

ORIGINAL RESEARCH

Postural Orthostatic Tachycardia Syndrome and Orthostatic Hypotension Following Hematopoietic Stem Cell Transplantation



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ABSTRACT

BACKGROUND Postural orthostatic tachycardia (POTS) and orthostatic hypotension (OH) commonly occur after hematopoietic stem cell transplantation (HSCT).

OBJECTIVES This study sought to determine the prevalence of POTS and OH before HSCT and the incidence of new cases after HSCT.

METHODS In this single-center, prospective study, patients were evaluated 30 days before and 30 and 100 days after HSCT. Blood pressure, heart rate, and plasma norepinephrine levels were measured in the supine position and after a 10-minute active stand test to assess for POTS or OH. After HSCT, adrenergic receptor (AR)-modulating autoantibody activity was measured in 8 subjects with POTS and 8 without.

RESULTS Among 46 patients, 40 (87.0%) underwent autologous and 6 (13.0%) allogeneic HSCT. Multiple myeloma was the most common indication (67.4%). Before HSCT, the prevalence of both POTS and OH was 4.3%. At 30 days after HSCT, POTS was present in 10 (25.6%) of 39 patients, including 9 (23.1%) new cases, and OH in 6 (15.4%), including 5 (12.8%) new cases. Patients with POTS at 30 days showed a significantly greater increase in norepinephrine levels upon standing (median 231% [Q1-Q3: 179%-343%]) compared with before HSCT (median 100% [Q1-Q3: 62%-183%]) ($P = 0.005$), which positively correlated with heart rate changes. AR-modulating autoantibody activity was also higher in patients with POTS vs those without and directly correlated with heart rate changes.

CONCLUSIONS Approximately 1 in 4 patients developed POTS after HSCT, characterized by exaggerated increases in norepinephrine upon standing and elevated AR-modulating autoantibody activity. (JACC CardioOncol. 2025;7:382-392)
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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Hematopoietic stem cell transplantation (HSCT) is a critical therapy for restoring marrow and immune function in patients with a wide range of acquired or inherited malignant and nonmalignant conditions.¹⁻³ HSCT achieves disease eradication through high-dose chemotherapy with or without radiation to ablate bone marrow, followed by infusion of donor-derived (allogeneic HSCT) or patient-derived (autologous HSCT) stem cells.^{3,4} The use of HSCT has increased substantially over the past decade, with an estimated 250,000 survivors in the United States—a number expected to more than double in the coming years.⁴ Despite improved survival due to advances in transplantation and post-transplant care, survivors remain at risk for treatment-related complications.⁵⁻⁷

More recently, postural orthostatic tachycardia syndromes (POTS) and orthostatic hypotension (OH) have been increasingly recognized in HSCT recipients.^{8,9} POTS, the most common form of orthostatic intolerance in younger individuals, is characterized by a significant increase in heart rate (HR) upon standing that is not associated with or secondary to a significant reduction in blood pressure (BP).¹⁰⁻¹² In contrast, the prevalence of OH increases with age—affecting approximately 10% to 30% of individuals over the age of 65 years—and is also common among hospitalized patients. OH is defined by a significant reduction in systolic BP, with or without compensatory tachycardia.¹³⁻¹⁵ Both syndromes can contribute to disability, reduced quality of life, increased risk of hospitalization, and mortality.^{8,16-19}

OH has been reported in a substantial number of patients after lung and kidney-pancreas transplantations and is associated with worse outcomes; however, POTS has not been reported after solid organ transplants.²⁰⁻²² Our prior retrospective analyses found that POTS and OH are commonly diagnosed following HSCT, affecting nearly one-third of patients, with 91% requiring pharmacologic treatment.⁸ Studies in adults with POTS or OH have also shown exaggerated neurohormonal responses to upright posture.

POTS is typically associated with symptoms of adrenergic activation and is characterized by a greater increase in plasma norepinephrine (NE) levels upon standing, reflecting an exaggerated sympathetic response.²³⁻²⁶ Whether similar neurohormonal abnormalities occur in patients undergoing HSCT and contribute to the development of POTS or OH remains unknown. Notably, POTS has been linked to viral infections like COVID-19.²⁷ Additionally, changes in adrenergic receptor (AR) autoantibody titers have

been associated with POTS, although their precise pathophysiologic role is still unclear.²⁸⁻³²

In this longitudinal, prospective study, we aimed to determine the prevalence of POTS and OH in patients undergoing evaluation for HSCT for malignant conditions, the incidence of new cases after HSCT, and the associated neurohormonal profile. Given the proposed role of modulatory autoantibodies targeting ARs in POTS, we also conducted a post hoc analysis to measure AR-modulating autoantibody activity in patients with and without POTS.^{28,29}

METHODS

In this longitudinal, prospective study, we approached 49 patients 18 years of age or older who were scheduled to receive undergo allogeneic or autologous HSCT for a hematologic malignancy at Virginia Commonwealth University Medical Center. Eligible participants were 21 years of age or older, English-speaking, able to provide informed consent, in sinus rhythm without evidence of arrhythmia or overt cardiac dysfunction, and without other known causes of autonomic failure—including, but not limited to, poorly controlled diabetes, poorly controlled hypertension, hypothyroidism, or prior sympathectomy. Additional exclusion criteria included the presence of organ system failure or systemic illness impairing cooperation (eg, cognitive impairment or physical limitations preventing safe standing assessment), as determined by the HSCT evaluation team. Patients unable to provide informed consent or who were pregnant or breastfeeding were also excluded. This study was conducted in accordance with the Declaration of Helsinki and approved by the local Institutional Review Board (protocol number HM20023693).

