular; LVESV, left ventricular end systolic volume; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; PPM, permanent pacemaker; QRSd, QRS duration.

*Indicates *P* < 0.05.

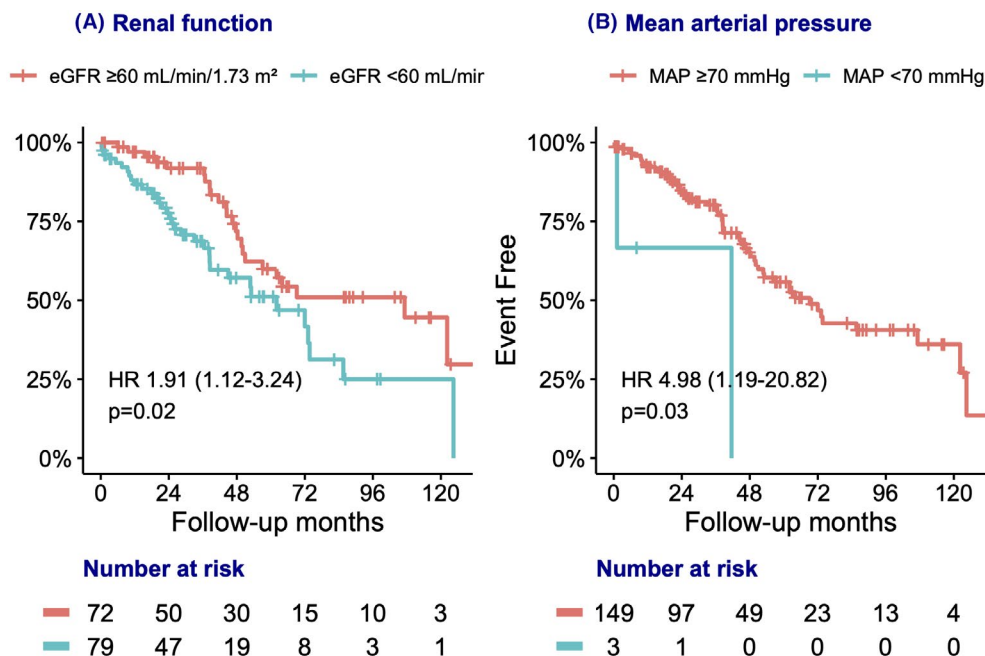


FIGURE 4 The unadjusted Kaplan-Meier curves comparing (A) renal function, and (B) mean arterial pressure as the predictors for survival free from the efficacy outcomes (heart failure hospitalization or death from any cause)

In our 11 years of experience with CRT implantation, nearly half of patients were non-ischemic cardiomyopathy. The LV function was quite severe, with an average LVEF of 22%. The parameters for ventricular dyssynchrony were apparent. Most of the patients' electrocardiography were LBBB patterns with an average QRS duration of 147 ms. These fit the latest guidelines' recommendation and met some of the favorable predictors for being CRT responders.¹⁴

The patients with ischemic cardiomyopathy were included around 55%–70% in various randomized controlled trials.¹⁵ Nearly 60% of patients who underwent CRT implantation in our center were also diagnosed with ischemic cardiomyopathy. However, there is no published data provided on the causes of heart failure in Thai patients. To date, the best available data was from the Thai ADHERE registry, which reported that 43.6% of patients who were admitted because of heart failure had severe LV systolic function, which was defined as LVEF $< 40\%$, and coronary heart disease was the cause of heart failure in 44.7%.⁶ These data may imply that nearly half of the Thai patients who presented with heart failure had an ischemic etiology, which was relatively lower than our study. Nevertheless, the Thai ADHERE registry was published in 2010, and this may be outdated. The updated registry toward the etiology of heart failure in Thailand should be reported to compare with other countries in terms of the cause of heart failure and treatment outcomes.

One of the concern issues was the lower optimal medication rate in this study. As a result of the limitation of this retrospective study, the definite cause of this problem could not find out. The lower body habitus of our patients might be an issue. So they could not tolerate the recommended doses. However, physician inertia is also one of the concerns. We should further study specific problems behind these concerns in Thai patients with heart failure.

4.1 | Efficacy of CRT

The composited efficacy outcome in our study, including free from heart failure hospitalization and death from any cause, was comparable to the previous long-term follow-up randomized controlled trials. There were 45% of patients met this composited outcome at 5-year follow-up. In the CARE-HF trial, this composited outcome occurred in 29% of patients in the CRT group with an average follow-up of 29.4 months.¹⁶ In comparison, this composited outcome was found in 33% of patients in CRT plus defibrillator arm in the RAFT trial with an average follow-up of 40 months.¹⁷ Death from any cause was found in 20% of patients in both trials, which was similar to our result. However, 14.5% of patients in the RAFT trial were cardiovascular death, but there was only 6% in our study even with the longer follow-up time of about 20 months. Some biases and limitations should be accounted for in these results, and two studies could not directly compare. Our patients were recruited years later. Hence, our study's lower rate of cardiovascular death might result from newer technology for implantation and more recent algorithm in CRT, as well as other adjunctive therapies, were applied more than in the RAFT trial. In contrast, heart failure hospitalization occurred in 18% and 16% of patients in the CARE-HF and RAFT trials, respectively. This outcome was slightly higher in our study. 33% of our patients were admitted because of heart failure at the 5-year follow-up. This result might be a consequence of multiple factors such as longer follow-up time and, most importantly, a lower rate of adequate heart failure medications.

As a result of the lack of a control group of patients with heart failure who did not receive CRT, our study could not directly imply that CRT implantation improves prognosis in such a population.

