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Clinical Outcomes of Complete Left Bundle Branch Block According to Strict or Conventional Definition Criteria in Patients with Normal Left Ventricular Function

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Background: Complete left bundle branch block (cLBBB) is associated with poor outcomes in patients with heart failure (HF) but appears to have minimal effects on cardiovascular (CV) mortality in relatively healthy adults. New criteria to define strict cLBBB have been proposed.

Objectives: The aim of this study was to stratify the potential risk of cLBBB according to conventional or strict criteria in patients with normal ejection fraction (EF).

Methods: Patients with cLBBB from 2010 to 2013 who underwent baseline echocardiography within 1 year and had a left ventricular ejection fraction (LVEF) > 50% were enrolled. A control group of patients without intraventricular conduction abnormalities matched for age and sex was included. Primary outcomes including CV mortality, HF admission, EF reduction of 40%, and total mortality were compared.

Results: A total of 137 patients with cLBBB were included, of whom 118 had strict cLBBB. The mean age was 72 ± 15 years and 56.2% were men. With a median follow-up of 4.3 years, normal LVEF patients with cLBBB but without a history of atrial fibrillation had a significantly higher risk of CV mortality ($p < 0.001$), EF reduction to 40% ($p < 0.001$), and admission for HF ($p < 0.001$). A similar risk of CV events was noted for the patients with conventional and strict cLBBB.

Conclusions: In patients with normal EF and without a history of atrial fibrillation, the presence of cLBBB led to a greater risk of CV mortality, HF admission and EF reduction to < 40%. Strict cLBBB carries a similar risk of CV events to conventional cLBBB.

Key Words: Ejection fraction • Left bundle branch block • Outcome

INTRODUCTION

Complete left bundle branch block (cLBBB) has a negative impact on left ventricular (LV) mechanical synchrony and may have deleterious effects on LV function. Most cases of cLBBB are noted in patients with underlying heart disease and might be associated with progressive conducting system disease. Nevertheless, cLBBB can also occur in asymptomatic patients with a structurally normal heart.[1] CLBBB appears to have minimal effects on cardiovascular (CV) morbidity and mortality in relatively healthy adults[2] and in patients with atrial fibrillation without heart failure (HF).[3] However, several reports have demonstrated that the risk of HF in patients with cLBBB is 3-5-fold higher than the risk in pa-

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tients without cLBBB,[4,5] and that it is associated with a greater risk of CV mortality.[6] CLBBB has been associated with worse outcomes in patients with congestive heart failure (CHF) and HF with reduced ejection fraction (EF) (HFrEF).[7-9] HF is a global pandemic despite significant advances in therapy.[10,11] Recent guidelines emphasize the role of prevention in HF management.[12,13] The impact of cLBBB in patients with normal left ventricular ejection fraction (LVEF) is unclear. Recently, new electrocardiographic criteria have been proposed for the diagnosis of cLBBB.[14] These criteria are stricter than the current criteria and thus increase the specificity of cLBBB diagnosis.

The impact of the new criteria of cLBBB in patients with a normal LVEF is unclear. Therefore, this study aimed to evaluate the prognostic significance of cLBBB according to conventional and strict criteria in patients with a normal LVEF.

