

# Low T3 Would Indicate Adverse Outcomes in Hospitalized Patients with Decompensated Heart Failure

*La T3 baja marcaría peor evolución en pacientes internados por insuficiencia cardíaca descompensada*

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## ABSTRACT

**Background:** Low T3 syndrome is associated with elevated circulating levels of cytokines and interleukins, reinforcing the hypothesis of a close relationship between the neuroendocrine system and certain inflammatory and immunological mechanisms involved in heart failure.

**Objective:** The aim of this study was to assess the outcome of patients admitted for decompensated heart failure according to T3 levels on admission, and events during hospitalization and follow-up.

**Methods:** This was a prospective, observational, analytical study, including 524 patients hospitalized for the first time with diagnosis of decompensated heart failure. In-hospital and follow-up mortality and readmissions were evaluated according to normal or low T3 levels on admission. Ninety-one patients with known dysthyroidism, hypo or hyperthyroidism, previous thyroid surgery, sepsis or acute coronary syndrome were excluded from the study. A subgroup analysis of patients receiving or not chronic amiodarone therapy was conducted, and prognostic variables were evaluated.

**Results:** Among the 433 patients analyzed, 40.0% had low T3 (LT3) levels. Age, albumin level, age > 75 years, and glomerular filtration rate (GFR) were independent predictors of LT3. Although adaptation of guideline-recommended treatments increased in both groups, treatment rates in the LT3 group were significantly lower than those in the normal T3 (NT3) group (LT3 vs. NT3: Betablockers 81.5% vs. 89.4%,  $p = 0.02$ ; ACEI/ARA II 78.5% vs. 87.9%,  $p = 0.001$ ; and anti-aldosterone agents 29.2% vs. 40.5%;  $p = 0.019$ ). In-hospital mortality was higher in the LT3 group (5.8 vs. 1.5%), with no difference in rehospitalizations or mortality rates at follow-up. In the subgroup of patients without amiodarone on admission (353), 37.8% had LT3. Patients in this subgroup had significant differences in in-hospital and follow-up mortality (5.3% in LT3 vs. 0.9% in NT3,  $p = 0.03$ , and 40.2% vs. 26.6%,  $p = 0.023$ ), respectively.

**Conclusions:** Decompensated heart failure patients with LT3 on admission would represent a subgroup with more severe disease and worse prognosis during hospitalization.

**Key Words:** Heart failure – Prognosis - Thyroid hormones- Euthyroid sick syndromes

## RESUMEN

**Introducción:** El síndrome de T3 baja se asocia con niveles elevados de interleucinas y citoquinas circulantes, lo que refuerza la hipótesis de una estrecha relación entre el sistema neuroendocrino y ciertos mecanismos inflamatorios e inmunológicos, involucrados en la insuficiencia cardíaca.

**Objetivo:** Evaluar la evolución de pacientes ingresados por insuficiencia cardíaca descompensada según niveles de T3 al ingreso, y eventos durante la hospitalización y en el seguimiento.

**Material y métodos:** Estudio prospectivo, observacional, analítico de 524 pacientes internados por primera vez con diagnóstico de insuficiencia cardíaca descompensada. Se evaluó la mortalidad intrahospitalaria, y al seguimiento y readmisiones de acuerdo con niveles de T3 normal o disminuida al ingreso. Se excluyeron 91 pacientes con distiroidismo conocido, hipotiroidismo o hipertiroidismo, cirugía tiroidea previa, sepsis o síndrome coronario agudo. Se realizó un análisis de subgrupo de pacientes según recibieran crónicamente amiodarona y se evaluaron variables pronósticas.