Forty-six patients agreed to participate in the study, and 3 declined. Patients were evaluated on 3 separate occasions: 30 ± 14 days before HSCT and twice after HSCT—at 30 ± 14 days and 100 ± 14 days. At each visit, patients rested supine for 10 minutes, after which BP and HR were measured according to the American Heart Association recommendations.¹⁰ Supine plasma NE levels were also obtained at this time. Patients then performed a 10-minute active stand test, during which BP and HR were recorded at 1, 3, 5, and 10 minutes after standing. Standing NE levels were measured at the 10-minute mark.

POTS was defined by an increase in HR of more than 30 beats/min within 10 minutes of active standing, without a significant drop in systolic BP (<20 mm Hg),

ABBREVIATIONS AND ACRONYMS

AR	= adrenergic receptor
AU	= arbitrary units
BP	= blood pressure
GVHD	= graft-vs-host disease
HR	= heart rate
HSCT	= hematopoietic stem cell transplantation
NE	= norepinephrine
OH	= orthostatic hypotension
POTS	= postural orthostatic tachycardia syndrome

TABLE 1 Clinical Characteristics of Patients who Underwent HSCT at 30 Days

	Patients Without POTS or OH (n = 23)	Patients With POTS at 30 d (n = 10)	Patients With OH at 30 d (n = 6)	P Value
Age, y	64 (61-69)	60 (34-67)	62 (52-64)	0.17
Male	15 (65.2)	5 (50.0)	5 (83.3)	0.40
Race				0.86
Black	6 (26.1)	2 (20.0)	1 (16.7)	
White	17 (73.9)	8 (80.0)	5 (83.3)	
Diagnosis				0.20
ALL or AML	2 (8.7)	3 (30.0)	0	
Lymphoma	2 (8.7)	2 (20.0)	2 (33.3)	
Multiple myeloma	18 (78.3)	5 (50.0)	3 (50.0)	
MDS or MF	1 (4.3)	0	1 (16.7)	
HSCT type				0.61
Autologous	21 (91.3)	8 (80.0)	5 (83.3)	
Allogenic	2 (8.7)	2 (20.0)	1 (16.7)	
GVHD	1 (4.3)	1 (10.0)	1 (16.7)	0.75
CV diseases and risk factors				
Hypertension	11 (47.8)	6 (60.0)	3 (50.0)	0.81
Coronary artery disease	1 (4.3)	0	0	0.70
Heart failure	1 (4.3)	0	0	0.70
Diabetes mellitus	4 (17.4)	1 (10.0)	2 (33.3)	0.50
Hypercholesterolemia	9 (39.1)	4 (40.0)	1 (16.7)	0.57
Chronic kidney disease	3 (13.0)	1 (10.0)	0	0.65
Smoking	7 (30.4)	4 (40.0)	1 (16.7)	0.62
Therapy				
Radiation therapy	6 (26.1)	1 (10.0)	0	0.25
Alkylating agent	9 (39.1)	5 (50.0)	4 (66.7)	0.47
Antimetabolite	4 (17.4)	4 (40.0)	1 (16.7)	0.34
Anthracycline	2 (8.7)	1 (10.0)	1 (16.7)	0.85
Antimethylation	3 (13.0)	0	0	0.32
Immunomodulatory	14 (60.9)	6 (60.0)	3 (50.0)	0.80
Kinase inhibitor	0	1 (10.0)	1 (16.7)	0.15
Proteasome inhibitors	18 (78.3)	5 (50.0)	3 (50.0)	0.18
Topoisomerase	1 (4.3)	1 (10.0)	1 (16.7)	0.57
Vinca alkaloids	1 (4.3)	3 (30.0)	0	0.06
Corticosteroids	17 (73.9)	7 (70.0)	4 (66.7)	0.93

Values are median (Q1-Q3) or n (%).

ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; CV = cardiovascular; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome; MF = myelofibrosis; OH = orthostatic hypotension; POTS = postural orthostatic tachycardia syndrome.

and accompanied by symptoms resolving with recumbency—such as lightheadedness, fatigue, nausea, palpitations, generalized weakness, blurred vision, exercise intolerance, or headache.^{8,10,13} OH was defined as a drop in systolic BP of ≥ 20 mm Hg and/or diastolic BP of ≥ 10 mm Hg within 3 minutes of standing, with or without compensatory tachycardia and with or without symptoms. At least 2 physicians reviewed orthostatic vital signs and clinical records to identify cases of POTS or OH after HSCT. Discrepancies were resolved by discussion. By definition, the two conditions were mutually exclusive: a drop in systolic BP of >20 mm Hg indicated OH and was not consistent with POTS.

We also measured AR autoantibody activity using an ex vivo assay in a random subset of 8 patients with POTS at the 30-day post-HSCT visit and 8 age- and sex-matched control subjects without POTS. Serum-induced activation of α_1 -AR or β_1 -AR was assessed in CHO-K1 cells expressing either α_1 -AR- or β_1 -AR-NFAT- β -lactamase, using the GeneBLazer β -lactamase reporter assay (Invitrogen/Thermo Fisher Scientific), a FRET (fluorescence resonance energy transfer)-based system that uses ratiometric readout to minimize variability and improve detection accuracy. Briefly, cells were plated in 96-well plates and incubated overnight. The next day, cells were treated with serum (1:50) for 5 hours, followed by a 2-hour incubation with the β -lactamase substrate CCF4-AM (LiveBLazer-FRET B/G Loading Kit; Invitrogen/Thermo Fisher Scientific). Plates were read using a BioTek multimode microplate reader. All samples were assayed in triplicate.

