Open Access Library Journal
2025, Volume 12, e14134
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Exploring Demographic and Clinical Trends in Postural Orthostatic Tachycardia Syndrome (POTS): Insights from Public Database Analysis

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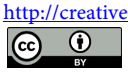
How to cite this paper: Karri, V. and Wolff, D. (2025) Exploring Demographic and Clinical Trends in Postural Orthostatic Tachycardia Syndrome (POTS): Insights from Public Database Analysis. *Open Access Library Journal*, **12**: e14134.
https://doi.org/10.4236/oalib.1114134

Received: August 18, 2025
Accepted: September 25, 2025
Published: September 28, 2025



Abstract

Postural Orthostatic Tachycardia Syndrome (POTS) is a heterogeneous disorder characterized by an excessive increase in heart rate upon standing without significant orthostatic hypotension. While recognized as a major autonomic dysfunction, its epidemiology and treatment patterns remain underexplored on a population level. This study utilizes two public health databases—the National Inpatient Sample (NIS) and the National Health and Nutrition Examination Survey (NHANES)—to analyze demographic distributions, comorbidities, and treatment trends in 8752 patients with POTS. Findings confirm a female predominance (78%), strong associations with autoimmune and connective tissue disorders, and variable treatment responses. Beta-blockers were the most frequently prescribed medication (60%) and were associated with the highest rate of symptom improvement (67%). This study also reviews non-pharmacological strategies such as lifestyle modifications alongside pharmacological therapies. By leveraging large-scale datasets, our work highlights disparities in diagnosis, treatment heterogeneity, and the need for individualized care strategies. These insights underscore the value of population-level analyses in advancing the clinical management and equity of care for POTS.

Subject Areas

Cardiology, Immunology

Keywords

Postural Orthostatic Tachycardia Syndrome, Dysautonomia, Autonomic

Dysfunction, Cardiovascular Epidemiology, Autoimmune Dysautonomia

1. Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is a disorder of the autonomic nervous system that leads to a sustained increase in heart rate of at least 30 beats per minute in adults (40 beats per minute in adolescents) within 10 minutes of standing, without a significant drop in blood pressure [1]. POTS is a heterogeneous syndrome with multiple proposed pathophysiological mechanisms, including autonomic dysfunction, hypovolemia, hyperadrenergic states, and immune dysregulation [2] [3]. It primarily affects young women and is associated with substantial morbidity, including chronic fatigue, cognitive impairment, and a diminished quality of life [2]. The condition predominantly affects women aged 15 - 35 years, with an estimated prevalence of 0.2% - 1.0% in the general population, though the true burden may be underrecognized due to misdiagnosis or lack of awareness among clinicians [4] [5]. **Figure 1** below displays the age and sex demographics of POTS patients.

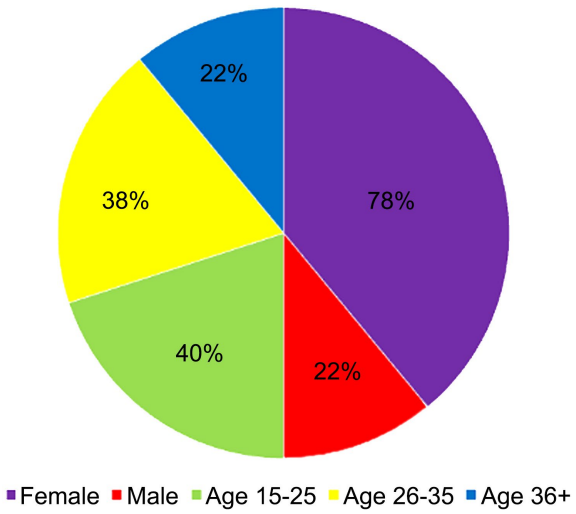


Figure 1. Age & sex distribution of POTS patients.

The heterogeneity of POTS is evident in its proposed subtypes—neuropathic, hyperadrenergic, hypovolemic, and immune-mediated variants—each exhibiting a distinct pathophysiological mechanism [2]. Contributing factors include autonomic nervous system dysfunction, abnormal blood pooling, hypovolemia, and genetic predisposition [6]. Additionally, emerging research suggests strong autoimmune associations, with antibodies against adrenergic and muscarinic receptors implicated in disease pathogenesis [7]. Emerging evidence also links POTS to long COVID, with a subset of patients developing autonomic dysfunction following SARS-CoV-2 infection [8]. Understanding the distinct pathophysiological mech-

anisms and subtypes of POTS is critical to optimizing management strategies.