**Resultados:** De 433 pacientes analizados, el 40,0% presentaban bajos niveles de T3 (BT3). La edad, albúmina, TFG y edad mayor de 75 años, fueron predictores independientes de BT3. Si bien se observó un aumento en ambos grupos en la adecuación de tratamientos recomendados por las guías, el grupo de BT3 mostró significativamente tasas menores de estos con respecto a aquellos con T3 normal (BT3 vs. NT3: betabloqueantes 81,5% vs. 89,4%,  $p = 0,02$ ; IECA/ARAII 78,5% vs. 87,9%  $p < 0,001$ ; antialdosterónicos 29,2% vs. 40,5%  $p = 0,019$ ). La mortalidad hospitalaria fue mayor en BT3 (5,8% vs. 1,5%) sin diferencias en readmisiones o mortalidad en el seguimiento. Del subgrupo de pacientes sin amiodarona al ingreso (353), 37,8% tenían BT3. Se halló que los pacientes de este subgrupo presentaron diferencias significativas en cuanto a mortalidad intrahospitalaria y mortalidad en seguimiento (5,3% en BT3 vs. 0,9% NT3;  $p = 0,03$  y 40,2% vs. 26,6%;  $p = 0,023$ ), respectivamente.

**Conclusiones:** Los pacientes ingresados por insuficiencia cardíaca descompensada con T3 baja al ingreso representarían un subgrupo de pacientes con enfermedad más grave y peor pronóstico durante la internación.

**Palabras clave:** Insuficiencia cardíaca - Pronóstico - Hormonas tiroideas - Síndromes del eutiroides enfermo

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## Abbreviations

<b>BNP</b>	B-type natriuretic peptide
<b>Hb</b>	Hemoglobin
<b>HF</b>	Heart failure

<b>DHF</b>	Decompensated heart failure
<b>TSH</b>	Thyroid-stimulating hormone

## INTRODUCTION

Heart failure (HF) is a major public health issue in developed countries and one of the leading causes of morbidity and mortality. (1) In recent years, it has been suggested that there is a multiple endocrine deficiency in HF that includes thyroid dysfunction. Numerous clinical and experimental evidence suggest that the thyroid hormone plays a key role in the modulation of frequency, myocardial contractility and systemic vascular resistance. (2, 3)

Both hypo and hyperthyroidism can cause HF and, similarly, HF can cause thyroid disorders. (4) Triiodothyronine (T3) is the most active metabolic form of this group of hormones. (5, 6) It regulates the expression of the genes involved in both myocyte structure and function, (7) and its action directly and indirectly influences systolic and diastolic function. States of dysthyroidism -even with no clinical manifestations- are associated with high rates of cardiovascular complications. (8) Assessment of thyroid-stimulating hormone (TSH) is used primarily for the diagnosis of thyroid dysfunction. Its normal levels are wide, ranging from 0.45 mUI/L to 4.49 mUI/L. If we find slight TSH elevations with normal T3 and T4 levels, we -controversially- call it subclinical hypothyroidism, due to scarce signs and symptoms.

Low T3 syndrome -also known as “euthyroid sick syndrome” because it occurs in patients without previous thyroid disorders or apparent primary gland disease- is characterized by biochemical alteration with normal TSH levels, normal or slightly low T4 levels, low free T3 and elevated rT3 concentration. It is associated with elevated circulating levels of cytokines and interleukins, reinforcing the hypothesis of a close relationship between neuroendocrine systems and the inflammatory and immunological mechanisms involved in HF. (8) This would be the result of the organism’s adaptation mechanism to chronic diseases, which would lead to reduction in total energy expenditure and protein catabolism, with decreased body mass and, consequently, altered musculoskeletal function, which also impairs myocardial function. (8) According to different series, low T3 in patients with HF is about 30%. (9-11) This relationship, its consequences and the need for treatment have not been fully analyzed worldwide. This led us to study the reality of our population regarding this syndrome.

The purpose of the present study was thus to assess whether low T3 values on admission for decompensated heart failure influence in-hospital (mortality) and follow-up (mortality and re-hospitalizations) outcomes in our patients. Also, we aimed to evaluate the differences between normal and low T3 populations.