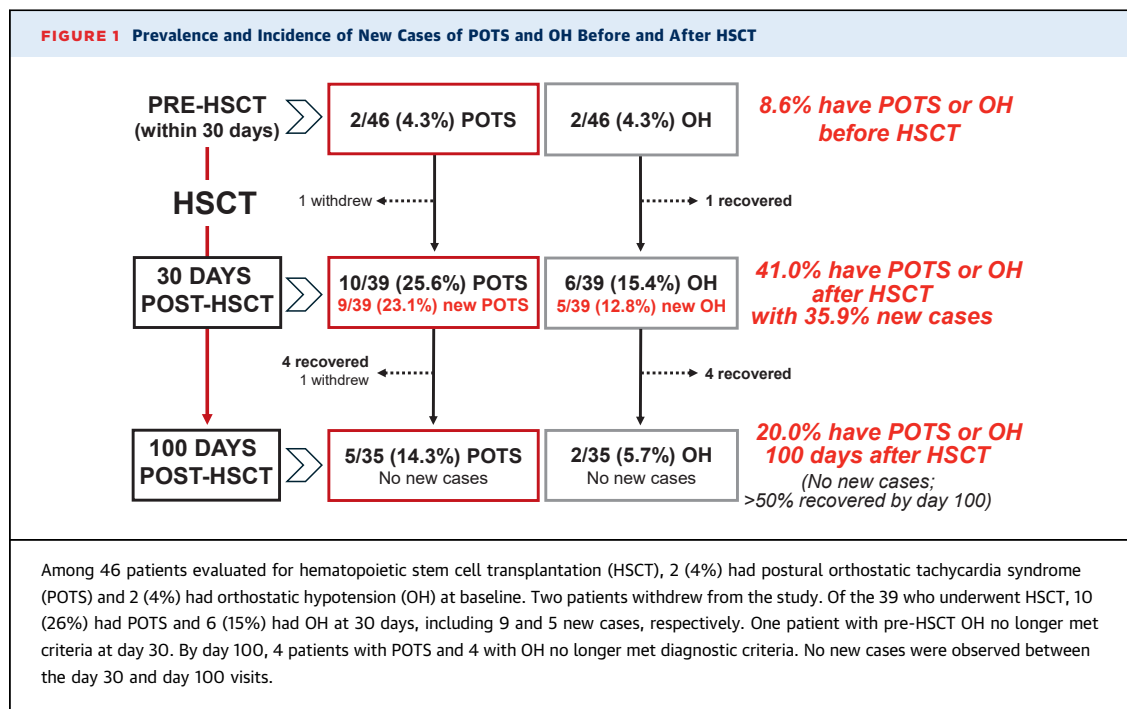
Negative (buffer) and positive (phenylephrine or isoproterenol) controls were included in each assay. Outputs were calculated as the ratio of emissions at 460/530 nm (blue/green) after background subtraction and expressed as fold change over buffer baseline in arbitrary units (AU). Given the additive effects of β_1 -AR autoantibodies enhancing the β_1 signal and α_1 -AR autoantibodies inhibiting the α_1 signal—both of which shift the dose-response curves of their respective agonists—a combined AR autoantibody activity was calculated by summing the AU from both assays.²⁸ To ensure rigor, the investigators performing the assays were blinded to group assignment.

STATISTICAL ANALYSIS. Continuous variables are presented as median (Q1-Q3) and compared between independent groups using the Mann-Whitney *U* test (for 2 groups) or the Kruskal-Wallis test (for more than 2 groups). Categorical values are expressed as count and percentage and compared using the chi-square test or Fisher exact test, as appropriate. Within-group differences (eg, orthostatic changes) were assessed using the Wilcoxon signed rank test. Association between continuous variables was evaluated using Spearman's correlation coefficient (*r*). The OR and 95% CI were calculated to compare the odds of having POTS or OH before vs after HSCT. All statistical tests were 2-sided, and a *P* value >0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, version 27.0.

RESULTS

CLINICAL CHARACTERISTICS OF THE COHORT.

Demographic and clinical characteristics of all



subjects evaluated pre-HSCT are summarized in [Supplemental Table 1](#). The median age was 64 years (Q1-Q3: 58-68 years), with 29 (56.5%) male patients and 35 (76.1%) who self-defined as White. Hypertension was the most common cardiovascular condition prior to transplantation (25 patients [54.3%]), followed by hyperlipidemia (18 patients [39.1%]). Prior coronary artery disease was reported in 2 (4.3%) patients, heart failure in 2 (4.3%), and atrial fibrillation in 1 (2.2%). Prior to HSCT, 6 (13.0%) patients were receiving β -adrenergic blockers—5 for hypertension—and none were on midodrine or fludrocortisone.

Forty (87.0%) patients underwent autologous HSCT and 6 (13.0%) underwent allogeneic HSCT ([Supplemental Table 1](#)). Among those receiving HSCT, 30 (65.2%) patients had multiple myeloma, 9 (19.6%) had lymphoma, and 5 (10.9%) had acute leukemia ([Supplemental Table 1](#)). Cancer therapy received before HSCT is shown in [Supplemental Table 1](#). Among the 6 patients who underwent allogeneic HSCT, 3 (50.0%) developed graft-vs-host disease (GVHD) by the 30-day follow-up, which persisted through the 100-day follow-up. Two patients withdrew from the study: 1 before the 30-day visit and 1 between the 30- and 100-day visits.

