

Guideline-Directed Medical Therapy, Clinical Outcomes, and Quality of Life in Heart Failure: Insights from a Multicenter International Consortium for Health Outcomes Measurement-Based Brazilian Cohort

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Abstract

Background: Real-world evidence integrating clinical outcomes and patient-reported measures in heart failure with reduced ejection fraction (HFrEF) remains scarce in middle-income countries. Standardized outcome measurement frameworks may enable more consistent evaluation of care quality and treatment effectiveness.

Objective: To assess the association of guideline-directed medical therapy (GDMT) with clinical outcomes and patient-reported quality of life (QoL) in patients with HFrEF within 1 year after index hospitalization, using the International Consortium for Health Outcomes Measurement standard set in a multicenter Brazilian cohort.

Methods: This prospective cohort study included adults hospitalized for decompensated HFrEF (ejection fraction $\leq 40\%$) across six private tertiary hospitals in Brazil. Clinical and patient-reported outcomes were collected using standardized instruments, including the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) and the Patient Health Questionnaire-2 (PHQ-2).

Results: A total of 2,375 patients were included (mean age, 75.9 ± 13.6 years; 69% male). During a median follow-up of 369 days, 26.1% died and 34.6% experienced heart failure-related rehospitalization. Older age was associated with higher risks of mortality and rehospitalization ($p \leq 0.003$). Use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors was associated with lower mortality (hazard ratio [HR], 0.58; $p = 0.001$), whereas beta-blockers showed a strong protective effect (HR, 0.40; $p < 0.001$). Mineralocorticoid receptor antagonists were associated with lower rehospitalization rates (HR, 0.79; $p = 0.032$). GDMT was associated with higher KCCQ-12 scores throughout follow-up ($p < 0.05$). Women and patients with recurrent rehospitalizations reported lower QoL ($p < 0.02$). PHQ-2 scores remained low and stable over time.

Conclusion: Standardized outcome measurement is feasible in real-world HFrEF care. GDMT was associated with improved survival and QoL, supporting more equitable and value-based management of HFrEF.

Keywords: Systolic Heart Failure; Patient Reported Outcome Measures; Quality of Life.

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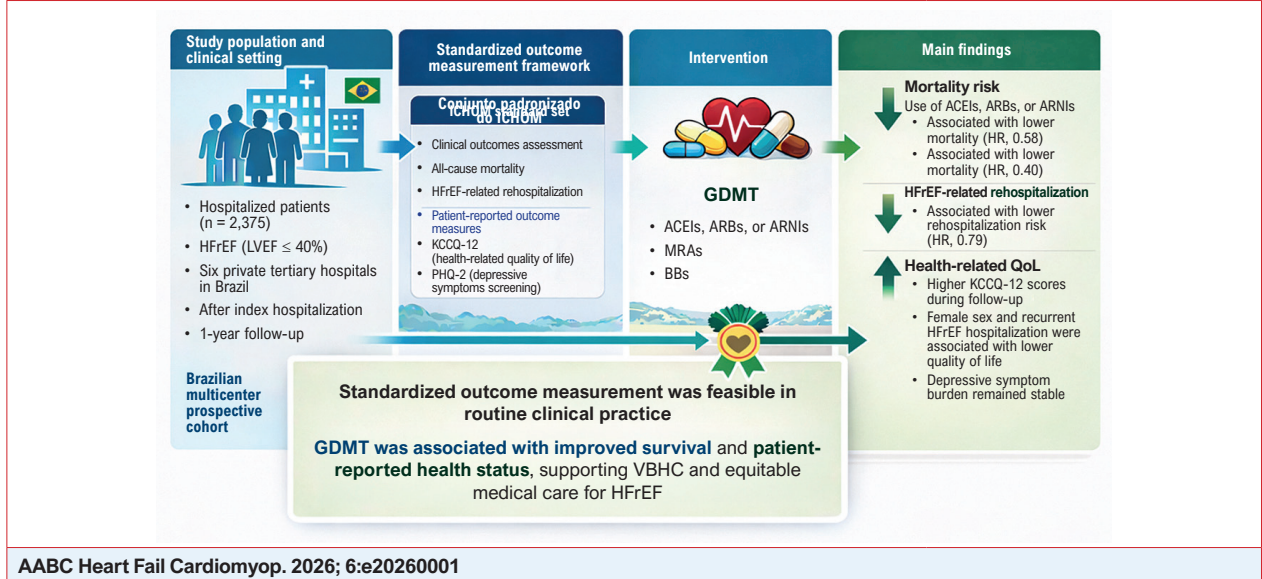
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Central Illustration: Guideline-Directed Medical Therapy, Clinical Outcomes, and Quality of Life in Heart Failure: Insights from a Multicenter International Consortium for Health Outcomes Measurement-Based Brazilian Cohort



ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BB: beta-blocker; GDMT: guideline-directed medical therapy; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; ICHOM: International Consortium for Health Outcomes Measurement; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; PHQ-2: Patient Health Questionnaire-2; QoL: quality of life; VBHC: value-based health care.