METHODS

Study population

All patients with electrocardiograms documenting cLBBB morphology obtained at National Taiwan University Hospital (NTUH) and affiliated branches between January 2010 and December 2013 were screened for inclusion. CLBBB was defined according to conventional and strict definitions. Conventional cLBBB was defined according to the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations:[14] native QRS duration ≥ 120 ms; broad R waves in leads I, aVL, V5, or V6; absent q waves in leads I, V5, and V6; R peak time > 60 ms in leads V5 and V6 but normal in leads V1, V2, and V3, when small initial r waves can be discerned in the above leads. Strict cLBBB was defined according to the criteria proposed by Strauss et al.: QRS duration ≥ 140 ms for men and ≥ 130 ms for women, QS or rS in V1-V2, mid-QRS notching or slurring in at least 2 contiguous leads (V1, V2, V5, V6, I, and aVL).[13] Patients > 20 years old with a diagnosis of cLBBB were cross-matched using the NTUH echocardiography database to search for patients with an LVEF of > 50% within 1 year of the index electrocardiographic cLBBB diagnosis. Patients without a baseline transthoracic echocardiogram or without regular follow-up data until June 30, 2017 at the outpatient clinic were excluded. Patients with echocardiographic reports with baseline EF ≤ 50%, LV hypertrophy or moderate or more severe aortic stenosis were also excluded. Baseline characteristics including underlying diseases [hypertension, diabetes mellitus, dyslipidemia (total cholesterol > 200 mg/dL), history of coronary heart disease, congestive HF, chronic obstructive pulmonary disease, chronic kidney disease, atrial fibrillation (AF), cerebral vascular accidents, and malignancy], and cardiovascular medication use [β-blocker, angiotensin converting enzyme inhibitor (ACEI), angiotensin-II receptor blocker (ARB), spironolactone and anti-arrhythmic agents] were reviewed from medical records and charts. LVEF was measured using the biplane method of disks (modified Simpson's method). Images were obtained using a Philips iE33 system (Philips Medical Systems, Andover, MA, USA). All echocardiography measurements were obtained in accordance with the recommendations of the American Society of Echocardiography.[15]

Controls without cLBBB were selected from the NTUH database using random matching at a 1:2 ratio according to age, gender, normal EF, and date of baseline echocardiography. Patients with fascicular block, ventricular V pacing pacemaker rhythm, echocardiographically documented LV hypertrophy or moderate aortic stenosis were excluded from the control group. Furthermore, patients without regular follow-up data until June 30, 2017 in the outpatient clinic were also excluded. The baseline characteristics were also recorded (Figure 1).

Outcome measurements

The primary outcomes included CV mortality, HF hospitalization, and occurrence of HFrEF, which was defined as EF < 40% and total mortality. CV mortality included acute coronary syndrome, HF, or stroke. Follow-up LVEF data were obtained in both groups but a follow-up echocardiogram was not required for a patient to be included in the study, and therefore not all patients had these data. Because of the varying lengths of the echocardiographic follow-up periods, the follow-up periods were divided into two groups: 2 years and 2-5 years.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata (version 14.1; StataCorp LP). Continuous variables were expressed as the

mean ± standard deviation. Comparisons between different patient groups were performed using nonparametric tests (continuous variables) or the chi-square test (discrete variables). Cox proportional hazard models were used to compare the outcomes among the strict cLBBB, conventional cLBBB and control groups. Kaplan-Meier cumulative event rate curves were plotted to compare event rates among the three groups. To verify the effect of AF on CV mortality and HF progression, subgroup analysis was performed if the baseline characteristics were evidently different between the two groups. A two-sided p-value < 0.05 was considered to be statistically significant.

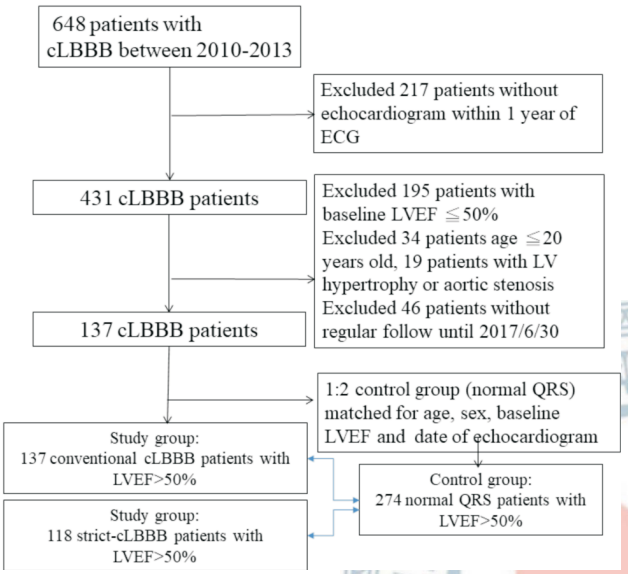


Figure 1. *Flow chart of case selection in patients with conventional cLBBB, strict-cLBBB and normal EF. Abbreviations are in Table 1, ECG, electrocardiography.*

RESULTS

Baseline clinical characteristics

Overall, 202 adults were diagnosed with conventional cLBBB and met the criterion of EF > 50% between January 2010 and December 2013. After excluding 46 patients without regular follow-up data and 19 patients with a history of aortic stenosis or LV hypertrophy, 137 patients met the criteria of conventional cLBBB and 118 patients had strict cLBBB. The mean patient age in the conventional cLBBB group was 72.0 ± 15.1 years and 60 patients (43.8%) were women. The mean LVEF was 64% (64.9 ± 8.1). In the age, sex, and baseline LVEF-matched control group, 274 patients were finally included.