PREVALENCE AND INCIDENCE OF POTS AND OH. Before HSCT, the overall prevalence of POTS and OH was 8.7% (4 of 46 patients), with 2 (4.3%) cases of POTS and 2 (4.3%) cases of OH. The 30-day post-HSCT follow-up was completed in 39 patients. [Table 1](#)

shows the clinical characteristics of the patients. POTS was observed in 10 (25.6%) of 39 patients, including 9 (90.0%) new cases. OH was present in 6 (15.4%) of 39 patients, including 5 (83.3%) new cases ([Figure 1](#)). By the 100-day follow-up, 5 (14.3%) of 35 patients remained symptomatic with POTS and 2 (5.7%) with OH. Four (40.0%) of the 10 patients with POTS at 30 days had recovered by 100 days, as had 4 (66.7%) of the 6 patients with OH. No new cases of POTS or OH were diagnosed between the 30- and 100-day visits ([Figure 1](#)). Compared with before HSCT, there was an increased likelihood of being diagnosed with POTS at 30 days post-HSCT (OR: 7.6; 95% CI: 1.6-37.2; $P = 0.012$). A similar trend was observed for OH (OR: 4.0; 95% CI: 0.8-21.1; $P = 0.10$), although it did not reach statistical significance.

At the time of evaluation, none of the patients had been diagnosed with other conditions known to cause orthostatic tachycardia or hypotension, such as severe dehydration, sepsis, arrhythmias, adrenal insufficiency, or thyroid disease. Among the 6 patients who underwent allogeneic HSCT, 2 (33.3%) experienced GVHD by the 30-day follow-up. Findings were similar at 100 days, except that 1 previously diagnosed patient had recovered and 1 new case was identified.

CLINICAL CHARACTERISTICS OF PATIENTS WITH POTS OR OH. The characteristics of patients who developed POTS or OH are summarized in [Table 1](#). The median age was 60 years (Q1-Q3: 34-67 years) in those with

TABLE 2 Changes in Blood Pressure, Heart Rate, and Norepinephrine Levels After Standing in Patients Following HSCT

	Absolute Δ HR (beats/min)	Absolute Δ SBP (mm Hg)	Absolute Δ DBP (mm Hg)	Norepinephrine Supine (pg/mL)	Norepinephrine Standing (pg/mL)	Absolute Δ Norepinephrine (pg/mL)	Relative Δ Norepinephrine (%)
Pre-HSCT							
POTS (n = 2) ^a	40 (34 to 40)	6 (2 to 6)	8 (7 to 8)	579 (146 to 579)	1,119 (813 to 1,119)	541 (414 to 541)	249 (41 to 249)
OH (n = 2) ^a	14 (0 to 14)	-23 (-63 to -23)	-3 (-13 to -3)	351 (158 to 351)	499 (187 to 499)	148 (29 to 148)	34 (18 to 34)
No POTS or OH (n = 42)	11 (8 to 17)	5 (-7 to 19)	6 (2 to 11)	396 (297 to 559)	814 (604 to 1,061)	353 (267 to 537)	92 (64 to 122)
30 d post-HSCT							
POTS (n = 10)	37 (34 to 48)	0 (-5 to 8)	2 (-3 to 17)	380 (255 to 648)	1,444 (773 to 2,234)	986 (497 to 1,492)	231 (179 to 343)
OH (n = 6)	30 (25 to 49)	-31 (-45 to -12)	-9 (-24 to 9)	506 (224 to 626)	1,531 (705 to 1,669)	985 (481 to 1,063)	180 (113 to 232)
No POTS or OH (n = 23)	13 (8 to 19)	2 (-9 to 12)	9 (0 to 13)	608 (340 to 748)	1,118 (924 to 1,811)	608 (382 to 1,032)	145 (67 to 170)
100 d post-HSCT							
POTS (n = 5)	34 (32 to 49)	-5 (-8 to 1)	-1 (-3 to 25)	723 (324 to 926)	1,209 (779 to 1,894)	486 (310 to 1,112)	89 (58 to 202)
OH (n = 1 or 2) ^{a,b}	25 (17 to 25) ^a	-19 (-32 to -19) ^a	5 (4 to 5) ^a	424 ^b	817 ^b	393 ^b	93 ^b
No POTS or OH (n = 28)	14 (5 to 19)	5 (-3 to 19)	9 (3 to 15)	568 (307 to 775)	1,072 (625 to 1,400)	460 (308 to 827)	98 (75 to 146)

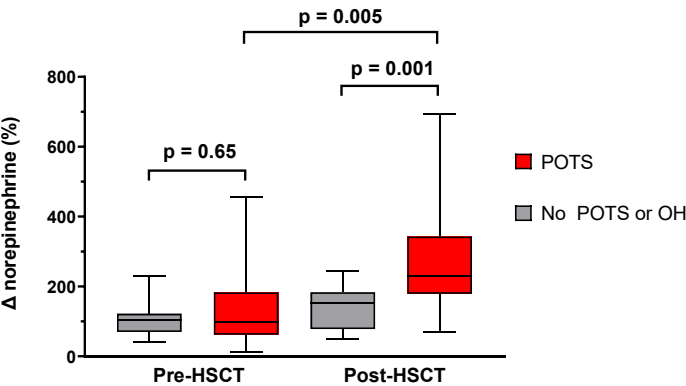
Values are median (Q1-Q3). At 30 days post-HSCT, supine and standing norepinephrine data were available for 10 of 10 patients with POTS, 5 of 6 with OH, and 20/23 with no POTS or OH. At 100 days post-HSCT, supine and standing norepinephrine data were available for 5 of 5 patients with POTS, 1 of 2 with OH, and 23 of 28 with no POTS or OH. ^aFor groups with n = 2, the absolute range is reported instead of the Q1-Q3 range. ^bWhen n = 1, the individual value is reported.

HR = heart rate; other abbreviations as in Table 1.

POTS and 62 years (Q1-Q3: 52-64 years) in those with OH. Male sex and White race predominated in both groups. No significant differences in baseline demographic characteristics, hematologic diagnoses, or transplant type were observed between patients with POTS or OH and those without. The prevalence of cardiovascular disease and use of cardiovascular medications also did not differ significantly between

groups. No clinical factors were associated with the development of POTS vs OH. Blood cell counts and standard metabolic panel values were comparable across groups. Similar findings were observed in the subgroup of patients who underwent autologous HSCT for multiple myeloma, the most common diagnosis and treatment. The number of patients receiving medications for POTS or OH is provided in Supplemental Table 2.

