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Impact of hyperthyroidism on in-hospital outcomes of patients with heart failure

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ABSTRACT

Congestive heart failure (CHF) exacerbations are a frequent cause of hospitalization. Thyroid hormones impact myocardial function; elevated levels of thyroxine, as seen in hyperthyroidism (HT), can worsen CHF symptoms. We retrospectively evaluated the Hospital Corporation of America (HCA) Enterprise Data Warehouse and examined mortality and length of stay (LOS) in patients hospitalized with CHF with and without a diagnosis of HT.

55,031 patients with CHF were identified. The presence of HT was not significantly associated with mortality (p = 0.24) nor LOS (p = 0.32). A significant difference in the distribution of sex (p = 0.001) and age (p = 0.002) was noted, with a higher percentage of females and a lower median age in patients with HT. There was a significant difference in LOS (p = 0.04) for patients with a cardiovascular comorbidity, who had a mean LOS of 6.33 days versus 5.31 days for patient without HT.

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Heart failure; hyperthyroidism; clinical research; clinical decision making; mortality; length of stay

1. Introduction

Elevated levels of thyroxine (T4), as seen in hyperthyroidism, can cause exacerbation of heart failure symptoms. Over 5 million individuals in the USA carry a diagnosis of congestive heart failure (CHF), and CHF exacerbations are a frequent cause of hospitalization [1]. An estimated 20 million Americans have been diagnosed with some form of thyroid disease [2]. When evaluating patients with clinical symptoms of heart failure, thyroid function must be assessed to identify if it is a potential contributing etiology.

We sought to determine if there was an association between hyperthyroidism and exacerbation of systolic, diastolic, or combined heart failure using a large electronic patient data warehouse of inpatient admissions. We hypothesized that patients with low TSH levels, indicative of acute and subclinical hyperthyroidism, would be likely to have abnormal cardiovascular hemodynamics which may aggravate heart failure, leading to prolonged length of stay, poorer prognosis, and increased mortality.

2. Methods and materials

2.1. Data source

We conducted a retrospective study using the Hospital Corporation of American (HCA) Enterprise Data Warehouse (EDW) for the year 2014. HCA is a private hospital corporation that encompasses 185 hospitals and 119 freestanding surgery centers located in 21 states in the USA and the UK. Data were selected for the study using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. The HCA EDW is a database compiling all inpatient admissions from across all HCA hospitals; it contains de-identified data and therefore exempted from Institutional Review Board approval per the US Department of Health and Human services regulation.

2.2. Study population

All adult patients (age ≥18 years) hospitalized in 2014 were identified. Using ICD-9-CM codes, individuals with heart failure were identified and categorized according to three broad categories of heart failure (i.e., systolic, diastolic, and combined). Hyperthyroidism was subsequently identified (see Appendix for ICD-9-CM codes) as well as demographic characteristics, such as sex, race, and age. According to the Elixhauser comorbidity measure, comorbidities were identified among heart failure patients. As the Elixhauser comorbidity index is based upon dichotomous variables (i.e., they are either present or absent), and has been validated with both ICD-9 and ICD-10 codes are utilized.

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2.3. Outcomes

The primary outcome of interest was mortality in hospitalized patients with heart failure with and without a concomitant diagnosis of hyperthyroidism. The secondary outcome was length of stay.

2.4. Statistical analysis

Descriptive statistics were used to summarize patient characteristics and comorbidities. Bivariate comparisons of patient characteristics, comorbidities, and outcomes between hyperthyroidism groups were conducted using two-sided Chi-Square and independent t-tests. Statistical significance was evaluated using $\alpha = 0.05$. To further explore associations between hyperthyroidism and study outcomes, hyperthyroidism cases were propensity score-matched to controls based on sex, age, race, and comorbidities that could influence study outcomes. Statistical analyses were conducted using Statistica (version 13, Dell Inc.,) and R (version 3.6.1, The R Foundation for Statistical Computing) software.

3. Results

3.1. Demographics

55,031 patients with heart failure were identified, of which 232 patients had a concomitant diagnosis of acute hyperthyroidism (Table 1). Table 1 demonstrates the breakdown of heart failure type in patients with hyperthyroidism. There was no significant difference in heart failure type between patients with or without hyperthyroidism ($p = 0.60$; $\chi^2 = 1.01$, df = 2). There was a significant difference in the distribution of sex ($p = 0.001$, $\chi2 = 10.4$, df = 1) and mean age ($p = 0.002$) between individuals with and without hyperthyroidism, with hyperthyroid individuals more likely to be female and younger (Table 1). Additionally, Caucasians were significantly more likely to have concomitant hyperthyroidism compared on non-Caucasians ($p = 0.01$, $\chi2 = 6.26$, df = 1) (Table 1).