According to the result in our study, the overall survival rate is higher than the Thai ADHERE study.⁷ A trend of increasing CRT implantation in Thailand is also demonstrated in the APHRS white book.¹¹ We may assume that CRT implantation accompanied with optimal medication in selected Thai patients with heart failure could improve their prognosis. However, we should further investigate a trend of mortality and morbidity in patients with heart failure in Thailand, especially those with CRT implantation.

4.2 | Left ventricular reverse remodeling as responders and the efficacy outcomes

Non-responders after CRT implantation because of symptomatic heart failure is still a significant issue. However, after CRT implantation for decades, the definition of response to CRT varies across trials. Functional response with New York Heart Association functional classification and an echocardiographic response indicating reverse LV remodeling are primary assessments for responders. The first evaluation method could not be reliable in our medical records. Hence, we tried to collect follow-up echocardiographic results. The widely used definition for the responder is a decrease in LVESV of $\geq 15\%$ and/or an absolute increase of $> 5\%$ of LVEF was implemented to 71.05% of patients who had follow-up echocardiographic data. There were 71.30% of patients who met this criterion and were defined as responders. The CRT response rate in our center has comparable to the previous trial, the PROSPECT trial.¹⁸

CRT responders related to changes in LV remodeling and demonstrated a better prognosis, as showed in an observational study. At the mean follow-up of 22 months, patients with more LV reverse remodeling had lower death and heart failure hospitalization.¹⁹ MADIT-CRT trial also showed each 10% reduction in LV end-diastolic volume was associated with a 40% reduction in death or heart failure hospitalization.²⁰ Our analysis concerning to outcomes of the responders was corresponding to these studies. Responders had a significantly lower risk of death from any cause, heart failure hospitalization, and cardiovascular death than non-responders. Hence, our study confirmed the more favorable prognosis of the responders.

One of the most consistent results of previous studies is that patients with ischemic cardiomyopathy were less likely to have a substantial reverse LV remodeling and any hard outcomes such as death and heart failure hospitalization. PROSPECT study reported that LVESV in men with ischemic cardiomyopathy was less likely to fall by $\geq 15\%$.²¹ Our study also showed a trend but without statistically significant may be because of small subjects.

4.3 | Safety of CRT

The technologies and techniques for CRT implantation were rapidly developed. Hence, not only the success rate improved but also lowered the rate of complications. Our study demonstrated CRT-related complications of 7.89%, and the most common complication was LV

lead dislodgement. During follow-up, the LV lead dislodgement was slightly higher than a systemic review of randomized control trials, which was 1.8%, varying from 2.9 to 10.6%.²² As other studies demonstrate the higher rates of LV lead dislodgement compared to atrial or RV lead. A randomized trial comparing active and passive fixation atrial leads demonstrated no dislodgement of atrial active fixation lead. As all our patients were implanted with active fixation atrial lead and no atrial dislodgement was reported.²³ Also, the acute dislodgement rate of RV leads was low. One registry revealed these complications of 0.56% for single-chamber and 0.97% for dual-chamber implantable-cardioverter defibrillators.²⁴ Nevertheless, other serious implantation-related complications included mortality were scarce in our study, which corresponded to the previous report.¹⁰

4.4 | Predictors of outcomes after CRT implantation

The most crucial benefit of CRT is lowering the risk of death and heart failure hospitalization. In our 5-year follow-up, there were 55% of patients remained free from these outcomes. Multiple factors could affect these outcomes. Our univariate analysis demonstrated that age greater than 60 years independently predicted a greater likelihood of death and heart failure hospitalization, but not multivariate analysis—this consistent result with one national observational registry. CRT demonstrated similar efficacy in patients aged 80 years or more with both clinical outcomes and reverse cardiac remodeling.²⁵ As currently, no guidelines use age as a criterion for discouraging CRT implantation. In our study, impaired renal function and low MAP were more pronounced predictors of worsening these outcomes. The renal dysfunction was associated with more significant mortality in CRT implanted patients.²⁶ Moreover, the baseline impaired renal function level and the decline in renal function over time were also associated with the outcomes.²⁷ The MAP is one of the critical hemodynamic factors. So, the low MAP level was considered low cardiac output and may result in low tissue perfusion. This parameter should count as a predictor for worse outcomes but not for a contraindication for CRT implantation. Blood pressure can also predict patients' prognosis, as demonstrated from the MADIT-CRT trial. The patients with low (< 100 mmHg) blood pressure were associated with more death and heart failure during 1-year after CRT implantation.²⁸

Consistent with previous findings, apart from CRT responders, impaired renal function and low blood pressure were independently associated with worsening in heart failure and survival. Hence, these two factors should be considered as predictors for patients' outcomes.

4.5 | Limitations

First of all, this study was retrospective design in one single center. All the results should be interpreted with all the bias as found in this

design. The patient selection for CRT implantation was based on the standard of care according to the guidelines. Some patients were referred in for CRT implantation and then referred back to their local hospital. Hence, there was no follow-up data from these patients. Although the responder rate remained the same as the previous study, the follow-up echocardiographic examination time was broadly varied and the lower. Lastly, even the predictors of outcomes corresponding to the previous trials, the hazard ratio in our study should be interpreted with caution because of the small number of patients.

5 | CONCLUSION

CRT implantation in appropriately selected patients is one of the cornerstone treatments in patients with heart failure. Our experience treating these patients had consistent efficacy and safety with previous randomized and observational studies. Although the responder rate remained the same as in previous trials but was a strong predictor for better outcomes.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

The institutional review board of the Royal Thai Army Medical Department approved this study protocol on February, 3rd 2021 (Issue No. S001h/64_Exp).

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