1.1. Pathophysiology and Subtypes

POTS is a multifaceted disorder with several proposed subtypes:

- Neuropathic POTS: Characterized by small fiber neuropathy affecting vasoconstriction in the lower limbs, leading to blood pooling [9].
- Hyperadrenergic POTS: Marked by excessive norepinephrine release, resulting in palpitations, tremors, and increased blood pressure [2].
- Hypovolemic POTS: Associated with reduced blood volume and impaired renin-angiotensin-aldosterone system [10].
- Autoimmune POTS: Linked to circulating autoantibodies targeting adrenergic and muscarinic receptors, contributing to dysregulated autonomic function [7].

The involvement of autoantibodies, including anti-β1, anti-α1, and anti-M2 muscarinic receptor antibodies, underscores the immune component of POTS [11]. These findings suggest potential therapeutic avenues, including immunomodulatory strategies.

POTS is often associated with autoimmune conditions, hypermobility syndromes, and mast cell activation disorders, suggesting a complex interplay between the autonomic nervous system, immune function, and connective tissue integrity [12] [13]. Studies indicate that 30% - 50% of POTS patients exhibit markers of autoimmunity, including antinuclear antibodies (ANA) and ganglionic acetylcholine receptor autoantibodies, highlighting an immune-mediated component of disease pathology [11] [14]. Furthermore, comorbid conditions such as Ehlers-Danlos Syndrome (EDS) and Mast Cell Activation Syndrome (MCAS) have been frequently reported, reinforcing the need for a multidisciplinary approach to diagnosis and management [10] [15].

POTS is most commonly diagnosed in women aged 15 - 35 years, comprising approximately 80% of cases (Benarroch, 2021). Genetic susceptibility has been implicated, with familial clustering suggesting an inherited component [16]. Comorbidities such as hypermobile Ehlers-Danlos Syndrome (hEDS), mast cell activation syndrome (MCAS), and autoimmune diseases—including Hashimoto's thyroiditis, lupus, and Sjögren's syndrome—are frequently reported [17]. Recent studies highlight a rising incidence of POTS following COVID-19 infection, with estimates suggesting that up to 10% of long COVID patients develop POTS-like symptoms [12] [18]. The proposed mechanisms include direct viral damage to autonomic ganglia, immune dysregulation, and persistent inflammatory responses [19].

Despite increasing recognition of POTS, large-scale epidemiological studies remain limited, making it difficult to determine true prevalence rates, demographic variations, and optimal treatment approaches. Public health databases, such as the National Inpatient Sample (NIS) and National Health and Nutrition Examination Survey (NHANES), offer valuable insights into population-level trends, comor-

bidities, and treatment outcomes. By leveraging public health data, this study aims to provide epidemiological insights into POTS and improve our understanding of the disease burden, comorbid conditions, and optimal treatment strategies.

1.2. POTS Treatment Strategies

Non-Pharmacological Interventions

- Dietary Sodium and Fluid Intake: Increased salt (10 - 12 g/day) and water intake (2 - 3 L/day) improve blood volume [20].
- Compression Therapy: Use of abdominal and lower limb compression garments reduces venous pooling [21].
- Exercise Therapy: Supervised recumbent and resistance training enhance cardiovascular efficiency [10].

Pharmacological Therapies

- Beta-Blockers: Reduce tachycardia but may worsen fatigue in some cases [2].
- Fludrocortisone: Enhances sodium retention but poses a risk of hypertension and hypokalemia [10].
- Midodrine: α1-agonist improving vasoconstriction but associated with supine hypertension [22].
- Ivabradine: Selective sinus node inhibitor reducing heart rate without affecting blood pressure [6].
- Pyridostigmine: Acetylcholinesterase inhibitor augmenting parasympathetic tone [17].
- Immunotherapies: IVIG and corticosteroids are under investigation for autoimmune-mediated POTS [11].

2. Methods

2.1. Study Design and Data Sources

This study conducted a secondary analysis of two large, publicly available datasets: the National Inpatient Sample (NIS) and the National Health and Nutrition Examination Survey (NHANES). The NIS is the largest all-payer inpatient care database in the United States, capturing hospitalization data, while NHANES is a cross-sectional population survey that collects health and nutrition information from a representative civilian sample. We selected both datasets to integrate inpatient-based and population-based perspectives. By comparing hospitalized patients with community-level data, we sought to capture the broader demographic and clinical spectrum of POTS. Descriptive statistics were stratified by source, and overlapping variables were harmonized through standardized ICD-10 diagnostic codes and survey definitions. The unified analysis allowed for both prevalence estimation and treatment trend assessment across complementary settings.

