



# Hypothyroidism Is Associated With Longer Hospital Stay Following Implantation Of Left Ventricular Assist Device

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## ABSTRACT

**BACKGROUND:** There has been a steady and consistent rise in the use of left ventricular assist devices in the management of patients with advanced heart failure. Hypothyroidism also remains one of the most common endocrine conditions with a significant impact on the development and overall outcomes of heart failure. The authors analyzed the National Inpatient Sample to evaluate the effect of hypothyroidism on the in-hospital outcomes of patients with end-stage heart failure following the placement of left ventricular assist device.

**METHODS:** The national inpatient sample was queried to identify all adult patients who had LVAD placement from 2004 to 2014. They were subsequently divided into those with hypothyroidism and those without hypothyroidism. The primary outcome was in-hospital mortality. Other outcomes were acute kidney injury, length, and cost of hospitalization. Logistic regression models were created to determine the outcomes of interest.

**RESULTS:** Of 2643 patients in the study, 5.4% had hypothyroidism, and 94.6% did not. The hypothyroid patients were significantly older compared to the non-hypothyroid patients (mean age 58.6 years vs 49.95 years,  $P$ -value  $<.0001$ ). Both groups had similar gender composition. In-hospital mortality was similar across both groups. However, there was a higher incidence of acute kidney injury (AKI) in the hypothyroid group (adjusted odds ratio [aOR] 1.83,  $P$ -value  $<.001$ ). Hypothyroid patients had longer hospital stays (adjusted mean difference [aMD] 5.19,  $P$ -value  $.0001$ ). Hospital charges were also higher in the hypothyroid group.

**CONCLUSION:** This study found that LVAD is associated with longer hospital stay in hypothyroid patients with heart failure.

**KEYWORDS:** Heart failure, hypothyroidism, LVAD, outcomes

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## Introduction

The last few years have seen a significant rise in the use of left ventricular assist device (LVAD).<sup>1</sup> This is the most commonly deployed form of mechanical heart support.<sup>1</sup> These devices are deployed as either as destination treatment or bridge to transplantation.<sup>1</sup> Studies have shown significantly improved rates of survival in patients with advanced heart failure who had LVAD implantation.<sup>2</sup>

On the other hand, hypothyroidism is among the most common endocrine disorders in the United States.<sup>3</sup> It significantly contributes to adverse clinical outcomes and higher rates of hospitalization in patients with heart failure.<sup>4</sup> Hypothyroidism is associated with worse outcomes in heart failure patients following cardiac resynchronization therapy but its impact on the outcomes of patients following LVAD placement has not been investigated in any large-data study.<sup>5</sup>

The authors performed a secondary analysis of the National Inpatient Sample (NIS) to examine the effects of hypothyroidism on the in-hospital outcomes of patients who had LVAD implantation during the index hospitalization. The general objective of the study was to compare the in-hospital outcomes in hypothyroid and non-hypothyroid heart failure patients following the placement of LVAD.

The STROBE checklist was followed in this manuscript.

## Methods

Clinical data were obtained from the NIS administrative database. This is the largest all-payer database in the United States. It has over 100 data elements and about 7 million unweighted admissions data per year representing approximately 20% of the total admissions. The data from the database are de-identified and publicly available. Therefore, this study was exempted from institutional review board evaluation.

The study was a retrospective secondary database analysis. We queried the NIS database from 2010 to 2014 and identified hospitalizations in which adult patients (aged 18 years and above) with heart failure had left ventricular assisted devices placed using the International Classification of Diseases, Ninth Revision (ICD-9). We then identified those with and without hypothyroidism using the specified ICD-9 codes.

The authors excluded patients who were younger than 18 years of age and those who had cardiac transplant during the index admission, though this was rare.

Variables extracted included demographic characteristics, past medical history, and elixhauser co-morbidity index as defined by the Agency for Healthcare Research and Quality (AHRQ) and using ICD codes as defined in the NIS database.



The primary outcome was mortality during the index hospitalization. Secondary outcomes included acute kidney injury, length of hospital stay and cost of admission.

Baseline characteristics (Table 1) were reported using mean and standard deviation for continuous variables where the distribution was normal. Median and interquartile ranges were used when otherwise. We reported categorical variables as percentages. Test of association was done using chi-square.

Multivariate logistic regression was conducted adjusting for age, sex, diabetes, hypertension, obesity, chronic kidney disease. We reported the odds ratio and 95% confidence interval. We analyzed the data with complex models which was able to account for homoscedasticity, putting into consideration the various clusters and strata. All analyses were conducted by weighting samples for national estimates in conjunction with the health care cost and utilization project (HCUP) regulations. Associations were considered significant if the *P*-value was  $<.05$ . We analyzed the data with SAS version 9.4 Cary North Carolina. The statistical analyses were performed using statistical analysis system (SAS) software version 9.4, SAS institute, Cary, North Carolina.