Introduction

Measuring clinical outcomes is essential for demonstrating process improvement, assessing therapeutic value, and enhancing health care efficiency. Its feasibility and impact in driving health care innovation are well established.¹

However, hospitals often measure outcomes that are easily captured within isolated interventions rather than those that matter most to patients. In addition, results are frequently assessed in a fragmented manner instead of across the entire continuum of care, where value is ultimately generated.²

Value assessment should incorporate long-term outcomes, including recovery, quality of life (QoL), functional status, and mental well-being, recognizing that their relevance may vary across populations and individuals.³ Within a value-based health care (VBHC) framework, providers may distinguish themselves by delivering superior outcomes for specific patient populations.

The International Consortium for Health Outcomes Measurement (ICHOM) promotes VBHC through a standardized and freely available methodology for measuring meaningful outcomes across different health conditions.⁴

In 2017, hospitals affiliated with the Brazilian National Association of Private Hospitals (ANAHP) launched a multicenter initiative to implement standardized outcome measurement in Brazil by locally adapting the ICHOM methodology. The primary objective was to evaluate mortality, readmission, and patient-reported QoL at 30 days,

6 months, and 1 year after index hospitalization for heart failure with reduced ejection fraction (HFrEF) between 2017 and 2023. The secondary objective was to identify clinical, demographic, and guideline-directed medical therapy (GDMT) variables associated with these outcomes.

Methods

Study design and population

This prospective, multicenter cohort study included patients hospitalized for decompensated HFrEF, defined as an ejection fraction ≤ 40% measured by echocardiography using Simpson's method at hospital admission.

Inclusion criteria were age ≥ 18 years, B-type natriuretic peptide ≥ 100 pg/mL or N-terminal pro-B-type natriuretic peptide ≥ 300 pg/mL, and intravenous diuretic use within the first 24 hours after diagnosis.

Exclusion criteria were age < 18 years, cardiogenic shock or ventricular assist device before study enrollment, candidacy for heart transplantation during hospitalization, transfer to another institution, pregnancy, and receipt of palliative care.

Study governance and data collection

The study was coordinated by executive and operational committees composed of representatives from participating hospitals and ANAHP.

Data were collected through the electronic platform of the ANAHP Hospital Indicator System (SINHA),⁵ developed to monitor consolidated hospital data according to predefined schedules. Access to the platform was password protected, allowing institutions to benchmark their results against aggregated data from participating centers. Individual patient data remained locally stored at the discretion of each institution.

Data collection followed the recommendations available on the ICHOM website, and case report forms were developed based on the corresponding data dictionary, supplemented by variables considered essential by the executive committee for patient follow-up. Data validation procedures adhered to ICHOM standards.^{6,7}

Risk stratification was performed using the New York Heart Association (NYHA) functional classification and the Acute Decompensated Heart Failure National Registry (ADHERE) risk score.⁸

Patient-reported outcomes

QoL was assessed using the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) and the Patient Health Questionnaire-2 (PHQ-2).

KCCQ-12 is a self-administered, disease-specific instrument for heart failure that evaluates physical limitation, symptoms, social function, self-efficacy, and the impact of heart failure on daily life. Scores range from 0 to 100, with higher scores indicating better QoL.

PHQ-2 evaluates the frequency of depressed mood and anhedonia over the previous 2 weeks. Scores range from 0 to 6, and values > 3 suggest depressive disorder.^{9,10}

Patients were followed up at 30 days, 6 months, and 1 year after discharge. QoL questionnaires were administered through scheduled interviews conducted by email, SMS, telephone, or in-person visits.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics of the study population.

Univariate and multivariable analyses were performed. Cox proportional hazards models were constructed to identify predictors of mortality and rehospitalization, whereas multiple linear regression models were used to identify predictors of changes in QoL.

All multivariable models included baseline variables with complete data available for more than 70% of the study population (Table 1). Hazard ratios (HRs) or odds ratios, 95% CIs, and p-values were reported.

The multivariable Cox models were adjusted for hospital-level clustering using frailty models with a Gamma distribution. Post hoc analyses following linear regression models were performed using Tukey's honestly significant difference method.

Missing data were handled using listwise deletion. Variables with significant associations in bivariate analyses were entered into multivariable models using a backward stepwise selection approach, with entry and removal criteria set at 5%.

Statistical significance was defined as $p < 0.05$. All tests were two-sided. Statistical analyses were performed using R version 4.4.1.

Results

General characteristics

A total of 2,375 patients were enrolled across six private tertiary hospitals, with capacities ranging from 100 to 600 beds. The mean age of the cohort was 75.9 years.

Figure 1 displays patient flow and follow-up throughout the study. By the end of follow-up, 631 patients (26.6%) were lost to follow-up, leaving 1,744 patients (73.4%) with complete outcome data available for the primary analyses. Among these patients, 455 (26.1%) died and 603 (34.6%) experienced at least one heart failure-related rehospitalization (Figure 1).

Baseline characteristics are summarized in Table 1. The cohort comprised 69% men and 31% women. The mean follow-up duration was 367.3 ± 368 days, with a median follow-up of 369 days (interquartile range [IQR], 58-427). Mean left ventricular ejection fraction was $30.7\% \pm 6.4\%$, with a median of 31% (IQR, 26%-36%).

Regarding pharmacological therapy, 66% of patients were receiving angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), including 16% treated with angiotensin receptor-neprilysin inhibitors (ARNIs), whereas 85% were receiving beta-blockers (BBs). Contraindications were reported in 30% of patients for ACEIs, 30% for ARBs, and 22% for ARNIs.