There were no significant differences in clinical characteristics including a history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease and CHF, were not significantly different between the conventional cLBBB and control groups (Table 1). Similar base-

Table 1. Patients' baseline characteristics among conventional cLBBB, strict-cLBBB and control group

	Conventional cLBBB (n = 137)	Strict cLBBB (n = 118)	Control (n = 274)	p value*	p value#
Age, years	72.0 ± 15.1	72.5 ± 14.6	71.7 ± 14.7	0.82	0.59
Male sex (%)	77 (56.2)	68 (57.6)	154 (56.2)	1.00	0.7
Hypertension (%)	101 (73.7)	89 (75.4)	184 (67.2)	0.17	0.22
DM (%)	43 (31.4)	40 (33.9)	65 (23.7)	0.09	0.06
Dyslipidemia (%)	38 (27.7)	31 (26.3)	93 (33.9)	0.20	0.29
CAD (%)	35 (25.6)	32 (27.1)	56 (20.4)	0.24	0.21
AF history (%)	34 (24.8)	30 (25.4)	46 (16.8)	0.05	0.04
CKD (%)	21 (15.3)	18 (15.3)	26 (9.5)	0.08	0.21
CVA (%)	12 (8.8)	10 (8.5)	25 (9.1)	0.90	0.95
CHF (%)	21 (15.3)	18 (15.3)	31 (11.3)	0.25	0.51
Medication use					
α-blocker (%)	8 (5.8)	8 (6.8)	19 (6.9)	0.67	0.50
b-blocker (%)	52 (38.0)	45 (38.1)	100 (36.5)	0.77	0.95
CCB (%)	49 (35.8)	62 (52.5)	128 (46.7)	0.40	0.49
ACEi/ARB (%)	70 (51.1)	62 (52.5)	128 (46.7)	0.40	0.49
Echocardiographic finding					
LVEF (%)	64.9 ± 8.1	64.6 ± 8.3	67.2 ± 7.5	0.05	0.06

* p value: conventional cLBBB vs. control group. # p value: strict-cLBBB vs. control group.
Values are shown as a mean (standard deviation) or number (percent).
ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; AF, atrial fibrillation; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease; cLBBB, complete left bundle branch block; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension.

line characteristics were noted in the strict cLBBB group.

Clinical outcomes between the cLBBB and control groups in patients with a normal LVEF

At a median follow-up of 4.3 years, 17 patients with strict cLBBB, 14 patients with conventional cLBBB and normal EF died from a CV-related cause. Only six patients had CV-related mortality in the control group. The incidence rate of CV mortality was 28.1 per 1000 person-years in the strict cLBBB group, 26.0 per 1000 person-years in the conventional cLBBB group, and 5.0 per 1000 person-years in the control group. Patients in the strict cLBBB and conventional cLBBB groups had greater risks of CV mortality (p = 0.001). Moreover, the incidence rates of admissions for HF were 42.4 per 1000 person-years in the conventional cLBBB group and 49.6 per 1000 person-years in the strict cLBBB group, which were significantly higher than in the control group (both p < 0.001). Thirty-one patients (26%) in the strict cLBBB group, 34 patients (25%) in the conventional cLBBB group, and 49 patients in the control group died. There were no significant differences in total mortality rate between the control group and strict cLBBB (p = 0.86) and conventional (p = 0.16) groups. cLBBB was associated with a worse clinical outcome even after adjusting for age, hypertension, diabetes mellitus and dyslipidemia (Table 2). Kaplan-Meier cumulative event rate curves for the conventional, strict cLBBB and control groups showed that both conventional cLBBB and strict cLBBB groups had greater risks of CV-related mortality and HF admission, and that the curve started differently early in the first 2 years and then continuously reduced (all p < 0.001) (Figure 2). However, the strict cLBBB group did not have a greater risk of CV mortality and HF admission than the conventional cLBBB group.

