

Original Research Paper

A Comparative Analysis of TSH Levels between Patients with Normal Sinus Rhythm and those with Atrial Fibrillation

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Abstract: Atrial Fibrillation (AF) is the most prevalent persistent cardiac arrhythmia observed within the general population and is associated with increased morbidity and mortality. Despite the rising global prevalence of AF, the majority of existing studies have primarily focused on white populations. For that reason, we have used a Korean hospital patient's blood test results to examine the link between AF and certain blood test results. Conducted at a tertiary medical institution, this retrospective study included patients with Normal Sinus Rhythm (NSR) and AF, excluding those on thyroid medications at diagnosis. Initially, 200 patients were evaluated, with 36 excluded, leaving 164 for the final analysis. In the NSR group, the average Thyroid Stimulating Hormone (TSH) level was 1.88 (normal range: 0.41-4.3 uIU/mL), with a standard deviation of 1.27. In the AF group, the average TSH level was 2.48, with a standard deviation of 1.91 ($p = 0.018$). AF was associated with both hyperthyroidism and hypothyroidism, which appeared to be a common precursor of thyroid dysfunction. The study highlights clinical risk factors for thyroid dysfunction in AF patients, despite limitations such as a small sample size and potential detection bias due to unrecognized new-onset AF.

Keywords: Arrhythmia, Atrial Fibrillation, Hyperthyroidism, Thyroid-Stimulating Hormone

Introduction

Atrial Fibrillation (AF) is a type of supraventricular tachycardia characterized by irregular and rapid atrial activation (Anderson *et al.*, 2020). It is the most prevalent arrhythmia in clinical practice, with its incidence rising over recent decades (Apostol *et al.*, 2019). AF is a significant public health issue due to its independent association with increased cardiovascular morbidity and mortality (Baumgartner *et al.*, 2017).

Most research on AF has historically focused on the Caucasian population in Europe and North America (Liu *et al.*, 2007). However, the burden of AF in Asia is increasing rapidly due to the aging population (Bekiaridou *et al.*, 2022). The impact of AF on hospitalization, mortality and economic burden in Asian populations is not well understood. To address this gap, a Korean hospital database was used to evaluate the AF-related hospital care burden, as well as the relationship between AF and certain blood test results. (Bellew *et al.*, 2015). This research aims to contribute to a deeper understanding of the epidemiology of AF in Asian populations and elucidate potential risk factors,

particularly focusing on thyroid function, which remains understudied in this context.

AF is highly common and can lead to heart failure, stroke and even death. Understanding modifiable risk factors can offer opportunities for prevention (Buccelletti *et al.*, 2011). The risk of AF is known to be higher in patients with subclinical hyperthyroidism, but the relevance of normal thyroid function variations or hypothyroidism to AF remains unclear (Chaker *et al.*, 2018). This study holds considerable significance within the realms of clinical cardiology and endocrinology research, offering novel insights into the association between AF and thyroid function within the Asian population (Kim and Kim, 2018). Through a meticulous examination of these interrelated phenomena, this research endeavors to address critical lacunae in current understanding while also contributing substantively to existing knowledge.

Thyroid function is closely associated with the cardiovascular system (Yamakawa *et al.*, 2021). Aberrations in thyroid hormone levels, either in excess or deficient conditions, can affect vital cardiovascular parameters such as heart rate, blood pressure and blood

circulation within the vessels (Jabbar *et al.*, 2017). Investigating thyroid function in AF patients allows for exploring the interactions between thyroid and cardiovascular health (Vasilopoulou *et al.*, 2024).

Thyroxine (T4) and Triiodothyronine (T3) represent key hormones derived from tyrosine and synthesized within the thyroid gland. Within the bloodstream, thyroxine predominates as the primary form of thyroid hormone (Osuna *et al.*, 2017). Through enzymatic action by deiodinases, thyroxine undergoes conversion into the biologically active Triiodothyronine (T3). Thyroid-Stimulating Hormone (TSH) regulates thyroid hormone secretion, with its production controlled by Thyrotropin-Releasing Hormone (TRH) from the hypothalamus, transported to the anterior pituitary gland (Bielecka-Dabrowa *et al.*, 2009).