Regarding functional status, 20% of patients were classified as NYHA functional Class II, 55% as Class III, and 24% as Class IV. According to ADHERE risk stratification, 47% were classified as Intermediate Risk 2, 22% as Intermediate Risk 1, and 3.6% as High Risk.

Table 1 also presents comparisons between patients with complete clinical outcome data and the overall cohort. Patients with available outcome data were slightly older (mean age, 77.7 vs 75.9 years; $p < 0.001$), had lower rates of BB use (82.0% vs 85.0%; $p < 0.001$), and presented higher mean serum urea levels (70.8 vs 68.5 mg/dL; $p < 0.001$).

Multivariable analysis

The results of the multivariable Cox regression analyses for 1-year mortality and rehospitalization are presented in Table 2 and Table 3.

Each additional year of age was associated with increased risks of mortality (HR, 1.02; 95% CI, 1.01-1.04; $p = 0.003$) and rehospitalization (HR, 1.01; 95% CI, 1.00-1.02; $p < 0.001$).

Use of ACEIs, ARBs, or ARNIs (HR, 0.58; 95% CI, 0.41-0.80; $p = 0.001$) and BBs (HR, 0.40; 95% CI, 0.28-0.57; $p < 0.001$) was associated with lower mortality, whereas mineralocorticoid receptor antagonists (MRAs) were associated with lower rehospitalization rates (HR, 0.79; 95% CI, 0.64-0.98; $p = 0.032$).

Use of mechanical circulatory support (MCS) devices was associated with increased mortality risk (HR, 4.58; 95%

Table 1 – Baseline characteristics of the study population

Characteristic	Overall cohort (n = 2,375)	Patients with QoL data (n = 661)	p-value	Patients with clinical outcome data (n = 1,714)	p-value
Age, years					
Mean (SD)	75.9 (13.6)	71.2 (13.1)	< 0.001	77.7 (13.4)	< 0.001
Sex, n/N (%)					
Male	1,639/2,375 (69%)	471/661 (71.3%)	0.287	1,168/1,714 (68.1%)	0.579
Female	736/2,375 (31%)	190/661 (28.7%)		546/1,714 (31.9%)	
LVEF, %					
Mean (SD)	30.7 (6.4)	30.5 (6.3)	0.472	30.8 (6.4)	0.622
ACEIs, n/N (%)					
Use	569/2,192 (26%)	183/644 (28.4%)	0.233	386/1,548 (24.9%)	0.504
Contraindicated	650/2,192 (30%)	169/644 (26.2%)		481/1,548 (31.1%)	
ARBs, n/N (%)					
Use	542/2,214 (24%)	167/640 (26.1%)	0.435	375/1,574 (23.8%)	0.670
Contraindicated	656/2,214 (30%)	172/640 (26.9%)		484/1,574 (30.7%)	
ARNIs, n/N (%)					
Use	356/2,228 (16%)	117/642 (18.2%)	0.197	239/1,586 (15.1%)	0.473
Contraindicated	491/2,228 (22%)	126/642 (19.6%)		365/1,586 (23.0%)	
BBs, n/N (%)					
Use	1,896/2,234 (85%)	596/648 (92.0%)	< 0.001	1,300/1,586 (82.0%)	0.019
Contraindicated	162/2,234 (7.3%)	26/648 (4.0%)		136/1,586 (8.6%)	
MRAs, n/N (%)					
Use	1,015/1,918 (53%)	337/580 (58.1%)	0.032	678/1,338 (50.7%)	0.220
Contraindicated	135/1,918 (7.0%)	37/580 (6.4%)		98/1,338 (7.3%)	
Cardiac devices*, n/N (%)	223/2,372 (9.4%)	74/660 (11.2%)	0.190	149/1,712 (8.7%)	0.478
MCS devices, n/N (%)	19/1,687 (1.1%)	2/485 (0.4%)	0.249	17/1,202 (1.4%)	0.605
NYHA functional class, n/N (%)					
Class I	0/1,766 (0%)	0/501 (0%)	0.646	0/1,265 (0%)	0.879
Class II	362/1,766 (20%)	110/501 (22.0%)		252/1,265 (19.9%)	
Class III	972/1,766 (55%)	277/501 (55.3%)		695/1,265 (54.9%)	
Class IV	432/1,766 (24%)	114/501 (22.8%)		318/1,265 (25.1%)	
ICU admission, n/N (%)	225/784 (29%)	65/245 (26.5%)	0.564	160/539 (29.7%)	0.744
Length of ICU stay, days					
Mean (SD)	6.2 (9.1)	5.7 (8.7)	0.438	6.4 (9.3)	0.698
Mechanical ventilation, n/N (%)	113/587 (19%)	20/139 (14.4%)	0.226	93/448 (20.8%)	0.601
Vasodilators, n/N (%)	220/1,101 (20%)	52/307 (16.9%)	0.266	168/794 (21.2%)	0.570
SBP					
Mean (SD)	127.6 (30.8)	128.2 (40.1)	0.722	127.4 (26.4)	0.824
ADHERE risk category, n/N (%)					
Low Risk	422/2,180 (19%)	130/615 (21.1%)	0.243	292/1,565 (18.7%)	0.785
Intermediate Risk 3	161/2,180 (7.4%)	60/615 (9.8%)		101/1,565 (6.5%)	

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Intermediate Risk 2	1,030/2,180 (47%)	277/615 (45.0%)	753/1,565 (48.1%)
Intermediate Risk 1	488/2,180 (22%)	126/615 (20.5%)	362/1,565 (23.1%)
High Risk	79/2,180 (3.6%)	22/615 (3.6%)	57/1,565 (3.6%)

*ICD or CRT. ACEI: angiotensin-converting enzyme inhibitor; ADHERE: Acute Decompensated Heart Failure National Registry; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BB: beta-blocker; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator; ICU: intensive care unit; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; QoL: quality of life; SBP: systolic blood pressure; SD: standard deviation.