3.2. Mortality

Among all patients evaluated, there was no significant difference in mortality between individuals with and without hyperthyroidism (3.1% vs 1.7%, $p = 0.24$) (Table 1). Similarly, significant differences in mortality were not observed between hyperthyroidism cases and controls for the propensity score-matched subsample (1.3% vs 1.7%, $p = 1.00$) (Table 2).

3.3. Length of stay

Among all patients evaluated, there was no significant difference in length of stay between individuals with and without hyperthyroidism (6.1 vs 6.3 days, $p = 0.72$) (Table 1). Similarly, differences in length of stay (0.93) were not observed between

Table 1. Demographics and comorbidities.

Variable	Without hyperthyroidism *N* (%)	With hyperthyroidism *N* (%)	*P* value
Heart Failure Type			
Systolic	19,127 (34.9%)	79 (34.1%)	
Diastolic	30,149 (55.0%)	125 (53.9%)	
Combined	5,523 (10.1%)	28 (12.1%)	
Heart Failure Present on Admission			0.54
Yes	52,849 (96.4%)	222 (95.7%)	
No	1,950 (3.6%)	10 (4.3%)	
Sex (*N* = 55,011)			0.001
Female	27,946 (51.0%)	143 (61.6%)	
Male	26,833 (49.0%)	89 (38.4%)	
Race (*N* = 54,516)			0.01
Caucasian	39,409 (72.6%)	150 (65.2%)	
Non-Caucasian	14,877 (27.4%)	80 (34.8%)	
Age	Mean (SD) = 73.0 (13.3) Median (IQR) = 75 (65–84) Min = 18 Max = 90	Mean (SD) = 70.3 (14.3) Median (IQR) = 72 (61–81.5) Min = 28 Max = 90	0.002
Comorbidity			
Cardiovascular	44,476 (81.2%)	194 (83.6%)	0.34^
Endocrine	14,104 (25.7%)	63 (27.2%)	0.62^
Liver	148 (0.3%)	0 (0%)	0.43^
Neurologic	1,015 (1.9%)	2 (0.9%)	0.26^
Pulmonary	11,742 (21.4%)	52 (22.4%)	0.71^
Other	12,982 (23.7%)	43 (18.5%)	0.07^
Mortality	1,672 (3.1%)	4 (1.7%)	0.24^
Length of Stay	Mean (SD) = 6.1 (5.8) Median (IQR) = 5 (3–8) Min = 0 Max = 283	Mean (SD) = 6.3 (5.2) Median (IQR) = 5 (3–8) Min = 0 Max = 43	0.72*

SD: standard deviation, IQR: interquartile range.

Table 2. Propensity score matched results (*N* = 460).

Variable	Without hyperthyroidism N (%)	With hyperthyroidism *N* (%)	*P* value
Sex			-
Female	142 (61.7%)	143 (62.2%)	-
Male	88 (38.3%)	87 (37.8%)	-
Race			
Caucasian	149 (64.8%)	150 (65.2%)	-
Non-Caucasian	81 (35.2%)	80 (34.8%)	-
Age	Mean (SD) = 70.4 (14.3)	Mean (SD) = 70.4 (14.3)	-
Heart Failure Type			0.54
Diastolic	134 (58.3%)	124 (53.9%)	
Systolic	75 (32.6%)	79 (34.4%)	
Other	21 (9.1%)	27 (11.7%)	
Cardiovascular	192 (83.5%)	192 (83.5%)	-
Endocrine	62 (27.0%)	62 (27.0%)	-
Liver	0 (0.0%)	0 (0.0%)	-
Neurologic	2 (0.9%)	2 (0.9%)	-
Pulmonary	52 (22.6%)	51 (22.2%)	-
Other	41 (17.8%)	43 (18.7%)	-
Mortality	3 (1.3%)	4 (1.7%)	1.00
Length of Stay	Mean (SD) = 6.1 (5.0)	Mean (SD) = 6.2 (5.2)	0.93

SD: standard deviation.

hyperthyroidism cases and controls for the propensity score-matched subsample (6.1 vs 6.3 days, p = 0.93) (Table 2).

4. Discussion

Hyperthyroidism is prevalent in 5–10% of the population, increasing in prevalence in the sixth decade and above. It is more common in women than men, with an estimated 5:1 ratio [3,4]. Hyperthyroidism leads to a hypermetabolic state, which in turn affects cardiovascular function. Long-term exposure to excessive thyroid hormone may exert unfavorable effects on cardiac function through impaired left ventricle performance and diastolic dysfunction. According to the American College of Cardiology and American Heart Association guidelines for heart failure, hyperthyroidism has been identified as the primary and contributory cause of heart failure [5]. Based on recommendations by the Heart Failure Society of America, all patients suspected to have heart failure should undergo evaluation of thyroid function as a part of their diagnostic work-up [6].