Several studies have explored the relationship between thyroid hormone levels and AF (Meng *et al.*, 2022). Thyroid hormones are crucial in cardiac electrophysiology, influencing ion channels that maintain heart rhythm (Fazio, 2004). TSH is a pituitary hormone that regulates the production and release of thyroid hormones, making it a crucial biomarker for assessing thyroid function (Olanrewaju *et al.*, 2024).

TSH has an inverse logarithmic relationship with free thyroxine (free T4), making small changes in serum-free T4 levels result in significant changes in TSH levels (Razvi *et al.*, 2019). Assessing TSH is a sensitive method for screening thyroid dysfunction (Soldin *et al.*, 2013). Overt thyroid disease is linked to atherosclerotic cardiovascular disease, indicative of overt hypothyroidism due to hypercholesterolemia and elevated blood pressure (Lee *et al.*, 2011).

In individuals diagnosed with hyperthyroidism, notable physiological alterations include elevated heart rate and a heightened propensity for arrhythmias. There is also an increase in Left Ventricular Mass (LVM), primarily due to concentric remodeling, correlating with modest systolic function improvement but often impaired diastolic function due to slower myocardial relaxation (Kannan *et al.*, 2018).

Various mechanisms may explain the influence of thyroid hormones on AF risk, such as elevated left atrial pressure from increased LVM and impaired ventricular relaxation, ischemic events from high resting heart rate and increased atrial ectopic activity.

In vitro investigations have revealed that Triiodothyronine (T3) shortens the repolarization phase of the membrane action potential and speeds up diastolic repolarization. Consequently, this phenomenon accelerates the pace of contraction within cardiac myocytes (Biondi *et al.*, 2002).

Reentry is theorized as a primary mechanism underlying the onset of AF (Kornej *et al.*, 2020). Multicircuit wavefronts originating within the atrium have the potential to disrupt normal sinus rhythm, thereby establishing a fibrillatory pattern. Hyperthyroidism, characterized by a shortened Action Potential Duration

(APD), plays a significant role in this process. APD dictates the refractory period, thus serving as a pivotal factor influencing the probability of reentry occurrence (Arnsdorf and Childers, 1970). This examination provides insights into the mutual influence of the thyroid and cardiovascular systems, elucidating how alterations in thyroid function may impact the occurrence of AF (Al-Makhamreh *et al.*, 2022).

Both hyperthyroidism and hypothyroidism can impact cardiac function and overall cardiovascular health. Overt hyperthyroidism induces a hyperdynamic cardiovascular state with increased cardiac output and reduced systemic vascular resistance. This state includes faster heart rate, enhanced left ventricular function and higher supraventricular tachyarrhythmia incidence (Udovcic *et al.*, 2017). Hypothyroidism exerts various effects on the hemodynamics of the cardiovascular system, such as diminished cardiac output and arterial compliance, heightened systemic vascular resistance, elevated risk of coronary artery disease and atherosclerosis, reduced diastolic pressure and increased heart rate (Chaker *et al.*, 2015). In contrast, hyperthyroidism impacts cardiovascular hemodynamics (Ahmad *et al.*, 2022). Heart failure and dilated cardiomyopathy can arise from hyperthyroidism and successful management of hyperthyroidism can mitigate the risk of heart failure (Lin *et al.*, 2021). Prevention of atrial fibrillation and thromboembolic events is crucial during hyperthyroidism treatment (Öztürk *et al.*, 2020).

Hypothyroidism occurs in about 4% of the population, becoming more common with age, while hyperthyroidism affects less than 0.5% (Reddy *et al.*, 2017). Despite hyperthyroidism's increased AF risk, its incidence in AF patients is low (0.7-5.2%) (Krahn, 1996).

Studies on TSH levels and AF have shown mixed results. Some suggest high-normal TSH levels increase AF risk, while others find no significant correlation. These conflicting findings highlight the complex relationship between thyroid function and AF, necessitating further exploration (Gammage, 2007).

Bucelletti *et al.* (2011) conducted TSH tests on all patients treated in the emergency department over 30 months and demonstrated that hyperthyroidism manifested in 10% of patients with new-onset AF (Bucelletti *et al.*, 2011).

