The subclinical hypothyroid state might predict 30-day readmission in patients admitted with acute heart failure syndrome and reduced left ventricular ejection fraction

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Abstract
Introduction: Thyroid hormone (TH) has an essential role on the functional capability of cardiac muscle with its gene modulation and induction of vasodilatory effects. There is considerable evidence to suggest the role of TH in patients with acute coronary syndrome, but less is known about its prognostic role in heart failure (HF) patients. We aim to evaluate the association between subclinical hypothyroid state (SCHS) and event rates including 30-day all-cause and HF readmission in patients with an index hospitalization for acute HF syndrome (AHFS).

Methodology: A retrospective chart review analysis of 2335 patients admitted with the diagnosis of AHFS between 1 January 2007 and 31 December 2017 was conducted. SCHS was defined as thyroid-stimulating hormone (TSH) level >4.50 mIU/L with a normal thyroxine (T4) level. Patients with pre-existing thyroid disease or receiving thyroid replacement therapy were excluded. HF with preserved ejection fraction (HFpEF) was defined as left ventricular ejection fraction (LVEF) >40% and HF with reduced ejection fraction (HFrEF) was defined as having LVEF ≤40%.

Results: The mean age of the 2335 AHFS population was 65 (± 14.8) years. Of the 2335 patients admitted with AHFS, 1228 (52.6%) patients were found to have HFrEF and 1107 (47.4%) with HFpEF. There were 170 (7.3%) patients with AHFS found to have SCHS. There were more males than females (54% versus 46%). The percentage of hospital readmission within 30 days was higher for patients with SCHS compared with those without SCHS in the HFrEF group (42% versus 30%, \(p=0.001\)). Hospital readmission within 30 days for patients with SCHS compared with those without SCHS in the HFrEF group did not differ (36.5% versus 31%, \(p=0.47\)). Additionally, all-cause mortality was higher among patients with SCHS compared with patients without SCHS in the HFrEF group (18.7% versus 7.0%, \(p<0.001\)). All-cause mortality was found similar in both arms of the HFpEF group (9.5% versus 7.7%, \(p=0.73\)).

Conclusion: During an index hospital admission for AHFS, SCHS was an independent predictor of readmission in 30 days in patients with HFrEF but not in patients with HFpEF. Additionally, it was related to adverse outcome such as all-cause mortality in HFrEF patients but not in HFpEF patients. Further studies regarding the concept of tissue thyroid and the potential for a therapeutic target are warranted.

Keywords: Subclinical hypothyroid, heart failure

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**Introduction**

Heart failure (HF) is responsible for 11 million physician visits each year and more hospitalizations than all forms of cancer combined. It is the first-listed diagnosis in 875,000 hospitalizations and contributes to approximately 287,000 deaths yearly. The expenditure of HF care is high and creates a significant burden on the United States healthcare system.

More specifically, the cost of HF management is projected to increase markedly; a 2.5-fold increase from $20.9 billion in 2012 to $53.1 billion by 2030. Of note, 80% of the costs are related to HF hospitalization. Preventable hospital readmissions are typically associated with poor quality care. As a result, the Centers for Medicare and Medicaid Services have instituted the Hospital Readmission Reduction Program (HRRP). The HRRP is a provision of the Affordable Care Act which now penalizes healthcare centers for abnormally high rates of preventable patient readmissions, including HF. To provide better care for their patients, it is imperative that healthcare centers seek to find methods to decrease event rates such as hospital readmission as well as to reduce length of hospital stay (LOS). With medical advancement, better understanding of HF pathophysiology led to improved management and prognostic outcomes. The metabolic model of HF assisted in characterizing the alterations in cardiac dysfunction which may also participate in disease progression. Metabolic remodeling includes mitochondrial malfunction, lack of adenosine triphosphate and ultimately pump failure secondary to contractile dysfunction.