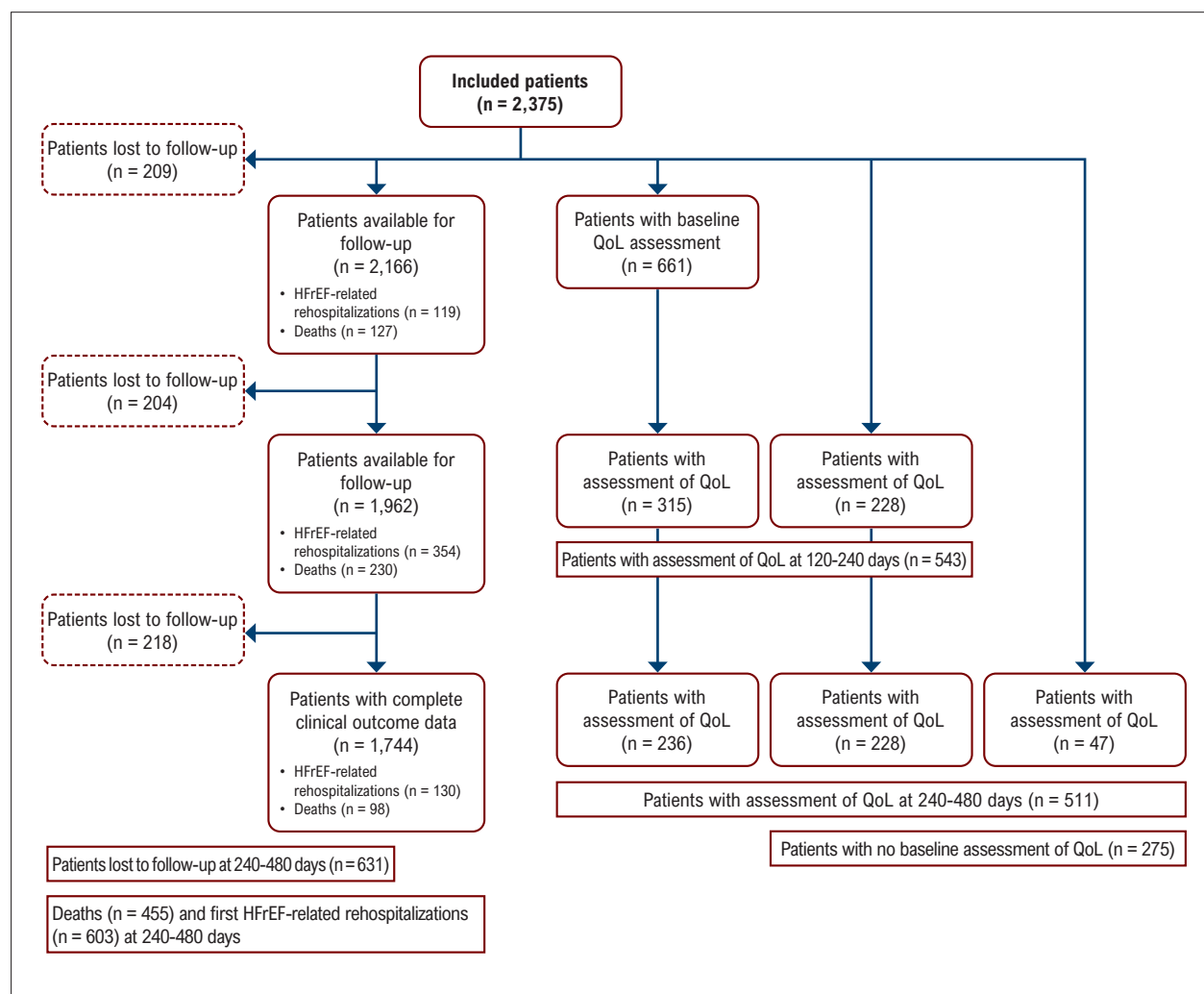


Figure 1 – Study flow diagram. HFrEF: heart failure with reduced ejection fraction; QoL: quality of life.

CI, 1.63-12.9; $p = 0.004$). Both NYHA Class III (HR, 1.55; 95% CI, 1.17-2.06; $p = 0.003$) and Class IV (HR, 1.42; 95% CI, 1.01-1.98; $p = 0.041$) were associated with higher rehospitalization risk.

Across ADHERE risk categories, progressively higher risks were observed. Intermediate Risk 3 was associated with increased rehospitalization risk (HR, 1.73; 95% CI, 1.07-2.80; $p = 0.024$). Intermediate Risk 2 was associated with

both mortality (HR, 2.29; 95%CI, 1.26-4.15; $p = 0.006$) and rehospitalization (HR, 1.76; 95% CI, 1.26-2.47; $p < 0.001$). Intermediate Risk 1 showed the strongest associations with mortality (HR, 3.65; 95% CI, 1.96-6.78; $p < 0.001$) and rehospitalization (HR, 2.66; 95% CI, 1.87-3.79; $p < 0.001$). High Risk was associated with rehospitalization (HR, 1.94; 95% CI, 1.05-3.60; $p = 0.035$), but not with mortality.