FIGURE 2 Orthostatic Changes in Norepinephrine in Patients With POTS and OH



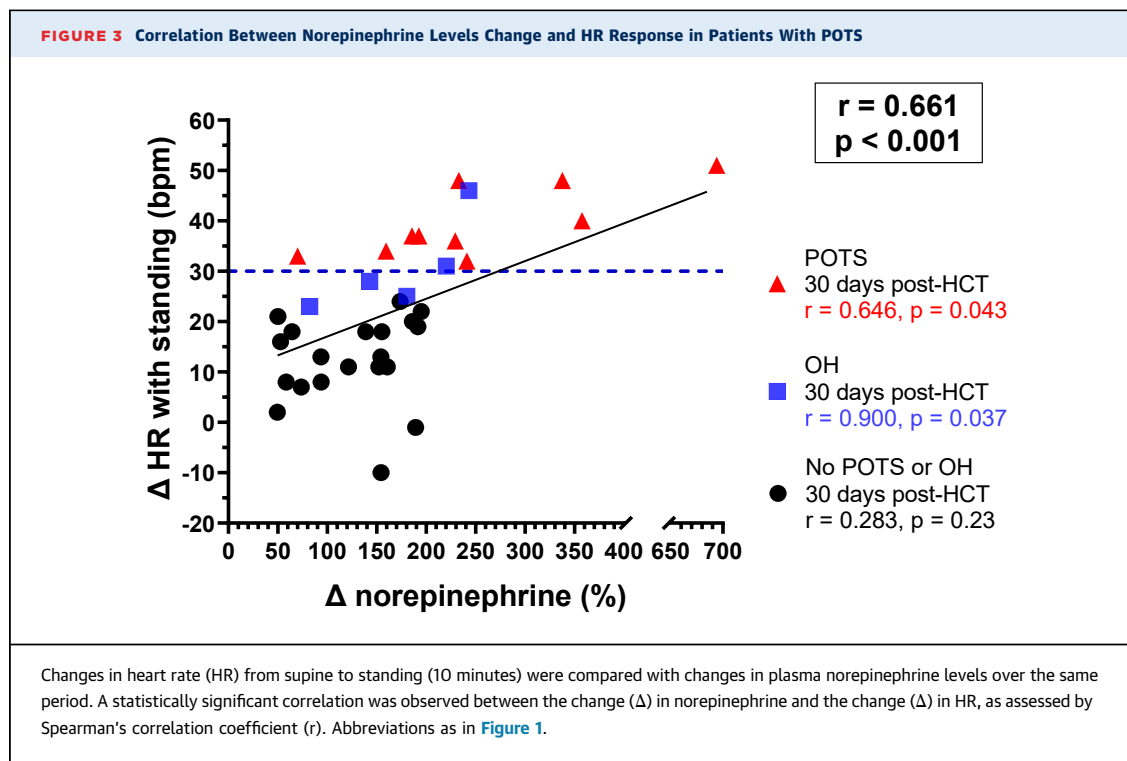
Plasma norepinephrine levels after 10 minutes of standing were compared with supine values. At the day 30 visit, patients with POTS showed significantly greater increases in norepinephrine after HSCT compared with both their pre-HSCT values and with patients without POTS. One patient with OH did not have a blood draw at day 30. Data are shown as median (Q1-Q3) (box) and maximum/minimum values (whiskers). Comparisons were made using Mann-Whitney *U* test (between groups) or Wilcoxon signed rank test (within group). Abbreviations as in Figure 1.

ORTHOSTATIC CHANGES IN NE LEVELS IN PATIENTS WITH POTS.

Given prior studies showing that patients with POTS exhibit elevated plasma NE levels upon standing,²³⁻²⁶ we measured supine and standing NE levels along with BP and HR. Supine HR did not differ significantly between patients with and without POTS. However, the median HR increase from supine to standing at 30 days after HSCT was significantly greater in patients with POTS than in those without POTS or OH (37 beats/min [Q1-Q3: 34-48 beats/min] vs 13 beats/min [Q1-Q3: 8-19 beats/min]; *P* < 0.001).

In the 10 patients with POTS at day 30 post-HSCT, the median increase in NE levels after standing was significantly higher at 30 days post-HSCT compared with pre-HSCT values (231% [Q1-Q3: 179%-343%] vs 100% [Q1-Q3: 62%-183%]; *P* = 0.005) (Table 2, Figure 2). These patients also had significantly greater increases than in those without POTS or OH at 30 days post-HSCT (145% [Q1-Q3: 67%-170%]; *P* = 0.001) (Figure 2, Table 2).

At 30 days post-HSCT, orthostatic changes in plasma NE levels were significantly correlated with



orthostatic HR changes in the overall cohort ($r = 0.661$; $P < 0.001$) and in patients with POTS ($r = 0.646$; $P = 0.043$) (Figure 3).

AR AUTOANTIBODY ACTIVITY IN PATIENTS WITH POTS. Previous studies have shown that patients with hyperadrenergic POTS exhibit increased AR autoantibodies activity, characterized by enhanced β 1-AR and diminished α 1-AR signaling.²⁸ To assess this, we compared AR autoantibody activity in plasma from 8 patients with POTS and 8 without at 30 days post-HSCT. Patients with POTS had significantly higher median activity than those without (25.6 AU [Q1-Q3: 23.8-26.2 AU] vs 22.0 AU [Q1-Q3: 20.5-23.3 AU]; $P = 0.006$), and this activity significantly correlated with the change in HR upon standing ($r = 0.653$; $P = 0.006$) (Figure 4, Table 3).

