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Detecting and Characterising Autonomic Dysfunction in Chronic Musculoskeletal Pain: A Cross-Sectional Comparison with Pain-Free Controls

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Abstract

Background/Objectives: Autonomic dysfunction is increasingly being reported in adults with chronic musculoskeletal pain (CMP). We assessed subjective and objective markers of dysautonomia in a CMP population. **Methods:** We recruited 100 adults with confirmed inflammatory or non-inflammatory musculoskeletal diagnoses associated with CMP attending rheumatology and orthopaedic clinics, and age- and sex-matched 56 pain-free controls. Participants completed the Composite Autonomic Symptom Score 31 (COMPASS-31) dysautonomia scale, Brief Pain Inventory and Hospital Anxiety and Depression Scale, and a 10 min Lean Test (LT). A positive LT was defined as either orthostatic hypotension (OH) or Postural Tachycardia Syndrome (PoTS), determined by standard thresholds for heart-rate and blood-pressure changes as defined in the existing literature. **Results:** Autonomic symptom burden was identified in 83% of CMP participants at the conventional threshold (COMPASS-31 score ≥ 17) and 72% at the higher threshold (≥28.67) compared with 11% and 0% of controls. Median COMPASS-31 was 41.8 (IQR 25.8–54.8) in CMP and 2.9 (0.4–10.8) in controls (median difference 35.1, 95%CI 29.6–40.4, $p < 0.001$). A positive Lean Test occurred in 28% of CMP participants (12% PoTS; 16% OH) and 5% of controls (OR 6.80, 95% CI 1.94–36.8, $p = 0.001$). In the CMP participants, COMPASS-31 discriminated poorly between a positive and negative LT (AUC 0.55, 95%CI 0.42–0.67). No statistically significant difference was detected between inflammatory and non-inflammatory conditions in this sample, on subjective (73% vs. 71%) and objective (27% vs. 29%) assessment. **Conclusions**: Dysautonomia is common in CMP. The poor discrimination of COMPASS-31 against objective Lean Test findings (AUC 0.55) indicates that subjective and objective measures provide complementary information, supporting consideration of both in autonomic assessment.

Keywords: dysautonomia; autonomic nervous system; orthostatic intolerance; COMPASS-31; postural orthostatic tachycardia syndrome; orthostatic hypotension

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1. Introduction

The International Association for the Study of Pain (IASP) defines pain as chronic when it persists for three months or longer and recognises that chronic pain should be

classified as a condition in its own right, not only as a symptom of underlying disease [1]. Musculoskeletal conditions are the leading contributors to persistent pain across countries and age groups [2]. Chronic musculoskeletal pain (CMP) affects approximately one in five adults worldwide [3] and represents a major source of personal suffering and economic cost [4]. Behind these figures lies a more complex reality: CMP is not a single condition. It varies widely between patients, and classifications based on symptoms or pain location may fail to capture the underlying mechanisms driving the pain [5]. Beyond local tissue damage, central sensitisation [6] is well established in CMP, and emerging evidence suggests that autonomic nervous system dysregulation is also common in this population [7].

The link between pain processing and the autonomic nervous system has been recognised for decades, with shared neuroanatomical pathways and functional interactions identified at multiple levels of the central nervous system [8]. Patients with CMP frequently report fatigue, dizziness on standing, and disturbed sleep. These are characteristic features of autonomic dysfunction (dysautonomia) and suggest considerable clinical overlap between the two conditions [9,10]. Autonomic dysregulation has historically been assessed using tilt-table testing, often in combination with formal autonomic function tests such as the Composite Autonomic Severity Score (CASS) [11]. However, the resource-intensive nature of these methods limits their use in routine clinical practice and large patient populations. This has driven the development and adoption of simpler, more accessible alternatives, including self-reported outcome measures (such as COMPASS-31) and bedside objective haemodynamic tests (such as active standing tests and the 10 min Lean Test). While these tools have shown promise in conditions with dysautonomia such as long COVID and ME/CFS [12,13], the objective haemodynamic profile of CMP remains poorly characterised. Existing evidence is largely limited to fibromyalgia [7] rather than the broader spectrum of musculoskeletal conditions that contribute to chronic pain.