## METHODS

This was a single center, prospective, observational, analytical study including 524 hospitalized patients with diagnosis of decompensated heart failure (DHF) -both initially and at discharge-, consecutively admitted in the Department of Cardiology of our hospital between June 2012 and October 2017. Inclusion criteria were DHF patients > 18 years of age with no previous hospitalization, who met the Framingham criteria. Patients with pre-existing thyroid disease or hormone replacement therapy, previous thyroid surgery, acute coronary syndrome, sepsis, infectious endocarditis, acute aortic syndrome, HF secondary to decompensated coronary disease, and comorbidities affecting thyroid function were excluded from the study. Patients under amiodarone therapy were not excluded.

On admission, all patients were evaluated clinically and through lab tests (routine protocol in our Department), assessing biomarkers, natriuretic peptides, TSH, T3 and T4, renal function, and electrolyte panel, among usual determinations. The thyroid profile test was performed in the central lab the morning following admission.

Patients were treated and discharged at the discretion of the attending physician. Long-term follow-up was conducted by telephone contact for those patients who were not followed up in the HF service, and in person for those who attended the service on a regular basis. In all cases, data from medical records were also reviewed to check whether patients had been readmitted or had died. It should be noted that this is a population whose medical care is only provided at our center (closed population).

Patients were divided into two groups according to T3 levels: normal T3 (NT3) 0.8-2 nmol/L (80 to 200 ng/dL), and low T3 (LT3) < 0.8 nmol/L (80 ng/dL). Median follow-up was 39 months (interquartile range 24-54).

In-hospital mortality, and mortality and rehospitalizations due to HF during follow-up were assessed.

## Statistical analysis

Statistix 7.0 software was used for the analysis. Quantitative variables with normal distribution were expressed as mean (m) and standard deviation (SD), and analyzed with Fisher’s test. Variables with non-normal distribution were expressed as median and interquartile range, and analyzed using the Mann-Whitney test. Dichotomous variables were expressed as percentages and analyzed using the chi-square test. Kaplan Meier survival curves were plotted and the Cox Mantel test was used to analyze mortality and rehospitalizations. Univariate and multivariate analyses -linear and logistic regression tests, according to the type of variables-, were performed on both groups. A p value <0.05 was considered statistically significant.

## Ethical considerations

The study was conducted according to current legal regulations to protect patients’ privacy and confidentiality. Data were obtained retrospectively from electronic medical records and computerized epicrisis. As no patient identification data were reported, no informed consent was requested.

This study was approved by the Ethics Committee of Hospital Churrucá-Visca.

## RESULTS

Among a total of 524 patients, 91 were excluded due to pre-existing thyroid disease ( $T3 > 3$  nmol/L), hormone replacement therapy, or lack of data. The remaining 433 patients were divided into two groups according to T3 levels on hospital admission: normal T3 (NT3) 0.8-2 nmol/L (80 to 200 ng/dL) (n: 260) and low T3 (LT3)  $< 0.8$  nmol/L (80 ng/dL) (n: 173). Median follow-up was 39 months (interquartile range 24-54).

In the LT3 group, the population was older with median age of 79 years, (69 years for the NT3 group) and with a higher percentage of patients  $>75$  years. This group included the same number of men and women, while in the NT3 group men were dominant, and longer hospital stay (5 vs. 4 days, respectively). The number of smokers was lower in the LT3 group than in the NT3 group (34.7 vs. 49%). Echocardiographic parameters showed that the LT3 group had smaller left ventricular systolic and diastolic dimensions and lower ejection fraction (EF) calculated according to Simpson's method (Table 1).

The analysis of HF classification according to EF showed that HF with reduced EF was present in 54.2% of LT3 patients compared with 46% in the NT3 group; mid-range EF occurred in 14.7% vs. 18.1% of patients, respectively, and preserved EF in 39.3% vs. 27.8%, respectively. In the LT3 group, a higher percentage of patients were pacemaker carriers or had atrial fibrillation (Table 1 and Figure 1).