Reduced LVEF

In the conventional cLBBB group, the 2-year and 5-year follow-up risks of LVEF reduction > 10% were 26% and 35%, respectively. In the patients with strict LBBB, 29% had a > 10% LVEF reduction after 2 years of follow-up, and 36% had a > 10% LVEF reduction after 5 years of follow-up (Table 3). There were significant reductions in LVEF between the control group and the conventional cLBBB and strict-LBBB groups after 2 years and 2-5 years follow-up echocardiography (p = 0.03 and p = 0.01 after 2 years, p = 0.001 after 2-5 years follow-up, respectively) (Figure 3).

Table 2. Cox proportional hazard ratio of event incidence rates among conventional LBBB, strict-LBBB and control group

	Event	Population	Person-year	Cumulative incidence	Incidence rate/10^3 person-years	HR	Crude 95% CI	p value	HR	Model 1 95% CI	p value
CV mortality											
Control	6	274	1163.4	0.02	5.2	1.00	-		1.00	-	
Conventional cLBBB	14	137	537.9	0.10	26.0	4.98	1.91-12.95	0.001	4.63	1.77-12.10	0.002
Strict-cLBBB	13	118	462.4	0.11	28.1	5.37	2.04-14.13	0.001	4.88	1.84-12.93	0.001
LVEF reduced to < 40%											
Control	2	158	722.8	0.01	2.8	1.00	-		1.00	-	
Conventional cLBBB	18	88	333.7	0.20	53.9	20.45	4.74-88.19	< 0.001	20.30	4.69-87.80	< 0.001
Strict-cLBBB	17	76	290.4	0.22	58.5	22.14	5.11-95.89	< 0.001	21.69	4.98-94.44	< 0.001
Heart failure admission											
Control	11	274	1151.1	0.04	9.6	1.00	-		1.00	-	
Conventional cLBBB	22	137	519.0	0.16	42.4	4.50	2.18-9.28	< 0.001	4.26	2.06-8.82	< 0.001
Strict-cLBBB	22	118	443.5	0.19	49.6	5.27	2.56-10.88	< 0.001	4.95	2.39-10.28	< 0.001
Total mortality											
Control	49	274	1163.4	0.18	42.1	1.00	-		1.00	-	
Conventional cLBBB	34	137	537.9	0.25	63.2	1.47	0.95-2.28	0.08	1.37	0.88-2.14	0.16
Strict-cLBBB	31	118	462.4	0.26	67.0	1.56	0.99-2.44	0.05	1.41	0.34-3.58	0.86

CI, confidence interval; cLBBB, complete left bundle branch block; CV, cardiovascular; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Model 1 adjusted for age, gender, hypertension, DM, and hyperlipidemia.