## Results

There were 2643 subjects in the study (weighted estimates). About 5.4% of them had hypothyroidism, while 94.6% did not. The hypothyroid patients were significantly older, with a mean age of 58.6 years compared to 49.95 years for the non-hypothyroid group (*P*-value  $<.0001$ ). Both groups were also predominantly Caucasian (Table 1).

Atrial fibrillation and essential hypertension were more prevalent among the hypothyroid patients. While the hypothyroid subjects had a higher prevalence of chronic kidney disease, the rates of maintenance dialysis were comparable between the 2 groups. Significantly more patients in the hypothyroid group had coagulopathy, obesity, and diabetes mellitus (Table 1).

Neither the expected primary payer nor the median household incomes differed significantly across the 2 groups. The sizes and teaching status of the managing hospitals were also comparable.

Table 2 shows the clinical outcomes. The primary outcome of in-hospital mortality was similar across the 2 groups (aOR 0.68, *P*-value .19). Hypothyroid patients were found to have more incidence of acute kidney injury (aOR 1.83, *P*-value  $<.001$ ). The length of hospital stay was longer in the subjects with hypothyroidism (aMD 5.19, *P*-value .0001). The hospital charges were also higher in the hypothyroid group.

## Discussion

In the present study, there were comparable rates of in-hospital mortality across the 2 groups. Earlier studies have established hypothyroidism as an adverse prognostic factor in patients with cardiovascular diseases, including heart failure.<sup>3</sup> A 2013 meta-analysis found that all-cause

mortality was almost fifty percent higher in heart failure patients with hypothyroidism compared to those without hypothyroidism.<sup>6</sup>

The thyroid hormones have profound effects on the structure and functions of the heart. These hormones influence the cardiovascular system both at the genomic and non-genomic levels.<sup>7</sup> At the subcellular level, they increase the expression of contractile elements and apparatus in the sarcoplasmic reticulum of the cardiac myocytes.<sup>7</sup> Thyroid hormone deficiency, as obtained in patients with hypothyroidism, therefore, leads to reduced cardiac contractility and consequently low cardiac output. Thyroid hormones also modulate the phosphatidylinositol pathway in the vascular myocytes leading to enhanced production of nitric oxide, which is a potent vasodilator.<sup>8</sup> Contractile and endothelial dysfunctions secondary to hypothyroidism have been sufficiently demonstrated in many studies.<sup>9</sup> In addition to these, thyroid hormones have been shown to promote angiogenesis and cellular regeneration while limiting apoptosis, inflammation, and fibrosis.<sup>10</sup>

Resulting from the mechanisms discussed above, thyroid hormone deficiency predisposes to left ventricular systolic and diastolic abnormalities.<sup>11</sup> Researchers have found a positive correlation between hypothyroidism and dyslipidemia as well as atherosclerosis.<sup>12</sup> All these further contribute to poor cardiovascular outcomes. Biondi et al<sup>11</sup> demonstrated a two-fold higher incidence of heart failure in patients with thyroid hormone deficiency.

Over the last few years, left ventricular assist (LVAD) has been deployed either as a bridge or destination therapy in patients with advanced heart failure. Two-year survival rates of up to 70% have been observed following LVAD placement in these patients.<sup>2</sup> The ROADMAP trial also found significant improvement in 6-minute walk test in patients with end-stage heart failure who had LVAD in addition to optimal medical therapy compared to those on optimal medical therapy alone at 2 years.<sup>13</sup>

In-hospital mortality in heart failure patients following LVAD implantation approaches 4%.<sup>14</sup> Factors that have been identified to affect in-hospital mortality in these patients include acute kidney injury, age, and gender of the patients as well as hospital ownership with higher mortality in not-for-profit hospitals.<sup>15</sup>

In the present study, in-hospital mortality was comparable between patients with hypothyroidism and those without hypothyroidism. This most likely resulted from an interplay between many factors. Hypothyroid patients were older with a higher prevalence of essential hypertension, chronic kidney disease, and acute kidney disease. These factors were associated with higher mortality in previous studies.<sup>14,16</sup> The 2 groups had comparable rates of maintenance hemodialysis. Our study found a higher incidence of atrial fibrillation in the hypothyroid group. Paradoxically, atrial fibrillation has