To address this gap, this study aimed to: (1) objectively detect orthostatic intolerance as a form of dysautonomia in patients with CMP using the 10 min Lean Test and (2) characterise subjective autonomic symptom burden in the same population. Both inflammatory and non-inflammatory musculoskeletal conditions were included and compared with pain-free controls, providing preliminary data on this broader CMP population.

2. Materials and Methods

2.1. Participants

This cross-sectional study recruited participants from the musculoskeletal outpatient clinics at Chapel Allerton Hospital, Leeds, between October 2024 and December 2025, including both rheumatology and orthopaedic clinics. Adults aged 18 or older with a confirmed musculoskeletal diagnosis and chronic pain lasting 12 weeks or longer were considered eligible for inclusion as CMP participants. Exclusion criteria included pregnancy, advanced heart disease (including severe heart failure, recent myocardial infarction, or current investigations for arrhythmias) and inability to speak English or provide written informed consent. Hospital staff and patient companions were invited to participate as pain-free controls, provided they had no CMP history. The absence of chronic musculoskeletal pain was the only requirement screened for at recruitment; other medical conditions and medications were not formally excluded but were recorded and are reported for both groups (Supplementary Table S1). The study was sponsored by the University of Leeds and conducted in accordance with Good Clinical Practice (GCP) guidelines and the UK Policy framework for Health and Social Care Research (2017). Ethical approval was obtained from Liverpool Central Research Ethics Committee (REC reference: 24/NW/0238) in July 2024.

2.2. Autonomic Dysfunction Assessment

Following informed consent, participants completed subjective assessment of autonomic dysfunction, pain, anxiety and depression using the Composite Autonomic Symptom Score 31 (COMPASS-31), Brief Pain Inventory (BPI) and Hospital Anxiety and Depression Scale (HADS) questionnaires, which took between 15 and 20 min to complete. They then underwent objective haemodynamic assessment using the 10 min Lean Test to evaluate their response to orthostatic stress.

COMPASS-31 was used to quantify autonomic symptom burden. It generates a total score from 0 to 100, with higher scores indicating greater symptom burden. A score of ≥17 was applied as the established threshold for dysautonomia [14], and a higher, more conservative threshold of 28.67, derived by ROC analysis against gold-standard cardiovascular autonomic testing in type 2 diabetes (sensitivity 77.8%, specificity 71.1%) [15], was also reported. As both thresholds were validated in diabetic rather than CMP populations, we applied both to bracket the prevalence estimate, and their use here should be regarded as exploratory.

2.3. 10 Min Lean Test Application

Prior to the test, participants were advised to avoid caffeinated beverages and heavy meals for at least two hours beforehand and to void their bladder before attending, to minimise any confounding effects on the autonomic nervous system. The test was conducted in a controlled clinical environment with regulated lighting, noise levels, and room temperature. The test procedure was explained to each participant before commencing. A show card displaying the most common autonomic symptoms was introduced to the participant and then displayed on the wall in front of them throughout the test. They were asked to remain calm and quiet during the test unless reporting symptoms and were informed of their right to stop at any point if they felt severely dizzy or at risk of fainting. Participants were asked to lie on the examination bed for two to five minutes before the first measurement was taken. This resting measurement served as the baseline blood-pressure and heart-rate recording. They were then asked to stand up and lean against the wall, maintaining approximately six inches (15 cm) between their feet and the wall, and a measurement was taken immediately upon standing. Ten further measurements were then recorded at one-minute intervals over the subsequent ten minutes. Heart rate and blood pressure were measured using Welch Allyn Connex Spot Monitor (Hillrom), comprising an automated oscillometric blood-pressure cuff and Masimo SET finger pulse oximetry for heart rate. Participants were asked to report any symptoms following each measurement.