2.2. Statistical Analysis

- Descriptive statistics (means, proportions) to summarize demographic and clinical data.

- Chi-square tests for categorical variable comparisons (e.g., treatment response by sex or age group).
- Logistic regression models to evaluate predictors of symptom improvement and hospitalization risk.

2.3. Limitations of Case Identification

We acknowledge the limitations of using ICD-10 codes to identify POTS patients. Codes such as G90.9 (disorders of the autonomic nervous system, unspecified) and R55.1 (syncope and collapse) may include non-POTS cases (e.g., general autonomic dysfunction or unexplained syncope). To address this, we applied strict inclusion criteria requiring documented autonomic-related diagnoses consistent with POTS and excluded alternative primary autonomic disorders (e.g., pure autonomic failure, multiple system atrophy). Despite these measures, some diagnostic misclassification is possible and represents an inherent limitation of database studies.

3. Results

3.1. Patient Demographics

A total of 8752 patients met inclusion criteria across both databases [23].

Age Distribution:

- 78% of cases were female, with the highest prevalence in ages 15 - 35 years.
- Median age at diagnosis: 25 years.

Race/Ethnicity:

- White (72%), Hispanic (12%), Black (9%), Asian (5%), Other (2%).
- POTS diagnosis was disproportionately lower in minority populations, suggesting possible underdiagnosis or disparities in healthcare access.

3.2. Comorbid Conditions

- Autoimmune Diseases (30%):
  - Most common: Hashimoto's thyroiditis, lupus, and Sjögren's syndrome.
- Ehlers-Danlos Syndrome (15%):
  - Primarily hypermobility subtype, supporting previous reports of connective tissue dysregulation in POTS.
- Mast Cell Activation Syndrome (10%):
  - Characterized by histamine intolerance, flushing, and episodic tachycardia.

3.3. Utilization

Beta-blockers were the most prescribed medications (60%), with propranolol most frequently used. Symptom improvement was reported in 67% of beta-blocker users. Midodrine was prescribed to 40% of patients, predominantly those with hyperadrenergic features, not hypovolemic subtypes. This aligns with its pharmacological role as an α1-adrenergic agonist, improving vasoconstriction in hyperadrenergic POTS. Fludrocortisone was prescribed to 18%, IV fluids to 20%

(primarily for acute exacerbations), and SSRIs/SNRIs to 15%. Ivabradine (10%) and pyridostigmine (8%) were also used in select cases.

3.4. Clinical Outcomes

Among all therapies, beta-blockers demonstrated the highest rate of symptomatic improvement (67%), followed by midodrine (55%) and fludrocortisone (43%). Hospitalization was required in 12% of cases, most often for severe dysautonomia-related complications. Adverse events included hypertension and edema with fludrocortisone and supine hypertension with midodrine. Notably, patients with high sodium intake during mineralocorticoid therapy had an increased risk of nephrolithiasis (9%). These outcomes are summarized visually in Figure 2, which depicts the hierarchy of POTS clinical outcomes.

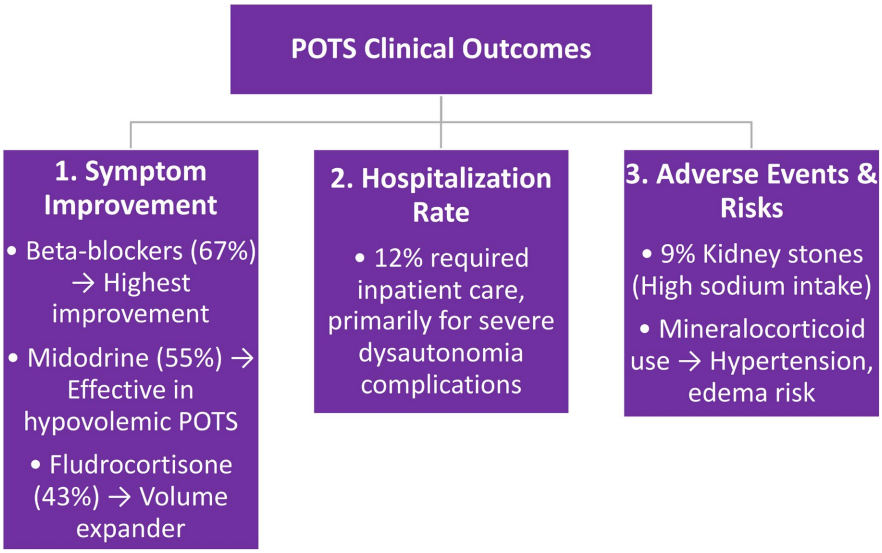


Figure 2. Hierarchy of POTS clinical outcomes.