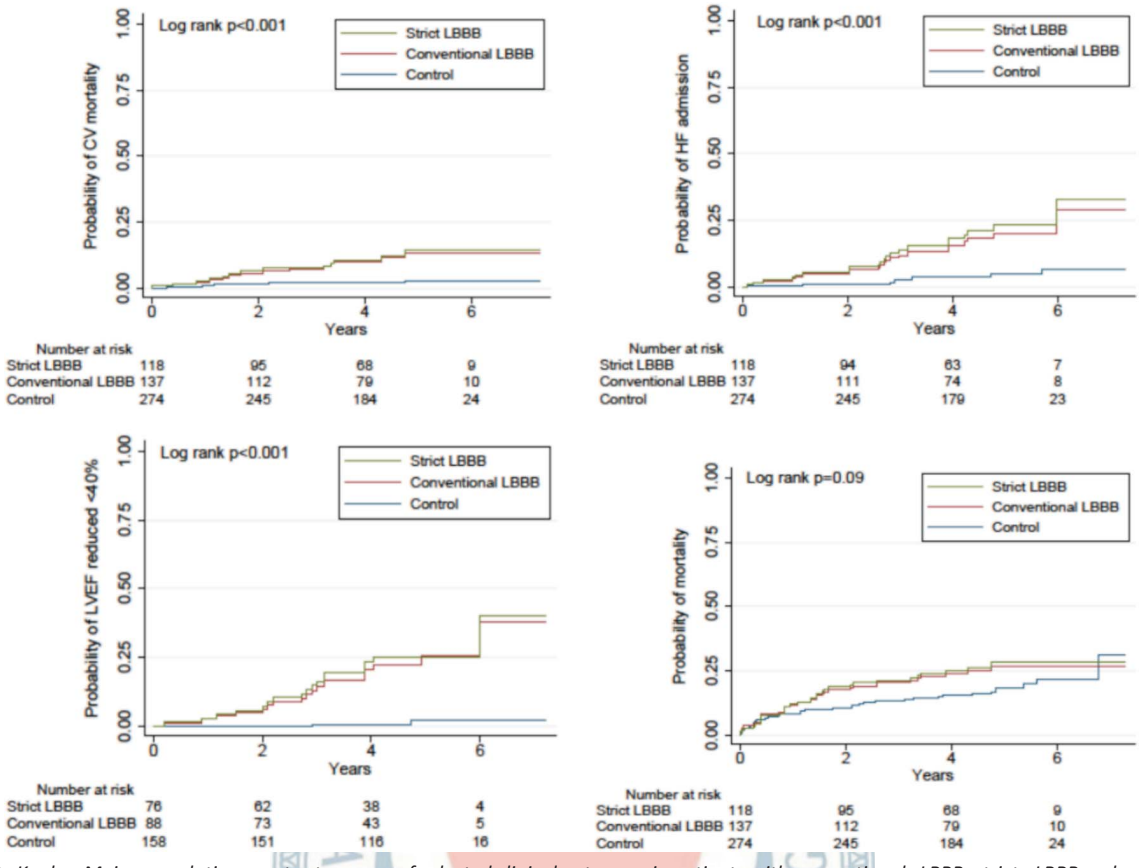


Figure 2. *Kaplan-Meier cumulative event rate curves of selected clinical outcomes in patients with conventional cLBBB, strict-cLBBB and normal EF.*

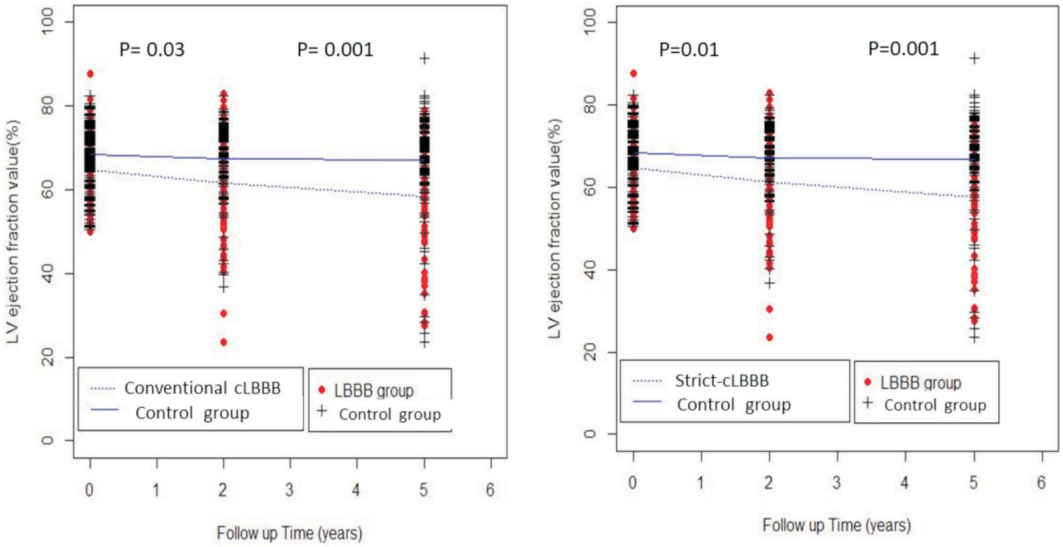
Table 3. Serial LVEF change among conventional cLBBB, strict-cLBBB and control group