All 10 min Lean Test classifications and definitions are presented in Table 1 [13,16]. A Lean Test was classified as positive when participants met the criteria for either postural orthostatic tachycardia syndrome (PoTS) or orthostatic hypotension (OH). PoTS criteria included a sustained heart-rate increase of ≥30 bpm over two or more consecutive minutes, without concurrent OH and with orthostatic symptoms reported during the test. When resting heart rate was below 60 bpm, an adjusted supine baseline of 60 bpm was used, in line with the Canadian Cardiovascular Society statement [17]. OH was defined as a drop in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg within the first three minutes of standing, and delayed orthostatic hypotension as the same fall occurring between four and 10 min of standing. Heart-rate thresholds of ≥25 and ≥20 bpm were additionally applied as exploratory, non-standard definitions.

While a positive Lean Test meets the haemodynamic criteria for PoTS, a confirmed clinical diagnosis additionally requires ruling out other potential causes that were not systematically assessed in this study, such as thyroid dysfunction and antihypertensive

or beta-blocker use. Participants are therefore described as meeting the haemodynamic criteria for PoTS rather than as having a confirmed clinical diagnosis.

Table 1. 10 min Lean Test classification definition.

Standard Classification	Definition
Orthostatic tachycardia (OT)	Sustained heart-rate rise of ≥30 bpm from adjusted baseline at two consecutive readings, without autonomic symptoms.
Postural orthostatic tachycardia syndrome PoTS	Sustained heart-rate rise of ≥30 bpm from adjusted baseline at two consecutive readings, with symptoms in the absence of OH.
Orthostatic hypotension (OH)	SBP drops ≥20 mmHg or DBP ≥ 10 mmHg within the first 3 min of standing.
Positive 10 min Lean Test (primary)	PoTS at T30 or OH
Non-standard classifications	Definition
Delayed orthostatic hypotension	SBP drops ≥20 mmHg or DBP ≥ 10 mmHg between four and ten minutes of standing.
PoTS (T25 threshold)	Sustained heart-rate rise of ≥25 bpm from adjusted baseline at two consecutive readings, with symptoms in the absence of OH.
PoTS (T20 threshold)	Sustained heart-rate rise of ≥20 bpm from adjusted baseline at two consecutive readings, with symptoms in the absence of OH.
Positive 10 min Lean Test	PoTS at any threshold or OH

Note: Adjusted baseline: where resting HR was below 60 bpm, a floor value of 60 bpm was applied in accordance with standard PoTS diagnostic criteria. Non-standard classifications using lower HR threshold and delayed drops in blood pressure were explored in line with previously published studies [13,16].

2.4. Statistical Analysis

The sample size was calculated a priori to detect a difference in Lean Test positivity of 30% in CMP participants versus 10% in pain-free controls (80% power, $\alpha = 0.05$), indicating a required sample of 100 CMP and 60 controls. The 30% assumption was derived from prior application of the same test in a chronic clinical cohort (long COVID) [13]. We recruited 100 CMP participants and 56 controls. The study was not powered for subgroup analyses. The primary outcome of this study was the between-group difference in 10 min Lean Test positivity. The remaining analyses, including subgroup comparisons, lower heart-rate thresholds (≥25, ≥20 bpm), ROC models and regression of symptom burden, were exploratory. These were interpreted as hypothesis-generating and no correction for multiple comparisons was applied.

All analyses were performed using Stata Version 19.5. Baseline and clinical characteristics were reported as mean (SD), median (IQR), or frequency (%) and were compared using Welch's unequal variances t-test for normally distributed variables (age, BMI, baseline heart rate, systolic and diastolic blood pressure) and the Mann–Whitney U test for non-normally distributed variables (COMPASS-31, HADS anxiety and depression, BPI severity and interference). Categorical variables were compared using Fisher's exact test, with odds ratios (ORs) and 95% confidence intervals (CIs) derived from logistic regression. Within the CMP group, the prevalence of dysautonomia on COMPASS-31 and of a positive 10 min Lean Test was compared between inflammatory and non-inflammatory conditions using Fisher's exact test.