Quality of life

Regarding assessment of QoL, 661 patients (27.8%) completed the KCCQ-12 at baseline. By the end of follow-up, 511 patients (21.5% of the total cohort) had completed the KCCQ-12. The reduction in the number of patients contributing to QoL analyses over time was mainly attributable to mortality (455 patients; 19.2% of the cohort) and missing or incomplete questionnaire data (1,458 patients; 61.4%).

Compared with the overall cohort, patients with available QoL data were significantly younger (mean age, 71.2 vs 75.9 years; $p < 0.001$) and more frequently treated with BBs (92.0% vs 85.0%; $p < 0.001$). This subgroup also had a lower prevalence of hospital-acquired infections (2.9% vs 4.7%; $p = 0.021$), higher use of MRAs (58.1% vs 53.0%; $p = 0.011$), and lower mean serum urea levels

(62.6 vs 68.5 mg/dL; $p < 0.001$). Significant differences were also observed regarding palliative care status ($p = 0.0165$) and ADHERE risk stratification ($p = 0.037$).

Table 4 summarizes mean KCCQ-12 scores and standard deviations at baseline and during follow-up (120-240 days and 240-480 days). Social limitation scores increased from 84.0 ± 25.6 at baseline to 86.0 ± 24.8 at 120-240 days and subsequently decreased slightly to 85.0 ± 25.4 at 240-480 days.

QoL scores increased from 73.2 ± 24.4 at baseline to 75.2 ± 25.2 at 120-240 days and further to 75.7 ± 24.5 at 240-480 days. Symptom scores remained stable throughout follow-up, with values of 91.1 ± 16.1 at baseline, 91.2 ± 16.8 at 120-240 days, and 90.6 ± 16.9 at 240-480 days. Physical limitation scores increased slightly from 84.2 ± 23.3 at baseline to 84.5 ± 25.0 at 120-240 days, followed by a decrease to 82.4 ± 25.9 at 240-480 days.

The mean overall KCCQ-12 score was 83.1 ± 18.4 at baseline, increased to 84.2 ± 18.9 at 120-240 days, and decreased slightly to 83.4 ± 19.6 at 240-480 days.

PHQ-2 scores showed a slight but non-significant decline over time, with mean scores of 0.73 at 30 days, 0.67 at 180

Table 2 – Multivariable Cox regression model for 1-year mortality

Variables	HR	95% CI	p-value
Age, years	1.02	1.01-1.04	0.003
ACEIs/ARBs/ARNIs	0.58	0.41-0.80	0.001
BBs	0.40	0.28-0.57	< 0.001
MRAs	0.91	0.64-1.29	0.593
MCS devices	4.58	1.63-12.9	0.004
HAI	1.02	0.47-2.22	0.960
NYHA functional class			
Class II	Reference	—	—
Class III	1.20	0.76-1.91	0.437
Class IV	1.48	0.89-2.47	0.130
ADHERE risk category			
Low Risk	Reference	—	—
Intermediate Risk 3	1.19	0.45-3.15	0.727
Intermediate Risk 2	2.29	1.26-4.15	0.006
Intermediate Risk 1	3.65	1.96-6.78	< 0.001
High Risk	2.31	0.80-6.61	0.120

ACEI: angiotensin-converting enzyme inhibitor; ADHERE: Acute Decompensated Heart Failure National Registry; ARNI: angiotensin receptor-neprilysin inhibitor; ARB: angiotensin receptor blocker; BB: beta-blocker; HAI: hospital-acquired infection; HR: hazard ratio; MCS: mechanical circulatory support; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

Table 3 – Multivariable Cox regression model for time to first rehospitalization within 1 year

Variables	HR	95% CI	p-value
Age, years	1.01	1.00-1.02	< 0.001
ACEIs/ARBs/ARNIs	0.83	0.67-1.02	0.076
MRAs	0.79	0.64-0.98	0.032
NYHA functional class			
Class II	Reference	—	—
Class III	1.55	1.17-2.06	0.003
Class IV	1.42	1.01-1.98	0.041
ADHERE Risk Category			
Low Risk	Reference	—	—
Intermediate Risk 3	1.73	1.07-2.80	0.024
Intermediate Risk 2	1.76	1.26-2.47	< 0.001
Intermediate Risk 1	2.66	1.87-3.79	< 0.001
High Risk	1.94	1.05-3.60	0.035

ACEI: angiotensin-converting enzyme inhibitor; ADHERE: Acute Decompensated Heart Failure National Registry; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; HR: hazard ratio; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

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Table 4 – Values of KCCQ-12 and PHQ-2 scores during follow-up, beginning at the baseline assessment of QoL (T30)

QoL domain, mean $\pm$ SD	Baseline (n = 661)	120-240 days (n = 543)	p-value	240-480 days (n = 511)	p-value
Social limitation	84.0 $\pm$ 25.6	86.0 $\pm$ 24.8	0.285	85.0 $\pm$ 25.4	0.412
QoL	73.2 $\pm$ 24.4	75.2 $\pm$ 25.2	0.070	75.7 $\pm$ 24.5	0.018
Symptom frequency	91.1 $\pm$ 16.1	91.2 $\pm$ 16.8	0.693	90.6 $\pm$ 16.9	0.625
Physical limitation	84.2 $\pm$ 23.3	84.5 $\pm$ 25.0	0.306	82.4 $\pm$ 25.9	0.388
Overall KCCQ-12 score	83.1 $\pm$ 18.4	84.2 $\pm$ 18.9	0.127	83.4 $\pm$ 19.6	0.288
PHQ-2 score	0.73 $\pm$ 1.41	0.67 $\pm$ 1.37	0.156	0.64 $\pm$ 1.40	0.975

KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; PHQ-2: Patient Health Questionnaire-2; QoL: quality of life; SD: standard deviation.