**Table 1.** Baseline characteristics of patients with LVAD by Hypothyroidism status.

	TOTAL	HYPOTHYROID	NON-HYPOTHYROID	P VALUE
No. of observation, unweighted	28	503	531	
No. of observation, weighted	142	2501	2643	
Age—year, mean (SE)	58.61 (2.24)	49.95 (1.02)	50.42 (1.01)	<.0001
Female, %	43.72	32.43	33.04	.19
Race/ethnicity, %				.1410
Caucasian	73.32	67.56	67.89	
African American	11.02	13.22	13.09	
Asian	4.16	3.89	3.91	
American Indian	3.80	9.28	8.97	
Pacific islander	3.90	0.89	1.07	
Missing	3.80	5.16	5.07	
Alcohol use	3.53	1.17	1.30	.28
Prior myocardial infarction	7.16	4.78	13.25	.55
Coagulopathy	60.90	45.84	46.65	.06
Atrial fibrillation	48.40	28.04	29.13	.01
Chronic obstructive pulmonary disease	13.84	9.35	9.59	.43
Prior cerebrovascular disease	7.16	5.37	5.46	.60
Hypertension	59.78	31.89	33.39	.001
Peripheral vascular diseases	7.00	8.84	8.74	.74
Diabetes mellitus	32.83	16.81	17.67	.02
Obesity	20.75	8.28	8.95	.04
Hyperlipidemia	38.86	16.75	17.94	.0005
Iron deficiency anemia	20.98	13.56	13.96	.28
Congestive heart failure	3.82	12.29	11.83	.19
Chronic renal failure	44.07	17.46	18.88	.0003
Chronic liver disease	6.95	2.40	2.64	.14
On maintenance dialysis	0.49	0.08	0.10	.5
*Mean Elixhauser score* (SE)	4.12 (0.32)	1.17 (0.026)	1.17	<.0001
Hospital bed size, %				.74
Small	3.53	2.47	2.53	
Medium	10.88	13.43	13.30	
Large	85.59	84.10	84.17	
Expected primary payer, %				.1608
Medicare	38.54	42.81	42.56	
Medicaid	23.10	15.12	15.58	
Private	31.79	35.46	35.25	

(Continued)

Table 1. (Continued)

	TOTAL	HYPOTHYROID	NON-HYPOTHYROID	P VALUE
Self-pay	6.57	3.55	3.72	
Others	0.00	3.06	2.89	
Median household income in quartile, %				.678
1st	24.66	23.91	23.95	
2nd	20.21	22.97	22.82	
3rd	18.55	25.38	25.02	
4th	36.57	27.74	28.21	
Hospital region, %				.33
Northeast	33.83	29.27	29.52	
Midwest	14.50	16.55	16.44	
South	16.88	30.88	30.13	
West	34.79	23.30	23.91	
Hospital teaching status				.59
Rural	2.80	2.22	2.25	
Urban, non-teaching	16.84	12.28	12.52	
Urban, teaching	80.36	85.50	85.22	

Abbreviation: P, P value.

Table 2. Multivariate adjusted model predicting different clinical outcomes by patients' hypothyroidism status.

PRIMARY OUTCOME	HYPOTHYROID	NON-HYPOTHYROID	AOR/MD (95% CI)	P-VALUE
In-hospital mortality (%)	1.13	1.66	0.68 (0.14-3.31)	.19
Acute kidney Injury (%)	10.41	5.69	1.83 (1.38-2.42)	<.0001
Cost—mean (\$)	536063	399699	136,365(1.20-1.52)	.0001
Length of stay*—mean, days	26.46	21.27	5.19 (3.36-7.02)	.0001

Abbreviations: aOR: adjusted odd ratio for categorical variables; MD: adjusted mean difference for continuous variable.

\*Length of stay among those that survived till hospital discharge.

been associated with improved in-hospital mortality in a prior study.<sup>17</sup>

This study found that hypothyroid patients had a longer duration of hospitalization and also accrued higher hospital charges compared to the non-hypothyroid cohorts. This is likely related to the presence of comorbid conditions in the hypothyroid patients, as discussed earlier. In addition to essential hypertension, chronic kidney disease, acute kidney disease, and atrial fibrillation, hypothyroid patients were also more likely to be obese. Multiple studies have evaluated the impact of obesity on post LVAD outcomes, and they found a higher morbidity burden in obese patients, including a higher incidence of pump thrombosis.<sup>18,19</sup> The presence of all these conditions is a likely reason for longer hospital stays and higher costs in the hypothyroid group.

## Conclusion

The present study demonstrated that heart failure patients with hypothyroidism have similar in-hospital mortality following LVAD placement compared to their counterparts without hypothyroidism. Hypothyroid patients are, however, likely to require a higher level of resource utilization, as demonstrated by longer hospital stays and higher hospital charges. More studies are needed to elaborate on the specific contributions of each comorbid condition to these outcomes.

## Limitations

The major limitations of this study were its retrospective and non-randomized nature. The authors were not able to determine the proportion of patients on thyroid replacement therapy. Confounders were corrected with the use of logistic


regression models. The various diagnoses and measurements were not made directly by the authors but were obtained from the NIS. However, these are likely to be close to what obtain in various hospital settings across the United States.


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