The association between COMPASS-31 total score as a subjective measure of dysautonomia and objective 10 min Lean Test outcomes was examined using linear regression for continuous heart-rate change measures and logistic regression for binary orthostatic outcomes (orthostatic hypotension and delayed orthostatic hypotension). The COMPASS-31 total score was used as a predictor in all models. Analyses were conducted in the full sample and separately in the CMP and pain-free control groups.

The discriminatory ability of the COMPASS-31 total score to predict a positive 10 min Lean Test was assessed using receiver operating characteristic (ROC) analysis, reported as area under the curve (AUC) with 95% CI. Three models were examined: COMPASS-31 score in CMP patients only, COMPASS-31 score in the full sample and an enhanced model incorporating all six weighted COMPASS-31 domain scores as separate variables, age and sex in the full sample. In addition, logistic regression adjusted for age and sex was applied to examine the domain-level predictors of a positive 10 min Lean Test in the full sample and within-CMP group. Statistical significance was set at $p < 0.05$. Because the enhanced ROC model was both developed and tested in the same sample, we performed bootstrap optimism adjustment (1000 replications) to obtain an optimism-adjusted AUC, using the bsvalidation command [18].

3. Results

3.1. Participant Characteristics

Of 612 individuals invited to participate (548 patients and 64 pain-free controls), 403 were eligible. Of these, 246 declined to participate, and 156 consented and were included in the final analysis (Figure 1). Participants were stratified into two groups based on the presence or absence of CMP: a CMP group ($n = 100$) and a control group ($n = 56$). Baseline characteristics are summarised in Table 2. The two groups were broadly similar in terms of sex and age: 78% of CMP participants and 77% of pain-free controls were female, whilst mean age was 46 years in the CMP group compared with 44 years in controls. The CMP group had a notably higher mean BMI than pain-free controls (30.1 vs. 25.2 kg/m^2).

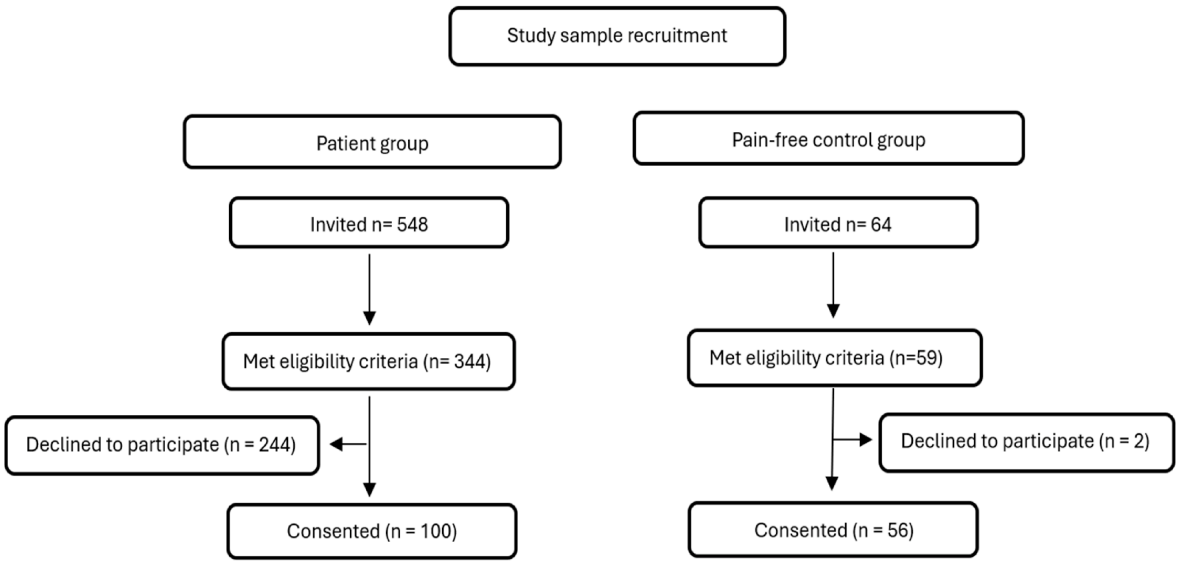


Figure 1. Study participant flow diagram.