Table 5 – Pairwise comparisons of variables included in the multivariable model for KCCQ-12 scores

Comparisons	Time	KCCQ-12 difference	95% CI	p-value
ADHERE				
Compared with Low Risk				
Intermediate Risk 3	Baseline	1.02	−6.71 a 8.74	0.9964
	120-240 days	−1.42	−9.94 a 7.09	0.9910
	240-480 days	−1.78	−11.14 a 7.57	0.9853
Intermediate Risk 2	Baseline	−1.12	−6.46 a 4.21	0.9787
	120-240 days	−2.24	−7.96 a 3.48	0.8220
	240-480 days	−5.09	−10.96 a 0.78	0.1247
Intermediate Risk 1	Baseline	−2.54	−8.72 a 3.64	0.7939
	120-240 days	−5.45	−12.01 a 1.12	0.1562
	240-480 days	−8.03	−14.86 a −1.21	0.0117
High Risk	Baseline	−2.07	−13.74 a 9.60	0.9887
	120-240 days	−2.57	−15.61 a 10.47	0.9833
	240-480 days	−4.96	−19.08 a 9.17	0.8738
Compared with no use				
ACEIs/ARBs	Baseline	4.36	1.08 a 7.65	0.0092
	120-240 days	3.84	0.30 a 7.39	0.0337
	240-480 days	4.00	0.41 a 7.58	0.0291
Compared with no use				
ARNIs	Baseline	0.94	−2.86 a 4.74	0.6261
	120-240 days	−1.22	−5.29 a 2.85	0.5563
	240-480 days	−1.00	−5.15 a 3.15	0.6377
Compared with age <40 years				
Age	Baseline	−3.6	−15.3 a 8.1	0.7492
	40-64 years	5.2	−7.1 a 17.5	0.5800
	240-480 days	2.6	−10.4 a 15.7	0.8826

≥ 65 years	Baseline	−2.3	−13.7 a 9.1	0.8842
	120-240 days	5.6	−6.4 a 17.6	0.5125
	240-480 days	2.3	−10.5 a 15.0	0.9096
Sex				
Female	Baseline	−4.8	−7.9 a −1.64	0.0029
	120-240 days	−2.6	−5.9 a 0.78	0.1332
	240-480 days	−7.6	−11.0 a −4.1	0.0001
Readmission				
1 or 2	Baseline	−6.2	−10.3 a −2.0	0.0014
	120-240 days	−5.2	−9.6 a −0.9	0.0134
	240-480 days	−3.7	−8.0 a 0.7	0.1211
≥ 3	Baseline	−5.0	−11.1 a 1.2	0.1377
	120-240 days	−5.6	−11.5 a 0.3	0.0667
	240-480 days	−5.0	−10.7 a 0.7	0.0976

ACEI: angiotensin-converting enzyme inhibitor; ADHERE: Acute Decompensated Heart Failure National Registry; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12.

days, and 0.64 at 365 days. Median scores remained 0 at all time points, and no statistically significant differences were observed (all $p > 0.15$).

Table 5 presents pairwise comparisons of KCCQ-12 scores across follow-up periods. At baseline, no significant differences in QoL were observed among ADHERE risk subgroups when intermediate- and high-risk categories were compared with the low-risk group. However, at 240-480 days, patients classified as ADHERE Intermediate Risk 1 demonstrated a significant reduction in QoL scores (−8.03 points; 95% CI, −14.86 to −1.21; $p = 0.0117$).

Use of ACEIs or ARBs was associated with significantly higher QoL scores at baseline (mean difference [MD], 4.36 points; 95% CI, 1.08-7.65; $p = 0.0092$), at 120-240 days (MD, 3.84 points; 95% CI, 0.30-7.39; $p = 0.0337$), and at 240-480 days (MD, 4.00 points; 95% CI, 0.41-7.58; $p = 0.0291$). Patients with LVEF $\geq 20\%$ maintained stable KCCQ-12 scores over time, while those with LVEF $< 20\%$ showed greater temporal variability, characterized by early improvement followed by partial loss of benefit during follow-up (Figure 2). Use of ARNIs was not associated with significant differences at any time point. In addition, no significant differences were observed across age groups.

Significant sex-related differences were identified, with women presenting lower QoL scores than men at baseline (−4.8 points; 95% CI, −7.9 to −1.64; $p = 0.0029$) and at 240-480 days (−7.6 points; 95% CI, −11.0 to −4.1; $p < 0.001$).

Patients with one or two rehospitalizations had significantly lower QoL scores at baseline (−6.2 points; 95% CI, −10.3 to −2.0; $p = 0.0014$) and at 120-240 days (−5.2 points; 95% CI, −9.6 to −0.9; $p = 0.0134$).