Heeringa *et al.* (2008) found that AF was associated with TSH levels. When thyroid parameters were within the normal range, patients with subclinical hyperthyroidism or even highly normal thyroid function had a significantly higher risk of developing AF, with a potential threefold increase in risk (Heeringa *et al.*, 2008).

Observed that individuals with higher free T4 levels had an increased risk of developing AF (Anderson *et al.*, 2020; Chaker *et al.*, 2018).

Reddy *et al.* (2017) observed no significant association between AF and normal thyroid function or hyperthyroidism.

Observed that recent-onset AF was commonly found in patients with abnormal TSH levels (Krahn, 1996; Kim *et al.*, 2018).

Gammage (2007) revealed that patients with AF exhibited an overall lower level of free T4 in their serum.

Northcote *et al.* (1986) discovered that treatment for hyperthyroidism leads to sinus rhythm conversion in as many as two-thirds of patients. In a prospective trial, the arrhythmia profile of hyperthyroid patients was examined before, during and after antithyroid therapy.

Staffurth *et al.* (1977) demonstrated that AF is more prevalent in male individuals and in patients with Triiodothyronine (T3) tozixosis.

This study aimed to investigate whether there is a marked difference in Thyroid-Stimulating Hormone (TSH) levels between normal patients and those diagnosed with AF. Additionally, this study aimed to determine whether TSH level can predict AF occurrence, contributing insights into the relationship between thyroid function and the likelihood of developing AF.

Materials and Methods

Study Design

The Institutional Review Board (IRB) at Dankook University granted approval for this study (DKU NON-2023-006). Adhering to the declaration of Helsinki, the research protocol received ethics committee approval from Dankook University. As the study utilized anonymized retrospective data, the requirement for informed consent was waived.

This study focused on outpatients visiting cardiovascular hospitals at certified tertiary medical institutions in Seoul, targeting patients who underwent blood and electrocardiogram tests before their doctor's appointment from January to July 2023.

We enrolled 100 patients with Normal Sinus Rhythm (NSR), reflecting a normal heart rhythm and 100 patients with AF. Thereafter, a comparative analysis of the blood test results was performed between these patients.

All 200 patients were assessed using the results obtained from the MAC 5500 HD (GE Healthcare), ensuring uniformity in the diagnostic process.

Selection of Participants

In the process of subject selection, pediatric cardiac interpretations were excluded from consideration, as

cases involving pediatric cardiac assessments need specialized expertise. Therefore, patients who visited the pediatric cardiology department and those ≤ 15 years old were excluded from the study. Additionally, in accordance with Article 2, paragraph 2, of the regulations on the implementation of bioethics law, individuals under the age of 18 (including middle and high school students) were excluded from the study. The final cohort of 200 participants were randomly selected, irrespective of sex and age. Among the selected patients, individuals with a history of thyroid disorders or those currently taking thyroid medications were excluded from the study.

TSH levels, along with pertinent demographic and clinical data, were gathered from the electronic health records of eligible patients.

Statistical Evaluation

Descriptive statistics summarized the demographic and clinical characteristics of both groups. Comparative analysis was performed to examine the relationship between TSH levels and AF. Logistic regression models were employed to adjust for potential confounding variables.

In this study, we set the effect size to 0.3, given that previous studies on TSH levels between patients with AF and the general population suggested that a median effect size of 0.5 standard deviations would be expected. The significance level (α) was 0.05 and the statistical power ($1-\beta$ err prob) was 0.8, indicating an 80% chance of predicting the relation between high TSH levels and AF. For simplicity, we used an independent sample t-test to compare the mean TSH levels between patients with AF and NSR. Using a sample size calculator, we selected a power analysis approach.

Results from calculations using the G power 3.1 program indicated that a sample size of 82 patients each in AF and NSR groups for the ECG test was required for the study (Fig. 1).