Table 2. Baseline demographic characteristics by group.

Demographic Characteristics	CMP Patients ($n = 100$)	Pain-Free Controls ($n = 56$)
Female gender, *n* (%)	78 (78%)	43 (77%)
Mean (SD) age (years)	46.5 (12.4)	44.3 (10.6)
Mean body mass index (SD) (kg/m^2)	30.1 (6.8)	25.2 (5.6)
Current smoker, *n* (%)	8 (8%)	1 (2%)
Ethnicity, *n* (%)		
Asian or Asian British	5 (5%)	10 (18%)
Black, Black British, Caribbean or African	9 (9%)	6 (11%)
Mixed or multiple ethnic group	2 (2%)	1 (2%)
White	82 (82%)	38 (68%)
Other ethnic group	2 (2%)	1 (2%)
Marital status, *n* (%)		
Single	36 (36%)	12 (21%)
Married or in domestic relationship	62 (62%)	42 (75%)
Prefer not to say	2 (2%)	2 (4%)
Job categories, *n* (%)		
Managers, directors, and senior officials	17 (17%)	4 (7%)
Professional occupations	21 (21%)	29 (52%)
Associate professional	8 (8%)	7 (13%)
Administrative and secretarial	9 (9%)	9 (16%)
Skilled trades occupations	3 (3%)	1 (2%)
Caring, leisure and other services	17 (17%)	4 (7%)
Sales and customer service	4 (4%)	0 (0%)
Elementary occupations	5 (5%)	0 (0%)
Student	4 (4%)	2 (4%)
Retired	7 (7%)	0 (0%)
Not provided	5 (5%)	0 (0%)

The CMP cohort comprised a heterogeneous range of musculoskeletal diagnoses (Table 3), with FM and OA most represented (29% and 27%, respectively), followed by RA (12%). Thirty participants had inflammatory conditions and 70 had non-inflammatory conditions. In 87% of participants, pain had persisted for over two years. The OA subgroup was the oldest (mean 54.7 years), and the FM subgroup had the greatest BMI (32.6 kg/m^2). Baseline demographic and haemodynamic characteristics by inflammatory category are presented in Supplementary Table S2.

Subjective outcomes are presented in Table 4. CMP patients demonstrated significantly higher scores across all patient-reported outcome measures (PROMs) compared with pain-free controls, including autonomic dysfunction (COMPASS-31 median 41.8 vs. 2.9; median difference 35.1, 95% CI 29.6 to 40.4; $p < 0.001$), pain severity (median 6.3 vs. 0.0; median difference 6.0, 95% CI 5.5 to 6.5; $p < 0.001$), and anxiety (median 12 vs. 3, median difference 8.0, 95% CI 7.0 to 10.0; $p < 0.001$). Subjective outcomes by inflammatory category are presented in Supplementary Table S3.

On objective assessment using the 10 min Lean Test, CMP patients also showed significantly higher resting heart rate (69 vs. 64 bpm, mean difference 5.5 bpm, 95% CI 2.0–8.9, $p = 0.002$), systolic blood pressure (127 vs. 117 mmHg, mean difference 9.1, 95% CI 4.1–14.1, $p < 0.001$), and diastolic blood pressure (81 vs. 75 mmHg, mean difference 5.8, 95% CI 2.5–9.2, $p < 0.001$) compared with pain-free controls. Heart-rate changes during the 10 min

Lean Test are summarised in Table 5, stratified by group. The maximum, average, and sustained heart-rate changes from baseline did not differ significantly between groups (maximum HR: mean difference 2.3 bpm, 95% CI −1.1–5.6, $p = 0.186$; average HR: mean difference 1.9 bpm, 95% CI −1.0–4.9, $p = 0.189$; sustained HR: mean difference 2.2 bpm, 95% CI −1.0–5.4, $p = 0.183$). The 10 min Lean Test outcomes by inflammatory category are presented in Supplementary Table S4.