Discussion

This prospective multicenter study provides a real-world assessment of clinical outcomes and QoL among Brazilian patients hospitalized with HFrEF using a standardized methodology based on ICHOM recommendations. To our knowledge, this represents the largest Latin American initiative to operationalize VBHC principles in measurement of heart failure outcomes. Our findings demonstrate the feasibility of implementing internationally standardized outcome metrics across a diverse network of private health care institutions in Brazil.

The study population reflected a typical profile of patients with advanced HFrEF, characterized by a high burden of comorbidities, widespread use of GDMTs, and predominance of NYHA functional Classes III and IV.¹¹ Consistent with previous evidence, older age was independently associated with higher risks of mortality and rehospitalization. Use of BBs and ACEIs or ARBs was significantly associated with lower mortality, reinforcing their established role in management of HFrEF.¹²⁻¹⁴ These findings are aligned with contemporary guideline recommendations supporting the prognostic benefits of GDMT.^{15,16} Likewise, the protective effect of MRAs on rehospitalization is consistent with prior randomized trials and further supports their role in comprehensive care for heart failure.¹⁷

However, the high prevalence of contraindications to standard therapies highlights persistent challenges related to multimorbidity and treatment tolerability in older adults.¹⁸ Notably, despite relatively preserved mean blood pressure levels, the elevated rates of contraindications to ACEIs, ARBs, and ARNIs may have been partially driven by the markedly impaired renal function observed in this cohort, which presented a mean creatinine level of 4.6 mg/dL.

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Our findings are consistent with those of the Brazilian BREATHE registry, which also described a high-risk heart failure population characterized by substantial mortality and suboptimal use of evidence-based therapies. Compared with BREATHE, our cohort was older and exclusively composed of patients with HFrEF, which may partly explain the high 1-year mortality observed. Importantly, whereas BREATHE primarily highlighted treatment gaps, our findings further demonstrate that the use of GDMT is associated with improved survival and QoL.¹⁹

Markers of disease severity also proved to be important prognostic indicators. Use of MCS devices was associated with increased mortality risk, likely reflecting the advanced disease status of this subgroup.^{20,21} In addition, both NYHA functional classification and ADHERE risk stratification were strongly associated with higher risks of rehospitalization and death, consistent with previous studies.²²

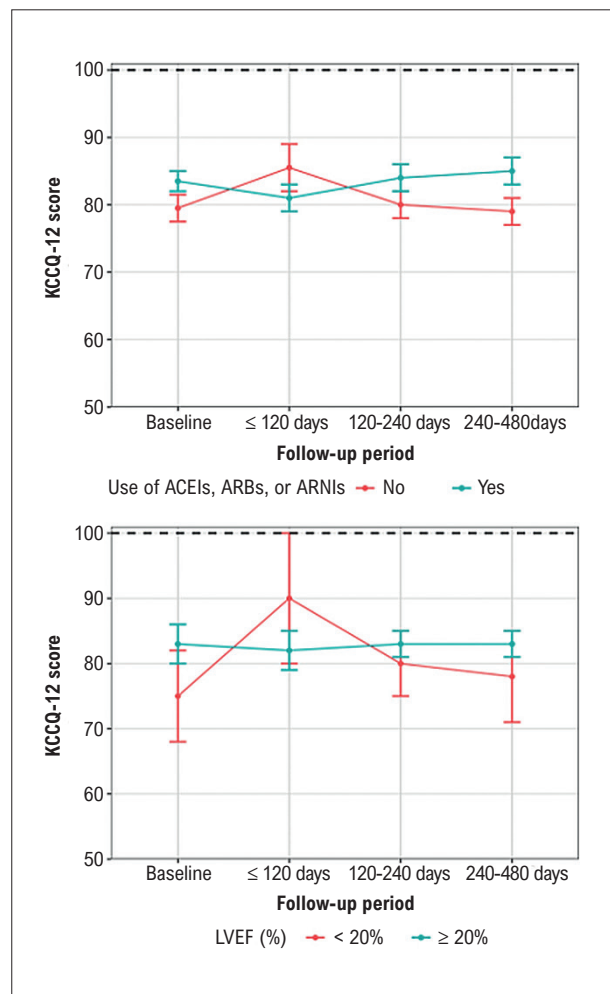


Figure 2 – Estimated mean KCCQ-12 scores over time according to the use of ACEIs, ARBs, or ARNIs. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; LVEF: left ventricular ejection fraction.

Beyond survival benefits, the use of ACEIs, ARBs, or ARNIs was consistently associated with higher KCCQ-12 scores throughout follow-up, independent of age, sex, readmission status, or ADHERE risk category. This finding highlights the dual benefit of these therapies in both prolonging survival and improving patient-perceived health status.

This relationship between therapy and health status is further supported by recent real-world evidence showing that both intensification and deintensification of heart failure therapies were associated with statistically significant and clinically meaningful changes in KCCQ-12 scores.²³ Notably, a substantially greater proportion of patients undergoing medication adjustments experienced large improvements in QoL (≥ 20 points), which suggests physician-guided therapeutic optimization may positively influence patient-reported outcomes.^{10,24} These findings reinforce the value of the KCCQ-12 and similar patient-reported outcome instruments not only as monitoring tools but also as mechanisms to support clinical decision-making and improve care quality in HFrEF.