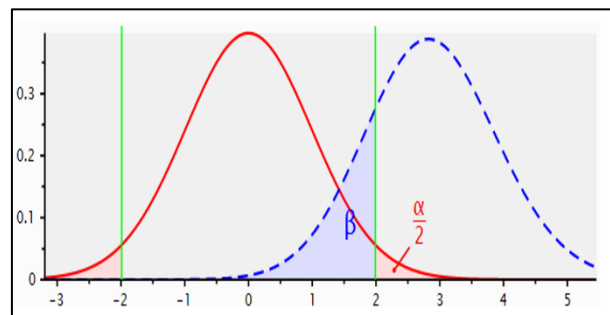


Fig. 1: Standard normal table of patients sample needed for the experiment *x-axis: Sample size/y-axis: Effect size/ α : Significance level/ $1-\beta$: Statistical power

Results

Our hypothesis posited that there is a discernible difference in TSH levels between patients with AF and those with NSR.

Among the 82 patients with an NSR, 73 patients had a TSH value within the normal range (0.41-4.3 uIU/mL), while six and four exhibited a TSH value lower and higher than the normal range, respectively (Table 1).

Among the 82 patients with AF, 71 patients had a TSH level within the normal range (0.41-4.3 uIU/mL). Additionally, two patients exhibited a TSH value lower than the normal range, whereas 10 had a TSH value higher than the normal range (Fig. 2) AF and NSR (Fig. 3).

Table 1: Distribution of patients with NSR and AF

	N	Average	Standard deviation	SE average
Patients with NSR	82	1.88	1.27	0.14
Patients with AF	82	2.48	1.91	0.21

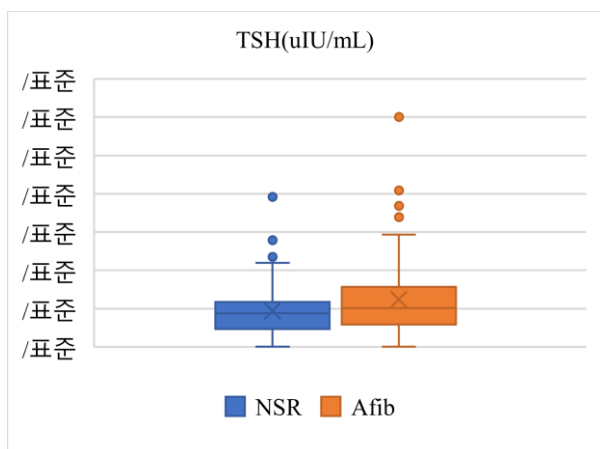


Fig. 2: Distribution of patients with NSR and AF

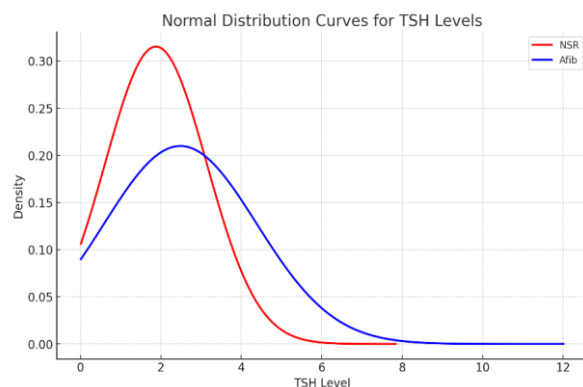


Fig. 3: Normal distribution curves for TSH Levels

Discussion

The analysis of the data suggests that there is not a substantial difference between the two groups. Examination of key statistical measures, including the Standard Deviation (SD) and Standard Error (SE), indicates comparable levels of variability within both patient groups. Despite efforts to discern meaningful distinctions, particularly in light of the small sample size, the findings do not provide compelling evidence of a significant disparity between the groups. These results highlight the nuanced nature of the data and underscore the importance of considering factors such as sample size and variability in interpreting group differences.

Anderson *et al.* (2020) revealed that elevated levels of free T4 were associated with a higher risk of AF and a higher free T4 level within the normal reference range was predictive of an increased risk of AF. Heeringa *et al.* (2008) indicated that individuals with high-normal thyroid function within the normal range of thyroid parameters had an elevated risk of AF.

Krahn (1996) demonstrated that patients with recent onset atrial fibrillation often exhibit abnormal TSH levels. The study prompts inquiries regarding the effectiveness of thyroid function testing in individuals with recent onset atrial fibrillation. Consequently, the study concluded that there is an association between atrial fibrillation and TSH levels.