Thyroid hormone (TH) has an essential role in the metabolic pathway with its gene-modulating and induction of vasodilatory effects. Although pre-existing TH deficiency is itself a risk factor for decompensated HF, abnormal thyroid-stimulating hormone/thyrotropin (TSH) in the presence of a normal thyroxine (T4) level (also known as subclinical hypothyroid state or SCHS) has been associated with poor outcomes in patients with cardiovascular (CV) disease. The prevalence of SCHS in the general HF population ranges invariably from 6% to 18%. According to a pooled cohort study, SCHS was noted in approximately 8% of the HF population with prevalence increasing to 10% in the elderly population. In the NHANE III survey, SCHS was found in 10% of patients with HF with reduced ejection fraction (HFrEF). Selvaraj et al. found that SCHS was present in 22% of patients with HF with preserved ejection fraction (HFpEF) and plays a prognostic role in this cohort of HF. Madathil et al. demonstrated utilizing cardiac magnetic resonance imaging (cMRI) that SCHS can lead to bioenergetic impairment which can be improved by TH replacement therapy.

There is considerable evidence to suggest the role of TH in patients with acute coronary syndrome (ACS), but less is known about its prognostic role in HF patients. The purpose of our study was to examine the association between SCHS and event rates including 30-day all-cause and HF rehospitalization as well as LOS in patients admitted with an index hospitalization for acute HF syndrome (AHFS). Particularly, we will retrospectively determine whether SCHS can predict outcomes in patients admitted for AHFS.

**Methodology**

**Study design**

A retrospective chart review of patients admitted with AHFS between 1 January 2007 and 31 December 2017 was conducted. A total of 2605 patients with HF were identified out of which 130 (5%) patients did not have thyroid function testing and were excluded from the study. Additionally, 80 (3.1%) patients receiving TH and 56 (2.1%) receiving amiodarone therapies were excluded. A total of 2339 HF patients were finally reviewed, of which 174 had confirmed SCHS during the hospital stay and 2165 did not have SCHS. Of the 174 (7.4%) patients with SCHS, four patients had a prolonged hospital stay and suspicion for euthyroid sick syndrome (ESS) was high with triiodothyronine (T3) results unavailable, and therefore they were further excluded from the study, making the total study population of 2335 patients. We collected data regarding patients’ baseline demographics, comorbid conditions, medication history, vital signs and laboratory parameters. We reviewed serum thyroid panel including TSH and free T4 levels during the current admission (index admission) and follow-up with subsequent hospitalizations. Transthoracic echocardiography (TTE), stress testing and coronary angiogram data were reviewed to assess the etiology of HF. The primary outcome in our study
was 30-day, 3-month and 6-month all-cause and HF rehospitalization as well as LOS in patients admitted with an index hospitalization for AHFS. Secondary outcomes were need for coronary care unit (CCU) admission and all-cause mortality at 1 year. We segregated all HF patients into two groups including HFrEF and HfPEF and studied the outcome data in each cohort. Follow-up information was obtained from retrospective review of charts.

The study was approved by the institutional review board (IRB#11091704) and the need for written informed consent was waived.

**Definitions**

The following definitions were used in our study:

- HfPEF: LVEF > 40%
- HFrEF: LVEF ≤ 40%
- SCHS: elevated TSH (4.5–19.9 mIU/L) level with a normal free T₄ level

Institutional reference range was used for free T₄ levels (0.8–2.0 ng/dL)

- Index admission: Current admission with AHFS taken as reference for follow-up data

**Statistical analysis**

Demographic information and clinical outcomes were stratified by SCHS status. Means and standard deviations (SDs) were reported for continuous variables. Frequencies and percentages were reported for categorical variables. ANOVA tests were used to assess the association between continuous variables and SCHS status. Chi-squared tests were used to assess associations between categorical variables and SCHS status. The results were expressed as counts (percentages) for categorical variables and mean (± SD) for continuous variables. Chi-squared tests were used to assess associations between outcome variables and SCHS status. Separate-multivariable logistic regressions were used to assess the associations between SCHS status and...
outcomes including discharge outcome, CCU admission status, 30-day, 3-month and 6-month readmission status controlling age, gender, heart rate, systolic blood pressure, HIV status, HFrEF and HFrEF status, Troponin and ProBNP levels and if treatment fulfilled guideline-directed medical therapy.

Results
Table 1 indicates demographic and clinical information stratified by SCHS status for all patients with HF. There were 2335 patients in the sample population. The mean age of the patient population was 65 (±14.8) years. Approximately 46% of the patients were female. Compared with patients without SCHS, patients with SCHS demonstrated lower mean arterial blood pressure (MAP) (93.7 versus 97.1, p = 0.025), higher ProBNP level (11,320.9 versus 7557.9, p = 0.003), higher peak Troponin level (0.750 versus 0.196, p = 0.065) and higher incidence of HIV (15.6% versus 9%, p = 0.026).

