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Does optimal adherence to medications improve heart failure outcomes and mortality?

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Abstract

Objective: To assess the level of adherence to medications, using the Morisky-Green test (MGT), and its relationship with the clinical profile of patients admitted to specialized heart hospital, and sociodemographic variables. **Methods:** This is a cross-sectional analytical observational study including patients with clinical history of HF hospitalized from 2015-2018. Clinical and hemodynamic profiles was defined upon hospital admittance and adherence to drug therapy using the MGT was performed. The main results of electrocardiographic exams were listed and cataloged. Data were analyzed to test the relationship between sociodemographic variables, clinical profile at hospitalization, mortality rates during hospital stay and adherence to medication. **Results:** A total of 306 patients with HF were analyzed. Mean age was 66.1±17.0 years. Higher mortality was observed in patients in NYHA functional class IV (83.3%), with wet-cold profile (50.0%) and an ejection fraction of less than 40% (62.5%).No statistically significant association between suboptimal adherence to drug therapy and more severe clinical profiles such as wet-cold and wet-warm was observed. Patients with optimal adherence to drug therapy had a statistically significant reduction in the risk of progressing to death, $p < .0001$. **Conclusion:** Optimal adherence to drug therapy was associated with reduced mortality. However, there was no significant correlation between the method (MGT) and the outcome of the clinical profile of decompensation.

Keywords: Treatment Adherence and Compliance; Drug Therapy; Heart failure; Decompensation; Mortality.

1. Introduction

Heart failure (HF) has a high prevalence and great impact on morbidity and mortality worldwide, and today it is a serious public health problem. In the United States, a report from the American Heart Association (AHA) shows that, in 2010, approximately 6.6 million (2.8%) of adults over 18 years of age had HF. It is estimated that in 2030, more than 3 million people will have HF, which represents a 25% increase in prevalence compared to 2010 (Ponikowski *et al*, 2016).

HF is a disease that, even with optimized clinical treatment, may present worsening or progression of symptoms being classified as "decompensated". Decompensated HF often leads to hospitalization and it is considered an important prognostic factor (Kemp & Conte, 2012).

For the assessment of patients with acute decompensation, the clinical-hemodynamic classification proposed by Stevenson has been used (Nohria *et al*, 2003).Patients presenting with clinical signs and symptoms of congestion are classified as "wet", and without congestion as "dry"; in the presence of low perfusion, they are classified as "cold" whereas those with adequate perfusion are classified as "warm"(Clerkin *et al*, 2019).

Many patients with optimized HF therapy have trouble following medication regimens due to their complexity, high costs, fear of side effects, and simple forgetfulness. As a result, poor adherence to treatment is one of the most important causes of decompensation (Ruppar *et al*, 2016). Despite the importance of adherence to medication, specific cut-off points are not clear. Although a specific desired adherence to medication is 100%, other studies have arbitrarily defined adherence as taking between 70-100% of medication (Evangelista *et al*, 2001; Gwadry-Sridhar*et al*, 2005), and one study reported that survival is significantly improved with an adherence rate of at least 88% (Wu *et al*, 2009).

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Thus, this study had as objective to assess the level of adherence to medications, using the Morisky-Green test (MGT), and its relationship with the clinical profile of patients admitted to a heart hospital, and sociodemographic variables.

2. Methods

2.1.Study design

This was a cross-sectional observational and analytical study conducted at the *Hospital do Coração de Sobral*, a specialized hospital for the prevention, diagnosis, and treatment of all cardiovascular diseases.

2.2.Ethical aspects

All ethical principles established by the National Health Council in Resolution number 466/2012 were respected and in accordance with the 1964 Helsinki declaration and its later amendments. The study was approved by Research Ethics Committee of the *Universidade Estadual Vale do Acaraú* (protocol number: 1.957.872). All patients signed an informed consent form to be included in the study.

2.3.Inclusion and exclusion criteria

Patients, admitted to the intensive care unit (ICU) of the hospital between January 2015 and June 2018, with a definitive clinical diagnosis of HF confirmed by Boston or Framingham criteria were considered eligible for the study. Those who presented signs of HF secondary to sepsis were excluded.

2.4.Data collection

2.4.1. Clinical and hemodynamic profile

The clinical and hemodynamic profile was defined according to classification by Stevenson (2003), using four hemodynamic profiles according to the findings on physical examination of pulmonary congestion and peripheral perfusion. Patients with decompensated HF are generally classified in one of the following subgroups: 1) no evidence of congestion or hypoperfusion (dry-warm); 2) presence of pulmonary congestion without signs of hypoperfusion (wet-warm); 3) presence of pulmonary congestion associated with hypoperfusion (wet-cold); 4) hypoperfusion without pulmonary congestion (dry-cold).