Table 3. CMP clinical characterisation.

Diagnosis	*n*	Age Mean (SD)	BMI Mean (SD)	BPI Severity, Median [IQR]	Pain > 2 yr, *n* (%)
Osteoarthritis	27	54.7 (9.5)	31.1 (5.8)	6.8 [5.5–7.9]	24 (89%)
Fibromyalgia	29	42.7 (10.9)	32.6 (6.2)	6.5 [5.8–7.5]	25 (86%)
Rheumatoid arthritis	12	50.3 (12.5)	29.8 (7.7)	5.4 [4.7–5.9]	11 (92%)
Ankylosing spondylitis	8	42.9 (12.4)	25.9 (4.3)	5.4 [4.8–6.2]	8 (100%)
Chronic low back pain	8	38.0 (13.5)	25.2 (6.8)	5.0 [3.6–7.1]	5 (63%)
Psoriatic arthritis	7	48.3 (8.4)	28 (6.6)	6.8 [6.2–7.8]	7 (100%)
Other	9	38.6 (12.7)	29.5 (8.9)	6.0 [3.8–7.0]	7 (78%)

IQR, interquartile range. "Other" comprises other non-inflammatory conditions (tendinitis, plantar fasciitis, frozen shoulder and chronic elbow pain ($n = 4$), lupus ($n = 2$), hypermobility ($n = 2$), and other inflammatory dermatomyositis ($n = 1$). By inflammatory status: 30 inflammatory (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, lupus, dermatomyositis) and 70 non-inflammatory (osteoarthritis, fibromyalgia, chronic low back pain, hypermobility, and the four other non-inflammatory conditions).

Table 4. Subjective outcomes.

Clinical Characteristics	CMP Patients ($n = 100$)	Controls ($n = 56$)	Estimate (95% CI)	*p*-Value
COMPASS-31				
Median score (IQR)	41.8 (25.8–54.8)	2.9 (0.4- 10.8)	MD 35.1 (29.6–40.4)	<0.001
Dysautonomia cut-off 17 *n* (%)	83 (83%)	6 (11%)	OR = 40.7 (15–110)	<0.001
Dysautonomia cut-off 28.67 *n* (%)	72 (72%)	0 (0%)	OR not calculable *	<0.001
Brief pain inventory				
Pain severity (IQR)	6.3 (5–7.4)	0.0 (0–0)	MD 6.0 (5.5–6.5)	<0.001
Pain interference (IQR)	6.9 (5.3–8.5)	0.0 (0–0)	MD 6.7 (6.1–7.3)	<0.001
Hospital Anxiety and Depression Scale				
Median anxiety score (IQR)	12 (8–16)	3 (1–5.5)	MD 8.0 (7.0–10.0)	<0.001
Anxiety cases, *n* (%)	64 (64%)	3 (5.4%)	OR = 31.4 (9.2–107.7)	<0.001
Median depression score (IQR)	10 (5.5–13)	0.5 (0–3)	MD 8.0 (7.0–9.0)	<0.001

IQR, interquartile range; MD, median difference (Hodges–Lehmann); OR, odds ratio. * No pain-free controls met this threshold; OR cannot be calculated.

Table 5. 10 min Lean Test Baseline and heart-rate changes measured by group.