	2 yrs					2-5 yrs				
	Conventional cLBBB (n = 79), strict-cLBBB (n = 71) Control (n = 103)					Conventional cLBBB (n = 65), strict-cLBBB (n = 58) Control (n = 108)				
	Increase	0%-5% decrease	5%-10% decrease	> 10% decrease	p value	Increase	0%-5% decrease	5%-10% decrease	> 10% decrease	p value
Control	53 (51.5)	29 (28.2)	13 (12.6)	8 (7.8)		48 (44.4)	32 (29.6)	18 (16.7)	10 (9.3)	
Conventional cLBBB	30 (38.0)	21 (26.6)	7 (8.9)	21 (26.6)	0.006	22 (33.9)	14 (21.5)	6 (9.2)	23 (35.4)	< 0.001
Strict-cLBBB	26 (36.6)	19 (26.8)	5 (7.0)	21 (29.6)	0.002	19 (32.8)	13 (22.4)	5 (8.6)	21 (36.2)	< 0.001

CLBBB, complete left bundle branch block.
Values are shown as number (percent).

Subgroup analysis in the AF history group vs. non-AF history group

There was no significant difference in a history of AF between the cLBBB and normal EF groups. To assess the contribution of AF to the primary endpoint, we performed subgroup analysis. Subgroup analysis showed that in the patients without a history of AF, those with cLBBB and normal EF still had a higher rate of CV mortality even after adjusting for age, gender, hypertension, diabetes mellitus, and hyperlipidemia [hazard ratio (HR) = 3.99, 95% confidence interval (CI) = 1.18-13.45, p = 0.03], EF reduction to < 40% (HR = 28.59, 95% CI = 3.69-221.65, p = 0.001), and HF admission (HR = 4.96, 95% CI = 1.87-13.13, p = 0.001). In patients with a history of AF, those with cLBBB with normal EF showed a non-significant trend for CV mortality and HF admission, but still had a significantly higher risk of EF < 40% (HR = 8.75, 95% CI = 1.01-75.87, p = 0.049) (Table 4).



(A) Conventional cLBBB vs. control group (B) Strict-cLBBB vs. control group

Figure 3. *Serial EF change among conventional cLBBB, strict-cLBBB and control group.*

Table 4. Subgroup analysis and Cox proportional hazard ratio of event rates between conventional cLBBB and control group

	AF history	Event	Population	Person-year	Cumulative incidence	Incidence density/10^3 person-year	HR	Crude 95% CI	p value	HR	Model 1 95% CI	p value
CV mortality												
Control	AF (-)	4	228	979.7	0.02	4.1	1.00	-		1.00	-	
cLBBB	AF (-)	8	103	413.5	0.08	19.3	4.67	1.41-15.50	0.01	3.99	1.18-13.45	0.03
Control	AF (+)	2	46	183.7	0.04	10.9	1.00	-		1.00	-	
cLBBB	AF (+)	6	34	124.4	0.18	48.2	4.32	0.87-21.42	0.07	4.38	0.86-22.23	0.07
LVEF reduced to < 40%												
Control	AF (-)	1	127	579.6	0.01	1.7	1.00	-		1.00	-	
cLBBB	AF (-)	12	64	247.4	0.19	48.5	29.41	3.82-226.32	0.001	28.59	3.69-221.65	0.001
Control	AF (+)	1	31	143.2	0.03	7.0	1.00	-		1.00	-	
cLBBB	AF (+)	6	24	86.3	0.25	69.5	9.65	1.16-80.58	0.04	8.75	1.01-75.87	0.049
Heart failure admission												
Control	AF (-)	6	228	971.0	0.03	6.2	1.00	-		1.00	-	
cLBBB	AF (-)	13	103	401.7	0.13	32.4	5.32	2.02-14.00	< 0.001	4.96	1.87-13.13	0.001
Control	AF (+)	5	46	180.0	0.11	27.8	1.00	-		1.00	-	
cLBBB	AF (+)	9	34	117.3	0.26	76.8	2.51	0.83-7.55	0.10	2.79	0.91-8.60	0.07
Total mortality												
Control	AF (-)	36	228	979.7	0.16	36.7	1.00	-		1.00	-	
cLBBB	AF (-)	23	103	413.5	0.22	55.6	1.48	0.88-2.50	0.14	1.33	0.78-2.25	0.29
Control	AF (+)	13	46	183.7	0.28	70.8	1.00	-		1.00	-	
cLBBB	AF (+)	11	34	124.4	0.32	88.4	1.30	0.57-2.95	0.53	1.33	0.58-3.07	0.51

AF, atrial fibrillation; CI, confidence interval; cLBBB, complete left bundle branch block; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Model 1 adjusted for age, gender, hypertension, DM, and hyperlipidemia.