Coronary artery disease was the prevalent etiology. Arrhythmias and inadequate treatment were the most common causes of decompensation, with no significant differences between the two groups. There was also no significant difference in the HF treatment with which patients were admitted, showing low use of HF modifying drugs (LT3 vs. NT3): Betablockers 56.7% vs. 58.7%; ACEI/ARA II 57.9% vs. 59.9%; anti-aldosterone agents 13.5% vs. 15.9%; amiodarone 22.2% vs. 15.1%; and diuretics 49.7% vs. 45.1%. At

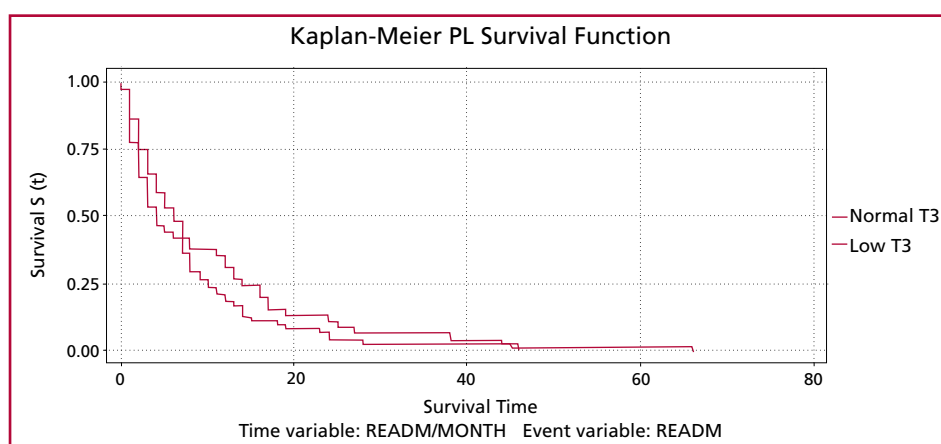
discharge, an association between LT3 and lower rate of patients achieving guideline-recommended treatments was observed (LT3 vs. NT3: betablockers 81.5% vs. 89.4%,  $p = 0.02$ ; ACEI/ARA II 78.5% vs. 87.9%,  $p = 0.001$ ; and anti-aldosterone agents 29.2% vs. 40.5%;  $p = 0.019$ ).

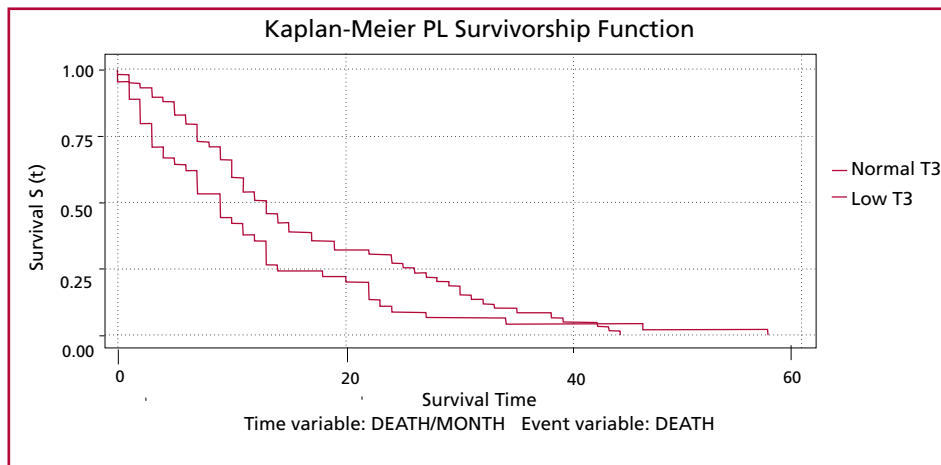
Significant differences were observed in biochemical assessments. Patients in the LT3 group presented significantly higher levels of B-type natriuretic peptide (BNP) (1,305 vs. 922 ng/mL), lower hemoglobin (Hb) (12.6 vs. 13.3 g/dL), higher creatinine values (1.21 vs. 1.10 mg/dL), and lower glomerular filtration rate (55 vs. 66 ml/min/1.73 m<sup>2</sup>) on admission. However, a low number of patients in this group presented with impaired renal function during hospitalization (29.4 vs. 40.2%), which was defined as increased serum creatinine  $> 0.3$  mg/dl, 25% increase of the value on admission; or decreased creatinine clearance  $> 10$  mL/min/1.73 m<sup>2</sup>. Albumin and blood proteins were lower in the LT3 group (3.1 g/dL vs. 3.4 g/dL and 6.2 g/dL vs. 6.35 g/dL, respectively) (Table 1).