2.4.2. Adherence to treatment

Adherence to treatment was assessed using MGT, which consisted of four objective questions associated with the treatment of HF: 1) Do you ever forget to take your medication? 2) Are you careless at times about taking your medication? 3) When you feel better, do you sometimes stop taking your medication? and 4) Sometimes if you feel worse when you take your medication, do you stop taking it? All these questions could be answered with either "yes" or "no", and each negative response was attributed one point (Morisky *et al*, 1986). Patients with a score of 4 were considered as having optimal adherence, and those with 0 to 3 points as having suboptimal adherence.

2.4.3. Causes of HF

The main causes of HF analyzed included hypertensive, ischemic, and valvular heart disease, and idiopathic HF. Classification was determined by local clinical investigator and patient records.

2.4.4. Analysis of complementary exams

The main results of electrocardiographic exams were listed and cataloged. Through echocardiographic analysis, patients were classified according to LVEF value:

- Normal LVEF (HF with preserved ejection fraction – HfpEF) typically considered as ≥50%;
- Reduced LVEF (HF with reduced ejection fraction - HFrEF) typically considered as <40%; and
- Intermediate LVEF (HF with mid-range ejection fraction – HfmrEF) in the range of 40–49% represents a 'grey area' (Ponikowski *et al*, 2016).

2.5. Statistical Analysis

The data were tabulated using Microsoft Excel (Microsoft Corporation, Richmond, WA, USA) and exported to the Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Chicago, IL, USA). All analyses were performed assuming 95% level of confidence ($\alpha = 0.05$).

Data were expressed as means and standard deviations or frequency distributions. We considered level of adherence to medication, clinical profile at hospitalization, and death as categorical variables, any analyses were conducted using Fisher's exact test (two-tailed) and odds ratio.

First, we tested whether the sociodemographic variables affected level of medication adherence; secondly, the relationship between clinical profile at hospitalization and adherence to medication was verified; and finally, we assessed whether adherence to drug therapy was associated with mortality rates during the hospital stay.

3. Results

A total of 306 patients with HF were analyzed. Mean age of the patients was 66.1±17.0 years. Most were male (61.8%) and married or in a consensual union (56.6%). Regarding occupation, 53.9% of patients were retired and 30.4% were economically active. 84.3% of the patients did not practice physical activity as part of HF rehabilitation treatment.

The most evident etiology was hypertension (45.4%) followed by ischemia and valvular (20.9% and 16.3%, respectively). The most prevalent risk factor was systemic arterial hypertension, present in 75.2% of patients. Most patients (55.9%) were in functional class IV according to NYHA (New York Health Association) criteria, and the most prevalent clinical profile at hospitalization was wet-warm (53.3%). Left bundle branch block was the most common electrocardiographic (21.6%) abnormality seen followed by atrial fibrillation (19.9%). Mean ejection fraction was 42.6±14.0% with 51.3% of patients classified as HFrEF. Death occurred in 7.8% of patients.

In the clinical-cardiological characterization of the sample, we found higher mortality in patients in NYHA functional class IV (83.3%, p= .040), with wet-cold profile (50.0%, p= .002) and an ejection fraction of less than 40% (62.5%, p= .017).

The assessment of adherence to medication using MGT, on ICU admission, revealed 65.5% of patients had an optimal adherence level to medication (Data not shown)

When assessing the relationship between sex, age, education, and employment with level of therapeutic adherence, no statistically significant association between these characteristics and the degree of adherence was observed (Table 1).

Table 1. Relationship between sociodemographic aspects and adherence to medication in decompensated heart failure patients admitted to the intensive care unit at the *Hospital do Coração* de Sobral (n=306).

Variables	Total		Adherence to medication				p-value[a]	OR (CI 95%)
			Suboptimal		Optimal			
	n	%	n	%	n	%		
Sex							.34	0.79 (0.48, 1.28)
Female	117	38.2	44	41.9	73	36.3		
Male	189	61.8	61	58.1	128	63.7		
Age							.25	0.75 (0.46, 1.21)
Up to 65 years	129	42.2	49	46.7	80	39.8		
65 years and older	177	57.8	56	53.3	121	60.2		
Education							.14	0.68 (0.42, 1.10)
Illiterate / No schooling	127	41.5	50	47.6	77	38.3		
Literate	179	58.5	55	52.4	124	61.7		
Employment							.32	1.96 (0.55, 6.93)
Retired / Economically active	296	96.7	100	95.2	196	97.5		
Unemployed	10	3.3	5	4.8	5	2.5		

Data expressed as absolute frequency and percentage; [a] Calculated using Fisher's exact test (two-tailed); OR odds ratio.