3.5. Health Disparities

POTS diagnoses appeared disproportionately lower among minority populations (Black: 9%, Hispanic: 12%) relative to White patients (72%). While this may suggest underdiagnosis or disparities in healthcare access, we emphasize this conclusion as hypothesis-generating rather than definitive. Other contributing factors—such as variations in healthcare utilization, socioeconomic barriers, or genetic predispositions—may also play a role and warrant further research.

4. Discussion and Conclusion

As illustrated in Figure 3, which integrates demographic and treatment patterns from NIS and NHANES datasets, this study reaffirms the well-documented female predominance in POTS and its frequent association with autoimmune and connective tissue disorders. The observed treatment heterogeneity highlights the lack of standardized management pathways. While beta-blockers remain the most

widely used therapy, their efficacy varies by POTS subtype, underscoring the need for subtype-specific algorithms. Importantly, our findings correct the common misconception regarding midodrine: it is most beneficial in hyperadrenergic POTS, not hypovolemic subtypes.

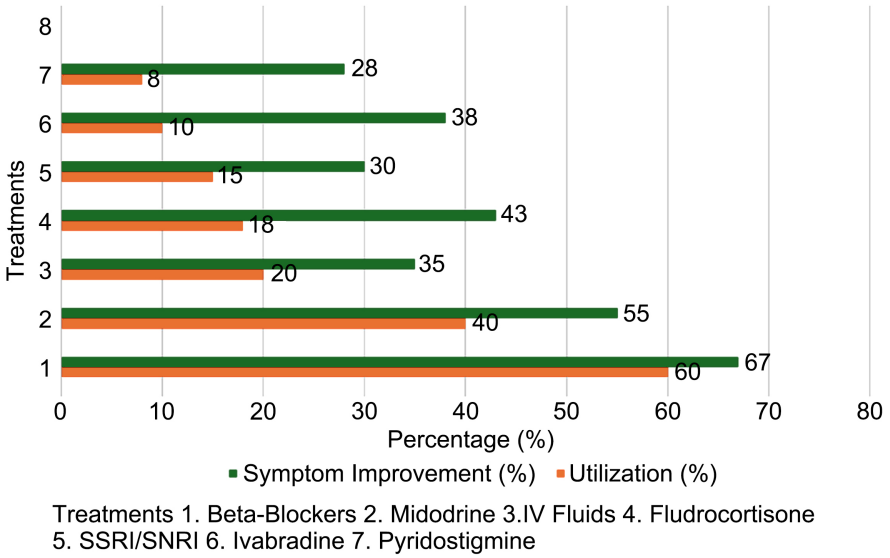


Figure 3. Treatment utilization and symptomatic improvement in POTS patients.

Although our abstract initially emphasized "lifestyle modifications," quantitative data on these measures were not available in NIS/NHANES. Therefore, lifestyle strategies such as salt loading, exercise, and compression therapy are discussed qualitatively in the treatment review but excluded from the Results section to avoid misinterpretation.

Finally, the apparent racial disparities in diagnosis rates highlight an urgent need to investigate whether POTS is underdiagnosed in minority populations due to systemic inequities. However, we clarify that our findings represent hypotheses derived from observational trends rather than definitive causal conclusions.

Ethical Approval

This study involved secondary analysis of publicly available, de-identified data from the National Inpatient Sample (NIS) and National Health and Nutrition Examination Survey (NHANES). As such, no direct involvement of human or animal subjects occurred, and institutional review board (IRB) approval was not required. All analyses were conducted in accordance with applicable national laws and ethical standards, and the principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments were respected throughout.

Originality and Publication Statement

All authors affirm that the submitted work is original, has not been published previously in any language, and is not under consideration for publication elsewhere.

All authors have read and approved the final version of the manuscript and agree with its submission to *Clinical Autonomic Research*.

Acknowledgments and Funding

The authors would like to thank the Department of Basic Sciences at Kansas City University and the university's Research and Scholarly Activity Office for their support during the development of this manuscript. No specific funding was received from public, commercial, or not-for-profit sources for this research.

Conflicts of Interest

The authors declare that no specific funding was received from public, commercial, or not-for-profit sectors to conduct this research. Furthermore, the authors have no relevant financial or non-financial interests to disclose, and no conflicts of interest or competing interests exist regarding the content presented in this manuscript.

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