Table 2 illustrates outcomes stratified by SCHS status in the whole sample population. The percentage of 30-day readmission and all-cause mortality at 1-year were higher for patients with SCHS compared with patients without SCHS (30-day readmission, 47.1% versus 38%, p = 0.003; all-cause mortality at 1-year 15.3% versus 7.3%, p < 0.001).

Table 3 shows outcomes stratified by SCHS status in HFpEF patients only. The 30-day, 3-month and 6-month readmission rates, CCU admission status and 1-year all-cause mortality did not differ between the two groups of HFpEF patients.

Table 4 demonstrates outcomes stratified by SCHS status for patients with HFrEF only. The percentage of mortality and 30-day readmission and all-cause mortality at 1-year were higher for patients with SCHS compared with patients without SCHS (30-day readmission 42.1% versus 30.3%, p = 0.001; all-cause mortality at 1-year 18.7 versus 7%, p < 0.001).

Table 5 indicates results from a regression analysis for the whole sample population. After controlling confounding factors, the odds ratios of requiring a CCU admission was 1.86 [confidence interval (CI) = 0.94, 3.54], 30-day readmission 2.82 (CI = 1.56, 5.09) and 3-month readmission 0.59 (CI = 0.33, 1.06).

Discussion
In this 10-year retrospective single-center study of all hospitalized patients with AHFS, we demonstrated that SCHS was associated with worse outcomes. The altered thyroid metabolic condition of SCHS can lead to a higher likelihood of 30-day all-cause readmission and 1-year all-cause mortality especially in those patients with HFrEF. On the other hand, SCHS was not associated with any adverse outcomes in patients with HFpEF. To the extent of our knowledge, this study is the first attempt to extensively investigate this clinical and prognostic correlation of SCHS in cohorts of HFpEF and HFrEF. SCHS has been reported in various studies to be associated with CV events.12–16 These events included risk of HF onset and progression, myocardial ischemia, vascular function abnormalities and dyslipidemia. Considering this information, the American College of Cardiology and American Heart Association has recommended TH level measurements to identify the etiology of HF exacerbation and progression, but the guidelines did not suggest an approach to management for the SCHS population.14–16 Based on TSH level, SCHS can be dichotomized into groups: First, a TSH greater than 4.5–5 mIU/L and second TSH level above 10 mIU/L.14 In our study, the average TSH in the SCHS group was observed as 9.62 mIU/L. In a multicentric pooled cohort study, the risk of all-cause and CV-related mortality was increased at TSH levels higher than 10 mIU/L.7 However, this study did not include hospital readmission as an outcome measure. Park and Lee showed in a study of 2404 subjects that SCHS is an independent risk factor for CV disease in general but did not consider HF-related outcomes specifically.13 Furthermore, in a review study by Biondi et al., the authors concluded that SCHS is associated with myocardial remodeling, relaxation abnormalities and reduced cardiopulmonary exercise capacity which can be improved with recovery to the euthyroid state with no data suggesting mortality benefit.4 In our study, SCHS was found in
| Table 1. Clinical and demographic information by subclinical hypothyroidism status for all patients with heart failure. |
|---------------------------------------------------------------|
| **Variables** | **HF with SCHS** | **HF without SCHS** | **Total n=2335** | **p-value** |
|---------------|-----------------|-------------------|-----------------|-------------|
| Age           | 63.9 [15.3]     | 65.4 [14.8]       | 65.3 [14.8]     | 0.19        |
| Gender [females] | 65 [38.2%]     | 1011 [43.3%]     | 1076 [46%]      | 0.86        |
| Average BMI   | 30.9 [12.9]     | 32.2 [13.7]       | 32.1 [13.6]     | 0.22        |
| Comorbidities |                 |                   |                 |             |
| CKD [eGFR of less than 60 ml/min] | 115 [67.6%] | 1423 [65.8%] | 1538 [66%] | 0.67        |
| DM            | 102 [60.0%]     | 1363 [63.3%]     | 1465 [63%]      | 0.44        |
| HTN           | 159 [93.5%]     | 1992 [92.1%]     | 2151 [92.2%]    | 0.59        |
| Smoking history | 93 [62.4%]     | 1189 [59.9%]     | 1282 [60.1%]    | 0.61        |
| Ischemic etiology of HF | 47 [28.0%] | 711 [32.9%] | 758 [32.5%] | 0.22        |
| DMT           | 112 [93.3%]     | 1459 [92.5%]     | 1571 [92.6%]    | 0.88        |
| SBP (mmHG)    | 130.7 [26.4]    | 128.5 [28.5]     | 96.8 [18.9]     | 0.03        |
| ProBNP (pg/ml) | 11,320.9 [16658.4] | 7557.9 [15188.1] | 7827.8 [15325.6] | 0.003       |
| TSH (index admission) (mIU/L) | 9.6 [3.8] | 2.8 [1.06] | 3.4 [3.6] | <0.001 |
| TSH (6 month) (mIU/L) | 9.2 [3.2] | 2.8 [1.06] | 3.6 [3.6] | <0.001 |
| Total T₃ (mIU/L) | 80.7 [26.3] | 88.9 [29.4] | 88.1 [29.2] | 0.001 |
| Free T₄ (mIU/L) | 1.6 [16.8] | 1.7 [4.1] | 1.8 [6.3] | 0.03 |
| Troponin      | 0.8 [6.1]       | 0.2 [2.7]        | 0.2 [3.1]       | 0.07        |
| LVEF (%)      | 35.7 [17.5]     | 43.4 [10.8]      | 42.9 [10.41]    | 0.36        |
| HFpEF         | 63 [3%]         | 1044 [44%]       | 1107 [47.4%]    |             |
| HFrEF         | 107 [4.6%]      | 1121 [48%]       | 1228 [52.5%]    |             |

BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, efferent glomular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; ProBNP, pro-brain natriuretic peptide; SCHS, subclinical hypothyroid state; T₃, triiodothyronine; T₄, thyroxine; TSH, thyroid-stimulating hormone.

| Table 2. Univariate outcome by subclinical hypothyroidism status for heart failure patients. |
|---------------------------------------------------------------|
| **Outcome variables** | **HF with SCHS** | **HF without SCHS** | **Total n=2335** | **p-value** |
|------------------------|-----------------|-------------------|-----------------|-------------|
| 1 year Mortality       | 26 [15.3%]     | 159 [7.3%]       | 185 [7.9%]      | <0.001      |
| CCU admission          | 8 [4.7%]       | 266 [12%]        | 274 [11.7%]     | 0.25        |
| Readmission in 30 days | 80 [47.1%]     | 822 [38%]        | 902 [38.6%]     | 0.003       |
| Readmission in 3 months| 30 [18%]       | 420 [19.4%]      | 450 [19.3%]     | 0.97        |
| Readmission in 6 months| 26 [15.3%]     | 498 [23%]        | 524 [22.4%]     | 0.81        |

CCU, cardiac care unit; HF heart failure; SCHS, subclinical hypothyroid state.
Table 3. Univariate outcome by subclinical hypothyroidism status for heart failure with preserved ejection fraction patients.

| Outcome variable       | HFrEF with SCHS (n = 63) | HFrEF without SCHS (n = 1044) | Total (n = 1107) | p-value |
|------------------------|---------------------------|-------------------------------|------------------|---------|
| 1 year Mortality       | 6 (9.5%)                  | 80 (7.7%)                     | 86 (7.8%)        | 0.73    |
| CCU admission          | 7 (11.1%)                 | 131 (12.5%)                   | 138 (12.5%)      | 0.65    |
| Readmission in 30 days | 23 (36.50%)               | 322 (31%)                     | 345 (31.2%)      | 0.47    |
| Readmission in 3 months| 17 (27%)                  | 278 (26.6%)                   | 295 (26.6%)      | 0.26    |
| Readmission in 6 months| 10 (15.9%)                | 233 (22.3%)                   | 243 (22%)        | 0.07    |

CCU, cardiac care unit; HFrEF, heart failure reduced ejection fraction; SCHS, subclinical hypothyroid state.