No statistically significant association between suboptimal adherence to drug therapy and more severe clinical profiles such as wet-cold and wet-warm was observed.

In the first comparison, patients with suboptimal adherence were 1.68 times more likely to be categorized as wet-cold than dry-warm, without statistical significance, p= .15. In the second comparison (wet-cold vs. dry-warm), patients with suboptimal adherence were 1.03 times more likely to be classified as wet-cold, also without statistical significance, p= .93 (Table 2).

Table 2. Relationship between clinical profile at hospitalization and adherence to medication in decompensated heart failure patients admitted to the intensive care unit at the *Hospital do Coração* de Sobral (n=306).

Patient Profiles	Total		Adherence to medication				p-value[a]	OR (CI 95%)
			Suboptimal		Optimal			
	n	%	n	%	n	%		
								1.68 (0.83 – 3.39)
Wet-cold	62	45.9	27	54.0	35	41.2	.15	
Dry-warm	73	54.1	23	46.0	50	58.8		
								1.03 (0.57 - 1.86)
Wet-warm	165	69.3	53	69.7	112	69.1	.93	
Dry-warm	73	30.7	23	30.3	50	30.9		

Data expressed as absolute frequency and percentage; [a] Calculated using Fisher's exact test (two-tailed); OR odds ratio.

In our assessment, we saw that patients with optimal adherence to drug therapy had a statistically significant reduction in the risk of progressing to death, p< .0001; in other words, they were 8.66 times less likely to die than those with suboptimal adherence (Table 3).

Table 3. Relationship between mortality and adherence to medication in decompensated heart failure patients admitted to the intensive care unit at the *Hospital do Coração* de Sobral (n=306).

Mortality	Total		Adherence to medication				p-value[a]	OR (CI 95%)
			Suboptimal		Optimal			
	n	%	n	%	n	%		
Death								8.66 (3.13, 24.00)
No	282	92.2	86	81.9	196	97.5	< .0001	
Yes	24	7.8	19	18.1	5	2.5		

Data expressed as absolute frequency and percentage; [a] Calculated using Fisher's exact test (two-tailed); OR odds ratio.

4. Discussion

The present study, in its clinical-cardiological analysis, reported that the highest mortality was related to left ventricular ejection fraction lower than 35%, in NYHA functional class IV, wet-cold profile, and suboptimal adherence to medication therapy. These results are in line with global statistics on risk factors for higher mortality in patients with HF (Ponikowski *et al*, 2016).

Due to the importance of patient adherence to medication and the clinical profile related to mortality, and the suspicion of the relationship between optimal adherence and the dry-cold profile, we decided to evaluate the relationship between the decompensation profile and adherence using the MGT.

It is important to highlight that the MGT, to assess adherence in hypertensive patients, presents variable performance in different studies with a sensitivity of 43% and specificity ranging from 45.3 to 81% (Prado *et al*, 2007;Bloch *et al*, 2008;Santa Helena *et al*, 2008). The lack of correlation between the MGT and the clinical outcomes motivated Morisky to expand this questionnaire, adding four more questions to the original ones, but as this new instrument has not yet been validated in Portuguese, we decided to use the four-question questionnaire.

As far as our review of the literature revealed, no other studies that assess the level of adherence to medication and the clinical profile of decompensated HF have been published.

This study has some limitations. The lack of an adequate comparative gold standard and the multiple determinants of adherence make it difficult to analyze the results. There is no consensus on a method to assess adherence that can be considered gold standard, which include direct methods (serum or tracer measurements) that are costly and difficult to perform in the case of multiple drugs, Such as in the treatment of HF, or indirect ones, such as dispensing-based calculations, medication count, questionnaires, and clinical response to drugs (Morisky *et al*, 1986). Furthermore, an inherent limitation of the cross-sectional design is the reverse causality bias, that is, when evaluating exposure and outcome at the same time, temporality related to previous and subsequent hospitalizations is lost.

In summary, adherence to drug therapy was associated with reduced mortality. Nevertheless, the results do not present a significant correlation between the method (MGT) and the outcome of the clinical profile of decompensation, which can be attributed to the fact of establishing different cutoff points for adherence, or of the limitations of the method itself, or of the difficulty to control subjective factors related to data collection. Thus, the method of assessing adherence must consider the resources available in health services, and the strategies employed must obey basic psychometric norms of reliability and validity. As this indirect strategy using MGT did not show correspondence, perhaps new studies with multimethod approaches are needed to assess correlation.

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