An examination of existing literature highlights the frequent occurrence of AF in patients with TSH levels deviating from the normal range of thyroid parameters. Therefore, individuals with thyroid dysfunction may be more susceptible to AF. Based on these observations, we have carefully examined the data, including consideration of SD and SE, it was observed that while patients with AF tended to have a higher prevalence of TSH levels beyond the normal range, the difference was not substantial. With a calculated p-value of 0.018 (<0.05), we considered this difference statistically significant. However, given the modest effect size and the overlap in variability between groups as indicated by SD and SE, the clinical significance of this difference may be limited. Therefore, while a statistical association between abnormal TSH levels and the presence of AF was detected, the magnitude of this association may not be clinically meaningful in our study population.

Our study has several limitations. First, the sample size was small. Conducting a study with only 164 participants restricted the ability to confidently establish significant differences in TSH levels between individuals with NSR and those with AF. The small sample size posed challenges to draw definitive conclusions regarding the observed differences. Second, because our study was observational, it was not possible to establish direct causal

relationships based on these findings. Because administrative registers were used, important clinical factors affecting outcomes, such as Body Mass Index (BMI), smoking status and thyroid autoantibody levels were not part of the analysis. This limitation prevents us from accounting for potential confounding variables and hinders our ability to draw definitive conclusions regarding causation. Third, while there is evidence suggesting an association between thyroid function and AF, particularly in the context of subclinical hyperthyroidism, there remains uncertainty about the relationship between variations in normal thyroid function or subclinical hypothyroidism and AF. This represents a research gap in understanding the full spectrum of thyroid function and its impact on AF development. Lastly, we acknowledge that our study was unable to identify patients with new-onset AF who were not diagnosed at a hospital and were treated by their primary care physicians, nor could we include patients with paroxysmal AF, which introduces the possibility of detection bias. To mitigate these limitations, we restricted our research to patients with a documented history of AF on previous ECG examinations and a confirmed diagnosis of AF.

Given the limited sample size of the study and its observational nature without clinical parameters correlated with the outcomes, addressing these limitations requires further investigations with a larger and more diverse sample. Expanding the sample size and incorporating additional clinical parameters would enhance the robustness of this study, providing more comprehensive insights into the relationship between AF and thyroid dysfunction.

Given that our study was conducted at a single institution over a limited duration, further research involving a larger and more diverse patient population from multiple institutions is needed. Expanding the scope to include data from various healthcare settings over extended periods could provide a more comprehensive understanding of the relationship between thyroid parameters and AF. This multi-institutional approach contributes to the generalizability and external validity of the findings.

Conclusion

Based on the outpatient data collected from patients, we compared TSH levels between patients with AF and those with NSR. Our findings indicate that individuals with AF tended to have a TSH level that deviated more from the normal range than the TSH level in individuals with NSR. These results suggest a potential association between AF and thyroid dysfunction. Drawing on the insights from previous studies and the findings of our study, it can be concluded that patients with AF are more susceptible to thyroid dysfunction.

This study focused on thyroid function tests in patients with AF. The results of TSH are crucial for a comprehensive evaluation of the health status of individuals with AF. These findings provide essential information for the establishment of integrated treatment plans that consider interactions with the cardiovascular system.

Based on these results, we identified a potential link between TSH and AF, which may aid in understanding the pathophysiological mechanisms and contribute to improved AF management.

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Author's Contributions

Ji Yeon Chang: Performed experiments, analyzed data, evaluated outcomes of experiments and composed manuscript.

Seung Hee Hong: Prepared figures and drafted manuscript.

Jae Kyung Kim: Conceptualized and devised research, revised and modified the manuscript and sanctioned the final version of the manuscript.

Ethics

The Institutional Review Board (IRB) at Dankook University granted approval for this study (DKU NON-2023-006). Adhering to the declaration of Helsinki, the research protocol received ethics committee approval from Dankook University. As the study utilized anonymized retrospective data, the requirement for informed consent was waived.

Disclaimers

The authors bear sole responsibility for the content and it may not necessarily reflect the official views of the institution.

Data Availability

Data used in this study are not publicly accessible due to privacy or ethical constraints. Access to the data can be granted to verified researchers upon request through communication with the corresponding author.

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