Multivariate analysis showed that age, albumin level, glomerular filtration rate, heart rate, and age  $>75$  years were independent predictors of LT3. Mortality and rehospitalizations were evaluated during a median follow-up of 39 months (interquartile range 24-54). Patients in the LT3 group evidenced significantly higher in-hospital mortality (5.8% vs. 1.5%,  $p < 0.01$ , OR 3.92, 95% CI, 1.21% - 12.7%), but mortality was higher during follow-up in the NT3 group (64% vs. 40.3%;  $p < 0.01$ ) (Figure 2). In the multivariate analysis LT3 on admission behaved as an independent predictor of in-hospital mortality, together with other factors such as maximum dose of furosemide used and need for inotropic agents during hospitalization. Other important data were the more frequent need for non-invasive ventilation (13.5% vs. 5.9%) and inotropic agents (5.8% vs. 1.5%) in the LT3 group. No significant differences in rehospitalization rates were observed (31% vs. 28.3%).

Since amiodarone can cause dysthyroidism, we assessed events in patients not receiving amiodarone on

Hospital readmission requirement. Relationship between normal T3 and low T3 groups and readmissions during follow-up without significant differences. Median follow-up period of 39 months





Survival. Relationship between normal T3 and low T3 groups and mortality during follow-up showing significant differences.

	NT3	LT3	p
Age	69 (61;78)	79 (68;85)	<0.001
Hospital stay (days)	4	5	0.011
LVDD (cm)	5.7	5.3	0.0016
LVSD (cm)	4.3	3.8	<0.001
LVEF (%)	38	40	0.032
Pacemaker carrier	5%	14%	0.0012
AF	31.4%	41.3%	0.034
BNP ng/ml	922 (496;1735)	1305 (678;3.570)	0.0034
Hb g/dl	13.3	12.6	<0.001
Creatinine (mg/dl)	1.10	1.21	<0.001
MDRD GFR (mL/min/1.73 m <sup>2</sup> )	66	55	<0.001
In-hospital GFR decline	40.2%	29.4%	0.023
Albumin g/dl	3.4	3.1	<0.001
Proteins g/dl	6.35	6.2	0.020

**Table 1.** Baseline characteristics on admission\*

\* Dichotomous variables were expressed as percentage and continuous variables as median and interquartile range. NT3: Normal T3. LT3: Low T3. LVDD: Left ventricular diastolic diameter. LVSD: Left ventricular systolic diameter. LVEF: Left ventricular ejection fraction. AF: Atrial fibrillation. BNP: B-type natriuretic peptide. Hb: Hemoglobin. MDRD: Modification of diet in renal disease (equation). GFR: Glomerular filtration rate.

admission. Therefore, 353 patients not taking amiodarone were analyzed. Two hundred and twenty of these patients (62.32%) had NT3 and 133 (37.67%) LT3. Patients without amiodarone were found to have significant differences in in-hospital and follow-up mortality, 5.3% in LT3 vs. 0.9% in NT3 ( $p = 0.03$ ) and 40.2% vs. 26.6% ( $p = 0.023$ ), respectively. No significant differences in rehospitalization rates were observed (28.4% vs. 26%). In the group of patients under amiodarone therapy on admission, no differences in these events were observed between NT3 and LT3.