Table 4. Univariate outcome by subclinical hypothyroidism status for heart failure with reduced ejection fraction patients.

| Outcome variable       | HFrEF with SCHS (n = 107) | HFrEF without SCHS (n = 1121) | Total (n = 1228) | p-value |
|------------------------|---------------------------|-------------------------------|------------------|---------|
| 1 year Mortality       | 20 (18.7%)                | 78 (7.0%)                     | 98 (8.0%)        | <0.001  |
| CCU admission          | 5 (5%)                    | 100 (9%)                      | 105 (8.6%)       | 0.27    |
| Readmission in 30 days | 45 (42.05%)               | 340 (30.3%)                   | 385 (31.4%)      | 0.001   |
| Readmission in 3 months| 22 (20.5%)                | 353 (31.5%)                   | 375 (30.5%)      | 0.46    |
| Readmission in 6 months| 15 (14.01%)               | 250 (22.3%)                   | 265 (21.6%)      | 0.42    |

CCU, cardiac care unit; HFrEF, heart failure reduced ejection fraction; SCHS, subclinical hypothyroid state.

Table 5. Logistic regression assessing the association between subclinical hypothyroid status and outcomes controlling confounders in all heart failure patients.

| Outcome variable       | Risk factor; SCHS status | Odds ratio (95% confidence interval) or estimate (95% confidence intervals) | p-value |
|------------------------|--------------------------|-----------------------------------------------------------------------------|---------|
| MODEL 1 Death in 1 year| No SCHS SCHS             | Ref 1.85 (0.78, 4.06)                                                       | 0.14    |
| MODEL 2 CCU admission  | No SCHS SCHS             | Ref 1.86 (0.94, 3.54)                                                       | 0.07    |
| MODEL 3 Readmission in 30 days | No SCHS SCHS | Ref 2.82 (1.56, 5.09)                                                     | 0.001   |
| MODEL 5 Readmission in 3 months | No SCHS SCHS | Ref 0.59 (0.33, 1.06)                                                     | 0.08    |
| MODEL 6 Readmission in 6 months | No SCHS SCHS | Ref 0.98 (0.54, 1.74)                                                     | 0.93    |

The variables adjusted for are: age, gender, heart rate, systolic blood pressure, HIV status, HFrEF and HFrEF status, Troponin and ProBNP levels and if treatment fulfilled guideline-directed medical therapy. CCU, cardiac care unit; SCHS, subclinical hypothyroid state.
7.3% of the population with pre-existing HF, having 5.7% incidence in HFrEF and 8.7% in HFrEF populations. Additionally, we investigated the recurrent hospitalization rates in the background of SCHS. We found that 30-day all-cause readmission in the HF population with SCHS was 47% compared with 38% in those without SCHS. The all-cause mortality in the SCHS population was noted to be 15.3%, which is similar to other findings observed in several other studies ranging from 6% to 17%.12–16

Age is proposed as a prognostic marker in the SCHS based on various observational studies. It has been postulated that SCHS in the elderly age group (≥65 years) is not a risk factor for CV mortality.14 Rodondi and Newman indicated in a prospective study of 2730 subjects that SCHS was prevalent in 12% of the population, and out of those, 6.4% had HF at baseline, 6.5% developed new-onset HF and 2% had recurrent hospitalizations.17 The authors concluded that although SCHS is associated with HF events in the elderly population, it is unrelated to increased mortality.17 Similar results regarding older populations were reported in an analysis from the Health, Aging and Body Composition Study of individuals.18 On the other hand, the PROSPER study concluded in a 3.2-year follow-up in elderly subjects that SCHS is not associated with CV events or mortality unless the TSH level is greater than 10 mIU/L.19,20 In our study, the mean age was 65 years and outcomes in terms of readmission rates

**Table 6.** Logistic regression assessing the association between subclinical hypothyroid status and outcomes controlling confounders in heart failure.