Reportedly, about one-third of patients may develop irreversible hyperthyroid cardiomyopathy [5]. Low output, or 'true,' heart failure can result from severe, long-standing hyperthyroidism and is characterized by decreased contractility, abnormal diastolic compliance, and pulmonary congestion. High output heart failure is characterized by paradoxical features including increased cardiac output and contractility [7]. Analysis of more than 25,000 participants from 6 prospective cohorts from the USA and Europe showed that the risks for hospitalizations and complications due to heart failure exacerbations were increased with both higher and lower TSH values [3]. The risk of developing heart failure is increased in patients with underlying heart conditions and the degree of heart failure may be dependent on the patient's age and severity of hyperthyroidism. Untreated hyperthyroidism and persistent high-output state leads to irreversible ventricular dilation and chronic heart failure, which can result in a fatal outcome [7]. In our retrospective study, we focused on patients diagnosed with hyperthyroidism and aimed to determine its effects on mortality (primary endpoint) and length of stay (secondary endpoint) selectively in those patients with a concomitant diagnosis of heart failure.

In our study, a significant difference (p = 0.005) in the distribution of sex among individuals with and without hyperthyroidism was noted, particularly with a slightly larger percentage of females with heart failure also having a diagnosis of hyperthyroidism. Additionally, a significant difference in age (p = 0.004) was also noted, with younger patients more likely to have hyperthyroidism. This may potentially be due to the increased prevalence of hyperthyroidism seen in women in their later decades.

No significant difference in heart failure type between patients with or without hyperthyroidism was demonstrated. Furthermore, presence or absence of hyperthyroidism did not have a clinical significance for the primary end point, mortality (p = 0.24), and secondary end point, length of stay (p = 0.32). A study by Mitchell et al. showed heart failure patients with abnormal thyroid function had a 60% higher risk compared to euthyroid patients [8]. This is contradictory to the results of our study likely because the patients had been evaluated for and diagnosed with thyroid disease previously and promptly treated. Thus, a euthyroid state was restored before the changes in ventricular function became irreversible.

Our study has several limitations. The heart failure diagnosis captured using chart review may have been present for the patient but not particularly flaring during the course of admission. Secondly, we did not confirm the degree of hyperthyroidism based on lab tests (e.g., TSH <0.01) during the current admission, which may be a more accurate assessment of acute and subacute hyperthyroidism during the course of the admission. Future studies of the impact of hyperthyroidism on acute inpatient CHF outcomes over time are warranted.

5. Conclusion

Among patients with heart failure, significant difference in sex (females > males) and age (mean age was lower in the hyperthyroidism group) was noted for patients with a concomitant diagnosis of hyperthyroidism. However, we did not observe a significant difference in mortality (primary endpoint) or length of stay (secondary endpoint). Further examination of this potential association is warranted.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix

Appendix. ICD-9 codes used for data analysis.

Heart failure	428.0, 428.20, 428.2, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40, 428.41, 428.42, 428.4 428.1, 428.9
Thyrotoxicosis/ hyperthyroidism	242.00, 242.01, 242.30, 242.31, 242.20, 242.21, 242.10, 242.11, 242.90, 242.91, 242.40, 242.80, 242.41, 242.81
Cardiovascular	427.31, 427.32, 427.0, 427.41, 427.42, 427.1, 427.5, 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 785.51, 401.1, 401.9 414.01, 443.9, 443.89
Pulmonary	415.1, 415.11, 415.12, 415.19, 491.0, 491.1, 491.8, 491.9, 492.0, 492.8, 493.0, 493.1, 493.2, 493.8, 493.9, 518.81, 518.82, 518.84
GI/Liver	570, 573.3, 790.4
Renal	584, 584.5, 584.6, 584.7, 584.8, 584.9, 39.95
Neuro	434.01, 434.11, 434.91, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9
Endocrine	250.02, 250.00, 250.01, 250.03, 357.2, 362.0, 362.07, 278.00, 278.01
Other	305.1, 305.00, 305.01, 305.02, 305.03, 304.21, 304.22, 304.23, 305.61, 305.62, 305.63, 304.30, 304.31, 304.32, 304.33, 305.20, 305.21, 305.22, 305.23, 304.40, 304.41, 304.42, 304.43, 305.70, 305.71, 305.72, 305.73, 304.00, 304.01, 304.02, 304.03, 305.50, 305.51, 305.52, 305.53, 785.50, 785.59