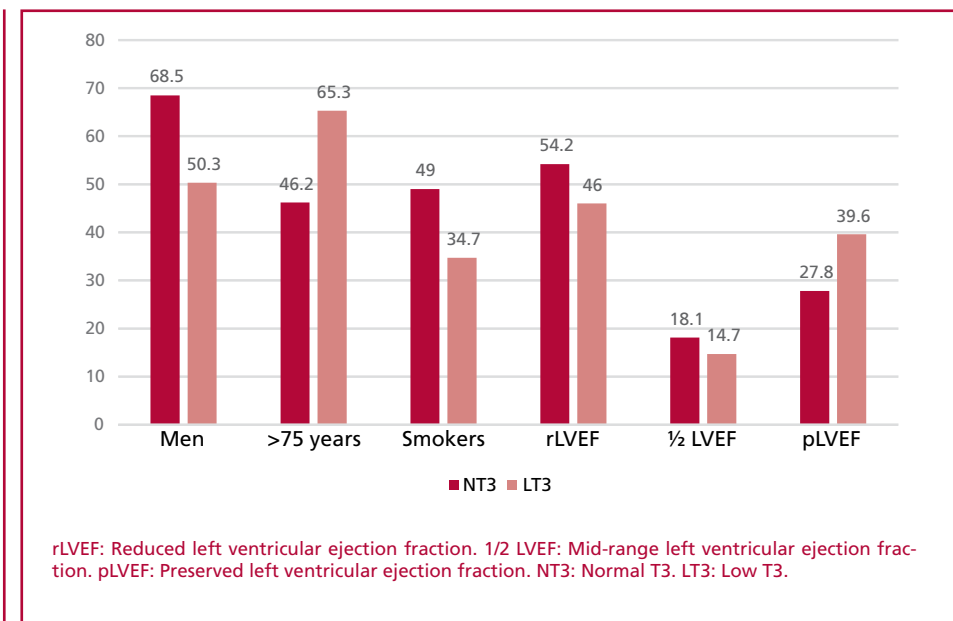
**DISCUSSION**

There is no perfect understanding of the causes that elicit LT3 syndrome in this group of patients. The typical high levels of neurohormonal activation in HF would be closely associated with the development of this particular type of thyroid dysfunction. In HF, LT3

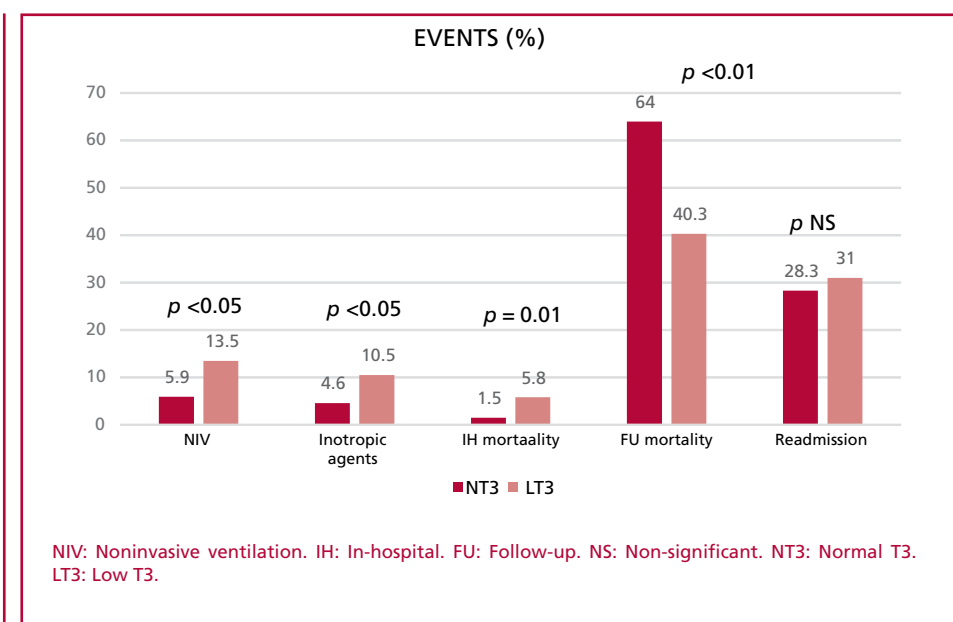
syndrome is associated with catabolic processes that may include insulin resistance, increased cortisol, and lipid, albumin and muscle mass reduction.