DISCUSSION

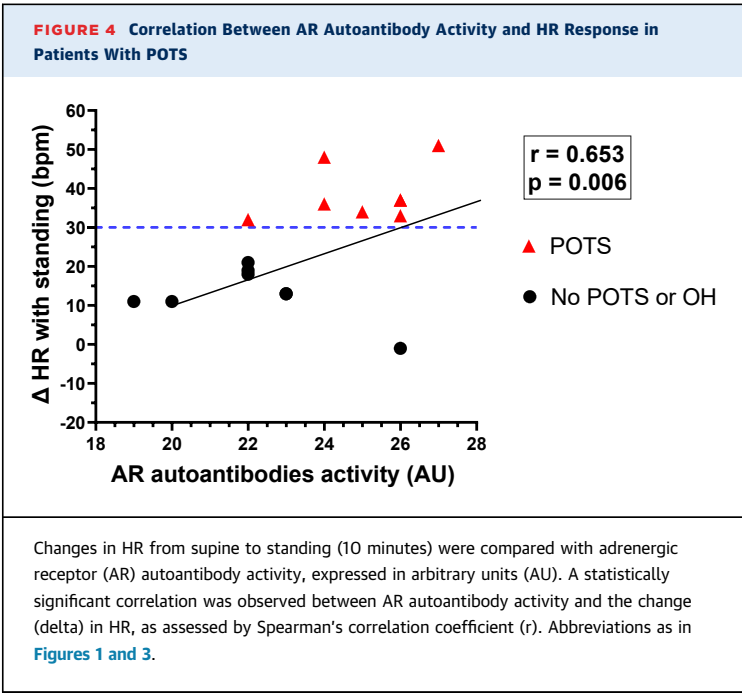
This study demonstrates that approximately 1 in 13 patients undergoing HSCT for hematologic malignancies had either POTS or OH before HSCT, and more than 1 in 3 developed new onset POTS or OH within 30 days post-HSCT, with an estimated OR >7 for POTS (Central Illustration).

Previous studies have shown that the development of POTS or OH can serve as an early marker of cardiovascular risk in cancer patients and is associated

with an increased all-cause mortality.¹⁶⁻²² Markers of orthostatic intolerance—such as elevated resting HR, abnormal HR recovery, and reduced HR variability—are robust predictors of all-cause mortality in non-cancer populations and may be similarly relevant in the oncology setting.³³⁻³⁵

Deuring et al³⁶ reported that, after a mean follow-up of 4.3 years in 145 allogeneic HSCT recipients, patients exhibited persistently elevated HR and reduced parasympathetic cardiac control (measured by respiratory sinus arrhythmia)—signs of autonomic dysfunction—along with greater fatigue and lower fitness scores. In our study, 8.7% of patients had POTS (4.3%) or OH (4.3%) before HSCT. Whether these conditions were related to cancer therapies or unrelated remains unclear. At 30 days post-HSCT, 36% of patients developed new onset POTS or OH. By 100 days, 20% remained symptomatic, with no additional cases identified between days 30 and 100. In this cohort, the development of POTS or OH was not associated with traditional risk factors described in other populations, such as age, sex, and use of antihypertensive medications. Although nearly 90% of adult patients with POTS are female,^{10,11,27} 50% of those who developed POTS post-HSCT in this study were male, and 83% of those with OH.

The prevalence of OH varies across solid organ transplant studies, ranging from 5% in lung transplant



recipients²⁰ to 34% in kidney transplant recipients.^{21,22} OH typically emerges within 1 to 3 weeks after transplantation and may persist for weeks to months.²⁰⁻²² In this study, OH was observed in 15% of patients at 30 days post-HSCT and decreased to 6% at 100 days, with no new cases in the interim.

In the study by Vecchiè et al,⁸ 23% of patients were diagnosed with OH—a higher prevalence than observed in our cohort. This difference may be partly attributable to demographic variation: 86% of patients in the present study underwent autologous HSCT and 65% had multiple myeloma, compared with 37% and 24%, respectively, in the Vecchiè et al cohort. Referral bias may also have contributed, as their study included patients referred to cardio-oncology. The mechanism of new onset OH after transplantation remains unclear, although some studies suggest a role for neuropeptides involved in the regenerative process.²³

This study population was composed predominantly of autologous HSCT recipients (87%). Several