DISCUSSION

Clinical outcomes and survival among the conventional cLBBB, strict-cLBBB and control groups

cLBBB is thought to be a natural degenerative process, which provides independent prognostic information in patients with HF, angina pectoris, and myocardial infarction.[7,9,17,18] cLBBB has been associated with a higher risk of HF over long-term follow-up in patients with impaired LV systolic function.[19] In cLBBB patients

with preserved LVEF, the treatment strategy is usually determined by the concomitant CV disease.[20] The present study demonstrated that in the presence of cLBBB, patients with both conventional and strict cLBBB had the greatest risk of CV mortality, HF admission, and EF drop to < 40%. Thirty-four (25%) patients with cLBBB died and 22 patients (16%) were admitted to our hospital for HF during a median follow-up period of 4.3 years, highlighting the importance of preventing HF in patients with cLBBB even with a normal EF. More importantly, differences in CV mortality, HF admission, and EF < 40% were noted early in the second year and persisted throughout the follow-up period, further suggesting the importance of regular follow-up for HF development.

Previous endocardial mapping studies have demonstrated that approximately one-third of patients diagnosed with cLBBB may actually have delayed LV conduction due to underlying hypertrophy or left anterior fascicular block.[14,21] In our data, only 19 patients (13.9%) who were diagnosed as having conventional cLBBB did not meet the criteria of strict cLBBB.[14] The relatively lower percentage of non-strict cLBBB may be due to relatively normal heart condition (normal LVEF, no history of aortic stenosis and LV hypertrophy) or just due to ethnic causes.

cLBBB and LVEF reduction

The severity of EF reduction at both 2-year and 2-5-year follow-up was significantly greater in both the conventional and strict cLBBB groups than in the control group for the patients who underwent follow-up echocardiography. The interrupted electrical activity caused by cLBBB may have unfavorable effects on LV mechanical synchrony, LV dilatation, and LV remodeling, eventually leading to a reduction in LVEF. A reduction in LVEF affects the quality of life and survival and is associated with a dramatic increase in economic burden on society/healthcare systems. Therefore, regular follow-up echocardiography may be beneficial in these patients. Future prospective studies should clarify the benefits of these approaches.

Clinical outcomes in the conventional cLBBB patients with or without a history of AF

In the present study, the cLBBB group had a higher rate of a history of AF. AF is considered to be both a cause and a consequence of HF.[22,23] In patients with CHF, a combination of electrical disturbances (cLBBB and AF) has been associated with a significant increase in mortality.[24]

In this study, we found that after excluding patients with a history of AF, those without AF in the conventional cLBBB group still potentially had a greater risk of CV mortality than the control group. Consistent with a previous report, we found the same result of a non-significant difference in CV mortality between the conventional cLBBB group and control group in patients with a history of AF.[3] This might be due to the relatively small number of cases. There are currently no specific prognostic markers for selecting patients at higher risk of LV function deterioration and developing clinically significant HF. However, some studies have reported LV function deterioration in cLBBB patients. Therefore, regular monitoring of LV function and further investigations in patients with cLBBB and normal LV function are required.

Limitations

This retrospective, single-center study has several limitations. First, patients without regular follow-up data in our hospitals were excluded. However, the aim of this study was to compare age- and sex-matched controls in the same hospitals, and bias may also have existed in the control group. Second, clinical outcomes such as HF admission were not always recorded, which may have led to underestimation of event rates.

CONCLUSION

Patients with conventional or strict cLBBB and normal LVEF have significantly worse clinical outcomes than patients with a similar LVEF but no cLBBB. New criteria of strict cLBBB did not show a greater risk than conventional cLBBB.

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CONFLICTS OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

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