In our cohort, overall KCCQ-12 scores showed modest improvement during mid-term follow-up, followed by a slight decline toward the end of the study period. Although incremental gains were observed in the social limitation and QoL domains, symptom scores remained relatively stable over time. This pattern suggests that, although clinical stabilization may be achieved with evidence-based therapies, additional interventions may be necessary to sustain and further improve patient-perceived health status in the long term.

Importantly, disparities in health-related QoL outcomes were also identified. Women consistently reported lower KCCQ-12 scores than men at baseline and during long-term follow-up, which corroborates prior research demonstrating sex-related differences in symptom perception and disease burden. The VIDA-IC multicenter study similarly showed that women with HFrEF had significantly lower KCCQ-12 overall summary scores than men, reflecting worse health-related QoL. In particular, women presented lower scores in the domains of symptom frequency, symptom burden, physical limitation, QoL, and social limitation, whereas no differences were observed in symptom stability or self-efficacy domains.²⁴ Furthermore, the BIOSTAT-CHF analysis reported a median KCCQ-12 overall score of 44 in women vs 53 in men ($p < 0.001$), reinforcing the consistency of sex-related disparities across heart failure populations.²⁵

Patients who experienced one or two hospital readmissions also demonstrated persistently lower QoL scores, highlighting the substantial clinical and psychological burden associated with recurrent hospitalization. These findings are consistent with the REPORT-HF registry, in which lower post-discharge KCCQ-12 scores were associated with higher readmission rates and poorer recovery of health status.²⁶

By integrating standardized clinical and patient-reported outcomes, our study extends previous registry-based evidence by demonstrating the feasibility of applying international outcome frameworks in Brazil. Moreover, our findings suggest that broader implementation of GDMTs may contribute to lower mortality, fewer rehospitalizations, and improved QoL,

while also providing evidence to support value-based strategies for improving medical care for heart failure.^{19,25}

From a health system perspective, the successful implementation of this outcomes measurement framework represents an important step toward incorporating VBHC principles into Brazilian health care. The ANAHP initiative illustrates how clinical governance, standardized data platforms such as SINHA,⁵ and coordinated institutional leadership can facilitate benchmarking, continuous quality improvement, and transparency, all of which are essential components of VBHC systems.

Nevertheless, important challenges remain. Interoperability across hospital information systems, sustained clinician engagement, and long-term patient follow-up continue to represent major barriers. In addition, incorporation of outcomes data into reimbursement and incentive models remains incipient. Expanding this approach to public health care institutions and more systematically incorporating social determinants of health may improve both scalability and equity.

Taken together, these findings emphasize the importance of integrated, patient-centered care in management of HFrEF. Future studies should explore value-based reimbursement models, investigate mechanisms underlying the observed disparities in QoL, particularly those related to sex and recurrent hospitalization, and evaluate the generalizability of these findings across different populations and health care settings, including the public health care system.

Study limitations

This study has important limitations. Missing data were handled using listwise deletion, which may have introduced selection bias. Baseline differences between the QoL and clinical follow-up subgroups suggest the possibility of selective attrition, and residual confounding cannot be excluded despite multivariable adjustment.

In addition, the study was conducted exclusively in private tertiary hospitals in Brazil, which may limit generalizability to other health care settings. Exposure to GDMTs was assessed only at baseline, without accounting for treatment adherence or dose titration over time, potentially leading to exposure misclassification.

Furthermore, suboptimal follow-up for patient-reported outcomes raises the possibility of response bias. This limitation was largely driven by operational difficulties in maintaining patient contact, particularly reliance on telephone-based follow-up, as well as patient and physician refusal and cognitive impairment, all of which may have contributed to non-random loss to follow-up.

Conclusion

In this prospective multicenter cohort, GDMTs, particularly ACEIs or ARBs and BBs, were associated with improved survival, lower rehospitalization rates, and better patient-reported outcomes among patients with HFrEF treated in the Brazilian private health care setting (Central Illustration).

Implementation of the ICHOM framework proved feasible and enabled standardized outcome measurement and

benchmarking across institutions. Further longitudinal studies are warranted to evaluate treatment adherence, medication titration, and disparities in clinical and patient-reported outcomes, thereby supporting the development of VBHC models aimed at improving QoL and reducing inequities in HFrEF management.

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Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Silva SA, Amaral K, Bernardez-Pereira S, Franken M, Escobosa DM, Ivo C, Costa LMA, Conceição FG, Lisboa L, Rizzi TN, Tamburim BR, Lopes LA, Yamaguti STF, Nasi LA, Maccari J, Pille A, Wolf JM, Volschan A, Montera MW, Ferreira SMA, Cardoso LF, Saretta R, Nascimento TCDC, Margarido O, Oliveira C, Tiburzio E, Ribeiro A; Statistical analysis: Silva AS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

The study was approved by the Research Ethics Committee of Associação Beneficente Síria – Hospital Sírio-Libanês (CAAE: 38654220.5.1001.0060; approval number 4,354,155). All participating centers obtained local ethics approval. All participants provided informed consent for the use of their data in outcomes assessment and quality improvement initiatives. Data were collected prospectively and analyzed in an anonymized manner, ensuring the confidentiality of participant information.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

All datasets supporting the results of this study are available upon request from the corresponding author.

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