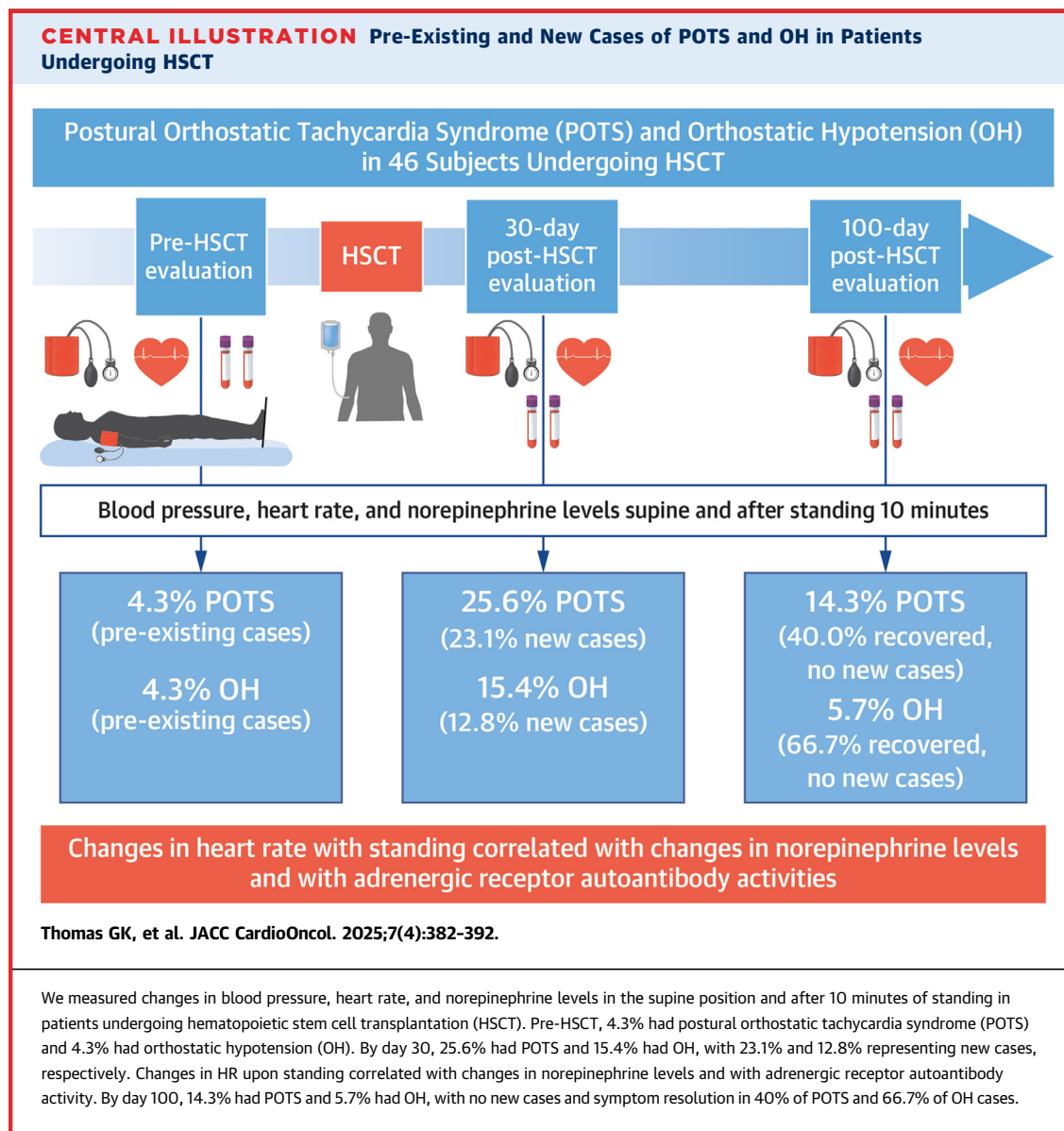
key differences between autologous and allogeneic HSCT may influence the likelihood of developing POTS or OH. Autologous HSCT involves reinfusion of the patient's own hematopoietic stem cells, eliminating the need for immunosuppression and avoiding alloreactive GVHD effects. In contrast, allogeneic HSCT requires immunosuppression to prevent GVHD, increasing the risk of infections from viruses and opportunistic organisms and exposing patients to agents that may contribute to POTS or OH. Although allogeneic HSCT is generally associated with a higher risk of adverse effects, one retrospective study reported a similar incidence of neurologic complications between autologous and allogeneic HSCT recipients.^{9,36} In our study, 50% of allogeneic HSCT recipients developed POTS or OH by 30 days post-transplantation, compared with 30% of autologous recipients. At 100 days post-HSCT, 66% of allogeneic HSCT recipients remained symptomatic with POTS, while 13% of autologous recipients had either POTS or OH. However, the small number of allogeneic cases limits the ability to draw definitive comparisons between transplant types.

The increased risk of POTS after HSCT was reflected in a more than 7-fold rise in incidence. Although the underlying mechanism remains unclear, our findings demonstrate enhanced sympathetic tone upon standing—a hallmark of POTS. Previous studies have shown that transplant patients exhibit increased sympathetic activity and reduced parasympathetic cardiac control, contributing to tachycardia and autonomic dysfunction.³⁶ Additionally, POTS has been associated with elevated AR autoantibody activity, which may amplify the tachycardia response to NE by increasing β 1-AR sensitivity and reducing α 1-AR sensitivity. The latter impairs orthostatic vasoconstriction and promotes greater NE release upon standing.²⁸ In this study, patients with POTS after HSCT exhibited a significantly greater increase in NE levels upon standing, indicating heightened sympathetic activation. NE changes also correlated with changes in HR, supporting a central role for adrenergic signaling in post-HSCT POTS.

We also found that patients with POTS had higher AR autoantibody activity, which may contribute to elevated plasma NE levels and excessive tachycardia. Naturally occurring autoantibodies help maintain homeostasis³² but can increase nonspecifically in response to systemic inflammation caused by injury, infection, or, in this case, HSCT. Such changes in autoantibody profiles have been observed after both autologous and allogeneic HSCT and may explain our findings.^{32,37}

TABLE 3 AR Autoantibodies Activity			
	POTS Post-HSCT (n = 8)	No POTS Post-HSCT (n = 8)	P Value
α 1-AR autoantibodies activity, AU	8.9 (7.8-10.2)	7.6 (7.0-9.0)	0.083
β 1-AR autoantibodies activity, AU	15.8 (14.8-17.1)	14.6 (12.4-15.9)	0.074
Combined AR autoantibodies activity, AU	25.6 (23.8-26.2)	22 (20.5-23.3)	0.006

Values are median (Q1-Q3).
AR = adrenergic receptor; AU = arbitrary units; other abbreviations as in Table 1.



The rise in AR autoantibodies during systemic inflammation may offer short-term benefit by increasing cardiac output and reducing systemic vascular resistance. Over time, however, these effects may become pathological, contributing to inappropriate tachycardia as seen in POTS²⁸ and potentially promoting heart failure.³⁸ Importantly, standard immunoassays that measure AR autoantibody titers are not clinically useful in POTS,³⁹ as antibody activity does not correlate with plasma concentration.