At the beginning, it was interpreted as a compensatory mechanism of HF, because this condition reduces total energy expenditure and protein catabolism. However, as was the case since the 1980s to the present, with the vision of the neurohormonal mechanisms of HF, in which it was also shown that their activation implies a poor prognosis and also influences in the pathophysiology of the disease, it seems that LT3 syndrome, although it may initially be a compensatory mechanism, would play an important role in the worsening and perpetuation of HF. Low T3 levels could not only be a marker of severity, but also a determinant of poor outcome. In severe diseases, there is decreased conversion of T4 to T3, which is the biologically active form. 5'-monodeiodinase is the enzyme

**Fig. 1.** Baseline characteristics



**Fig. 2.** Significant variables of in-hospital and follow-up evolution



involved in this deiodination in the peripheral tissue. Type I is widely distributed in the body, particularly in the liver and kidneys, so deterioration of these organs in HF due to congestion or poor perfusion may cause LT3, and this may become more evident in more severe patients.

In our population, 39.95% of patients admitted with HF showed LT3 on admission and worse hospital evolution. These data, associated with higher levels of natriuretic peptides and creatinine (with greater glomerular filtration rate decline) on admission, older age and coexistence of AF, lower hemoglobin, albumin and total proteins, and longer hospital stay, would indicate more severe patients with altered conversion of T4 to T3 and hence poor prognosis during hospitalization due to increased congestion or hypoperfusion

on admission. Actually, an interaction was observed between LT3 and need for inotropic agents.

Only a few studies have demonstrated that LT3 syndrome is associated with adverse prognosis in HF patients. (5, 6) In patients with heart disease, LT3 syndrome was related to higher mortality, (6) longer hospital stay, and greater rate of admission in the intensive care unit. (5) In a recent study, patients with HF and LT3 showed higher cardiac and all-cause mortality with some interactions. Given its pathogenesis, LT3 is probably a “marker” for more severe disease. However, low serum T3 levels could worsen cardiac function. (6-9) In addition, there have been advantages and disadvantages to the benefit of hormone replacement therapy. (9-11) Therefore, there is still room for debate whether LT3 may be a “cause” of poor prognosis.



One of the limitations of this research work is the lack of thyroid profile levels during all patients' follow-up, since we cannot assess what the levels were after discharge in order to discriminate between those who suffered a transient decrease due to decompensation, those who continued with decreased levels, or those who required a different treatment. This could explain the same rate of rehospitalization, since both populations showed no differences in BNP at discharge, so it could be inferred that both populations were similar in terms of congestion. On the other hand, we cannot explain a priori the different mortality rates between both groups during follow-up, which was higher in the NT3 group. Neither could we explain the difference in the worsening of kidney function in the NT3 group, since there was no difference in the maximum doses of diuretics, blood pressure, weight loss, or functional class at discharge.

### CONCLUSION

Our population of patients with LT3 admitted for HF worsening was a subgroup with more severe disease associated with worse prognosis during hospitalization (mortality), although NT3 patients showed poorer prognosis during follow-up. No differences in rehospitalization were observed. We consider it important to detect this subgroup of patients in order to adapt the treatment, as they will have a worse in-hospital evolution. Hormonal replacement still remains controversial.

### Conflicts of interest

There is a conflict of interest of the Pulmonary Hypertension Area with Bayer Msl pharmaceutical company.

(See author's conflicts of interest forms on the website/ Supplementary material)

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