| Outcome variable          | Risk factor; SCHS status | Odds Ratio (95% confidence interval) or estimate (95% confidence intervals) | p-value |
|---------------------------|--------------------------|--------------------------------------------------------------------------------|---------|
| MODEL 1 Death in 1 year   | No SCHS SCHS            | Ref 1.81 (0.05, 34.91)                                                        | 0.707   |
| MODEL 2 CCU admission     | No SCHS SCHS            | Ref 1.04 (0.33, 2.65)                                                         | 0.945   |
| MODEL 3 Readmission in 30 days | No SCHS SCHS      | Ref 1.01 (0.99, 1.02)                                                         | 0.311   |
| MODEL 5 Readmission in 3 months | No SCHS SCHS  | Ref 1.27 (0.94, 1.72)                                                         | 0.113   |
| MODEL 6 Readmission in 6 months | No SCHS SCHS  | Ref 0.65 (0.14, 2.88)                                                         | 0.568   |

The variables adjusted for are: age, gender, heart rate, systolic blood pressure, HIV status, HFrEF and HFrEF status, Troponin and ProBNP levels and if treatment fulfilled guideline-directed medical therapy. CCU, cardiac care unit; SCHS, subclinical hypothyroid state.

**Table 7.** Logistic regression assessing the association between subclinical hypothyroid status and outcomes controlling confounders in heart failure with reduced ejection fraction patients.

| Outcome variable          | Risk factor; SCHS status | Odds ratio (95% confidence interval) or estimate (95% confidence intervals) | p-value |
|---------------------------|--------------------------|--------------------------------------------------------------------------------|---------|
| MODEL 1 Death in 1 year   | No SCHS SCHS            | Ref 1.8 (0.95, 3.57)                                                          | 0.001   |
| MODEL 2 CCU admission     | No SCHS SCHS            | Ref 2.36 (1.47, 3.9)                                                          | 0.07    |
| MODEL 3 Readmission in 30 days | No SCHS SCHS      | Ref 0.75 (0.54, 1.05)                                                         | 0.001   |
| MODEL 5 Readmission in 3 months | No SCHS SCHS  | Ref 1.27 (0.94, 1.72)                                                         | 0.113   |
| MODEL 6 Readmission in 6 months | No SCHS SCHS  | Ref 1.32 (0.98, 1.78)                                                         | 0.065   |

The variables adjusted for are: age, gender, heart rate, systolic blood pressure, HIV status, HFrEF and HFrEF status, Troponin and ProBNP levels and if treatment fulfilled guideline-directed medical therapy. CCU, cardiac care unit; SCHS, subclinical hypothyroid state.
and all-cause mortality were significant. Although the difference in disease patterns in the younger versus older age groups is not well elucidated in the literature, we contemplate that the body’s physiological dynamic and metabolic rate is adjusted to higher TSH levels with advancing age. On the contrary, the higher metabolic requirement in the younger age group can be unmasked by the slightest alteration in TH levels necessitating supplementation.16–20

The pathophysiology of SCHS and HF-related outcomes is vaguely explained in the literature. Genetic and molecular studies have illustrated that alteration of myocardial gene expression induced by deficient TH in SCHS can ultimately lead to diastolic and systolic dysfunction with deleterious effects on cardiac stroke volume.15,16 This SCHS-driven decrement in preload and afterload will lead to renal hypoperfusion, activation of the renin–angiotensin–aldosterone system and worsening of homeostatic balance. Persistent hyponatremia and impaired free water clearance can lead to HF decompensation, resulting in increased hospitalization and issues with diuretic efficacy. The vascular endothelial dysfunction governed by the SCHS can lead to higher systemic vascular resistance exerting more demand on an already failing heart. These subtle changes at the molecular level may not be evident clinically due to compensatory mechanisms and may eventually express in the form of reduced exercise capacity hinting toward a cardiometabolic disturbance. The symptomatology varies with the individual’s genotype, duration and degree of occult thyroid abnormality as well as predisposing increased risk of CV events.18–20

The association of SCHS in the context of HFpEF and HFrEF is not elaborated in many studies.