POTS and OH can be debilitating, delaying recovery and worsening the quality of life by exacerbating fatigue, limiting exercise capacity, and, in some cases, persisting for years after transplantation. Their occurrence in post-HSCT patients suggests that

orthostatic vital signs and evaluation of fatigue or other autonomic symptoms should be routinely included in follow-up assessments with oncology teams. If concerning signs are present, referral to a cardio-oncologist may be warranted for further evaluation.

Given our findings suggesting a central role for adrenergic signaling in the development of POTS post-HSCT, treatment with a nonselective β -AR blocker such as propranolol may be appropriate. Propranolol antagonizes both β_1 -AR and β_2 -AR receptors, thereby inhibiting the chronotropic and vasodilatory effects of adrenergic stimulation.

Ivabradine, a sinoatrial node inhibitor, may also be a suitable treatment for patients with POTS after

HSCT. It has also shown efficacy in individuals with idiopathic POTS and has been reported to reduce NE levels.^{27,40,41} Its proposed mechanism involves interruption of a positive feedback loop in which adrenergic activation leads to tachycardia, which in turn further amplifies adrenergic drive via central autonomic pathways that senses pulsatility.⁴² Jammal Salameh et al⁴² described how blood pressure pulsations modulate central neuronal activity via mechanosensitive ion channels and proposed a brain-wide network of “heartbeat sentinel neurons” that mediate interoceptive modulation of cognition, mood, and autonomic tone—a mechanism by which the brain may perceive the pulse internally. Accordingly, inhibition of the tachycardia response with ivabradine may disrupt this feedback loop and blunt symptoms of sympathetic activation. Ivabradine may also reduce NE spillover by lowering sinoatrial node pacemaker activity, thereby decreasing sympathetic tone without the negative inotropic effects associated with beta blockers.⁴³

If further studies confirm a role for AR autoantibodies in post-HSCT POTS, therapeutic strategies aimed at modulating autoantibody production could be explored in clinical trials.

To our knowledge, this is the first prospective study to show that nearly one-third of patients develop POTS or OH after HSCT, with POTS accounting for two-thirds of cases. The transient nature of symptoms in many patients is also notable. While POTS following viral infections such as COVID-19 often improves over time,²⁷ the condition is defined by symptoms lasting more than 6 months. Therefore, the syndrome described here would not meet conventional criteria for POTS. This distinction is informative: it suggests that the mechanism of POTS post-HSCT may differ from other forms and is also reassuring, as many patients showed improvement by day 100.

These findings are consistent with our prior retrospective analysis, in which all patients reported a favorable response to treatment. In 60% of cases, treatment was discontinued after a median duration of 120 days (Q1-Q3: 33-333 days).⁸ We also show that POTS following HSCT is associated with a significantly greater increase in NE levels upon standing and higher AR autoantibody activity—both of which correlate with changes in HR—supporting a central role for adrenergic signaling in post-HSCT POTS. No specific risk factors were identified to explain the incidence of POTS and OH in this population.

STUDY LIMITATIONS. First, this was a small cohort, and the lack of statistical significance in some analyses does not rule out a true effect. A larger sample

size may allow for the identification of meaningful predictors.

Second, POTS and OH are heterogeneous syndromes with multifactorial pathophysiology. The absence of detailed data on physical activity before, during, and after HSCT limits our ability to assess the role of deconditioning. We relied on the standard clinical evaluations by the HSCT team to assess other causes of autonomic dysfunction and did not apply strict criteria for defining poorly controlled diabetes or hypertension, which may have led to under-recognition of relevant comorbidities. Although we found no group differences in blood cell count or standard metabolic panel values, this does not exclude the possibility that other factors contribute to symptoms, HR response, or NE levels.

Third, the small number of patients who initiated treatment prevented evaluation of the relative effectiveness of different therapies. Fourth, we followed patients for only 100 days and were therefore unable to determine how many remained symptomatic beyond 6 months—a key criterion for a formal diagnosis of POTS. Finally, this was a single-center study, which may limit generalizability. However, it was conducted at a large institution serving a demographically diverse population.

CONCLUSIONS

POTS and OH are common complications following HSCT, with POTS being the predominant form. Our findings support a central role for adrenergic signaling in post-HSCT POTS, associated with increased activity of naturally occurring AR autoantibodies (**Central Illustration**). No specific risk factors have yet been identified, highlighting the need for greater clinical awareness and further research to facilitate early intervention and to define the natural history, prevention, and optimal management of these syndromes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: POTS and OH are common but often underrecognized complications after HSCT. In this study, more than one-third of patients developed new onset POTS or OH within 30 days post-transplantation. In patients with POTS, orthostatic increases in NE levels significantly correlated with HR changes and elevated activity of naturally occurring AR autoantibodies, supporting exaggerated sympathetic activation as a key mechanism. Given their impact on functional status and quality of life, orthostatic vital signs should be routinely assessed during follow-up after HSCT to enable timely detection and management.

TRANSLATIONAL OUTLOOK: The observed increase in adrenergic signaling in patients with POTS after HSCT suggests that therapies targeting sympathetic overactivity and tachycardia—such as autonomic rehabilitation, nonselective β -AR blockers, or ivabradine—may help alleviate symptoms and improve outcomes. Identifying biomarkers for early risk prediction could enable more personalized follow-up and intervention. Future studies should investigate how HSCT-related factors contribute to the development of POTS or OH, ultimately guiding prevention and treatment strategies for cancer survivors.

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APPENDIX For supplemental tables, please see the online version of this paper.



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