We found in our HFrEF population that SCHS was associated with an increased risk of 30-day readmission in SCHS group (42%) compared with those without SCHS (30%). The all-cause mortality was also notably higher in HFrEF with SCHS (18.7%) compared with those without SCHS (7%). The Cardiovascular Health Study described, based on their TTE experience, that SCHS is associated with a higher incidence of HFrEF events especially when the TSH level exceeds 10 mIU/L.15 Similar results were reported by Rodondi and Newman with TSH levels greater than 7 mIU/L followed by Iacoviello et al. reporting SCHS (TSH greater than 5.5 mIU/L) associated with recurrent HF hospitalization during follow-up of HFrEF patients in the outpatient setting.17,19 These findings were further illustrated by Baris et al. showing that the adverse outcomes (readmission and mortality rates) were associated with the degree of thyroid dysfunction with a parabolic association between TSH levels and risk of HF events (p-value for quadratic pattern < 0.01).20 In contrast, in a study on 1032 HFrEF patients by Frey and Kroiss, subclinical thyroid dysfunction was not deemed a marker of disease progression.21 This study included all subclinical thyroid dysfunction including hyperthyroid state, and thus results cannot be generalized to the SCHS cohort only.

In recent studies exploring the role of SCHS in HF subjects, much emphasis has been placed on TTE data to reveal its utilization in the HfPef cohort.4,22,23 Kinugasa and Yamamoto described the specific pattern of HF progression in the SCHS population which included ventricular filling and stiffness restriction.23 In the real world, this pathophysiology resembles evolutionary mechanisms of HFpEF, indicating an association of HFpEF with SCHS. Biondi et al. referred that SCHS is associated with diastolic dysfunction and has less impact on systolic function.4 Kosar et al. examined a step further using tissue Doppler imaging and concluded that diastolic dysfunction is not only limited to the left ventricle but also includes the right ventricle in the setting of SCHS.24 However, outcome data, specifically readmission and mortality events in the HFpEF population, remained an area of ambiguity. In a study of 249 HFpEF subjects, SCHS was associated with higher mortality (29.6%) compared with the euthyroid state.25 Our study with a larger population showed that SCHS in HFpEF is not associated with any adverse outcomes, including all-cause readmission and mortality rates.

The data regarding management of SCHS to avoid HF-related events are mainly restricted to the reversal of cardiac imaging findings.26–28 In a small-scale study of 42 subjects, it was concluded that TH should be replaced in SCHS to prevent progression to clinically significant cardiac dysfunction.27 Similar findings were proposed by Erkan et al. in a study on a female population with correction of diastolic dysfunction using TH replacement therapy.28 On the contrary, the TRUST trial was unsuccessful in validating such findings.29 Although this study included the SCHS population and maintained a euthyroid state with TH
replacement therapy, the outcome considered in this study did not include CV events. Currently, the indications for SCHS management include symptomatic hypothyroidism, TSH greater than 10 mIU/L and younger populations. This management protocol did not include the HF population and may require more elucidation in terms of outcomes and prognosis.

Our study has certain limitations. First, a retrospective design was used, thus we were limited to the information obtained by the electronic medical records and without direct patient contact. The study included patients from a single center, which cares for an inner-city population with specific demographic characteristics. Our study group represented a relatively small population of SCHS compared with some larger HF studies, which can affect study power. However, we believe that even with this small patient population our study was able to answer some interesting clinical questions. The primary and secondary outcome measures of readmission and mortality rates presented in this study are not only restricted to HF but included all-cause related events which can have an impact on our results. In limited literature obesity is reported to be associated with SCH but less is known about the outcomes. Our subjects with SCH had obesity, which may be confounder in our findings. The T₃ levels were unavailable in our patient population so we excluded the ESS population from our study based on clinical judgment. Although there may be an association of ESS with HF events, this area was beyond the scope of our study based on the laboratory limitation of unobtainable T₃ levels on all HF patients. We included all-cause related events in hospitalized patients and excluded events in the outpatient setting which may have different outcomes. Another limitation is that as this was a single-centered study, we did not have complete access to the records if patients were readmitted to a different hospital. Lastly, we did not segregate our SCHS population based on autoimmune thyroid disease, which may have an impact on our results. Despite these limitations, our study highlights the potential association of SCHS and HF-related events that have both clinical and prognostic implications in the care of these patients.

**Conclusion**

SCHS is associated with distinct clinical and prognostic outcomes in the HF population. During an index hospital admission for AHFS, SCHS was an independent predictor of readmission in 30 days in patients with HFrEF but not in patients with HFpEF. Additionally, it was related to adverse outcome such as all-cause mortality at 1-year. Further studies regarding the concept of tissue thyroid and the potential for a therapeutic target needed to validate our findings are warranted.

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**Conflict of interest statement**

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