10 min Lean Test	CMP ($n = 100$)	Controls ($n = 56$)	Difference in Means	95% CI	*p*-Value
Baseline measure					
Mean baseline heart rate, bpm (SD)	69.4 (9.7)	64 (10.7)	5.5	2–8.9	0.002
Baseline heart rate < 60 bpm, *n* (%)	12 (12%)	22 (39%)	OR 0.21	0.09–0.47	<0.001
Mean Baseline SBP, mmHg (SD)	126.5 (17.1)	117.4 (13.9)	9.1	4.1–14.1	<0.001
Mean Baseline DBP, mmHg (SD)	81.2 (12.3)	75.4 (8.7)	5.8	2.5–9.2	<0.001
Heart-rate changes during 10 min Lean Test					
Maximum HR change, bpm (SD)	21.1 (10.3)	23.4 (10.1)	2.3	−1.1–5.6	0.186
Average HR change, bpm (SD)	14.9 (8.9)	16.8 (8.8)	1.9	−1.0–4.9	0.189
Sustained HR change, bpm (SD)	17.7 (9.6)	19.8 (9.8)	2.2	−1.0–5.4	0.183

3.2. 10 Min Lean Test

The prevalence of each orthostatic-intolerance classification identified on the 10 min Lean Test is shown in Table 6, stratified by group. CMP participants had significantly higher

rates of orthostatic intolerance across all definitions compared with pain-free controls. Orthostatic tachycardia (OT) without symptoms was more frequent in controls (11% vs. 1%). Overall, 28% of CMP patients had a positive 10 min Lean Test compared with 5% of controls (OR = 6.80, 95% CI 1.94–36.8, $p = 0.001$). This difference remained significant across progressively stricter control definitions, excluding those reporting any comorbidity and then, additionally, any medication (Supplementary Table S5).

Table 6. 10 min Lean Test classification by group, *n* (%).

Classification	CMP ($n = 100$)	Controls ($n = 56$)	OR (95% CI)	p-Value
Heart-rate responses				
Orthostatic tachycardia (OT)	1 (1%)	6 (11%)	0.09 (0.002–0.73)	0.018
PoTS—standard (T30 threshold)	12 (12%)	1 (2%)	7.43 (1.05–326.3)	0.042
PoTS (T25 threshold)	18 (18%)	3 (5%)	3.85 (1.05–21.4)	0.040
PoTS (T20 threshold)	25 (25%)	5 (9%)	3.38 (1.17–12.0)	0.021
Blood-pressure response				
Orthostatic hypotension (OH)	16 (16%)	2 (4%)	5.10 (1.13–47.5)	0.029
Delayed orthostatic hypotension	22 (22%)	3 (5%)	4.94 (1.38–27.1)	0.009
Composite outcomes				
Positive 10 min Lean Test—primary definition (PoTS T30 + OH)	28 (28%)	3 (5%)	6.80 (1.94–36.8)	0.001
Positive 10 min Lean Test—broad definition (T20 and above + OH)	41 (41%)	7 (13%)	4.82 (1.92–13.9)	<0.001

Odds ratios, 95% confidence intervals and p-value from exact logistic regression, with pain-free controls as the reference category; an odds ratio greater than 1 indicates higher odds in the CMP group. T30 = sustained heart-rate rise ≥ 30 bpm, T25 = ≥25 bpm, T20 = ≥20 bpm from adjusted baseline.

Adjusted logistic regression was undertaken to evaluate the robustness of the difference in Lean Test positivity and to determine whether it could be attributed to potential confounders (Supplementary Table S6). CMP participants had higher odds of Lean Test positivity than pain-free controls in unadjusted analysis (OR 6.87, 95% CI 1.98–23.8, $p = 0.002$), and estimates did not change after adjusting for age, sex and BMI (adjusted OR 7.38, 95% CI 2.03–26.76, $p = 0.002$). It also remained stable when opioid, TCA, and gabapentinoid use were entered into the model (adjusted OR 7.21, 95% CI 1.95–26.72, $p = 0.003$). The between-group difference remained stable after adjustment; however, as the study was not powered to detect covariate effect, residual confounding cannot be excluded.

3.3. Exploratory Comparison by Inflammatory Status

Within the CMP group, dysautonomia prevalence was similar in inflammatory ($n = 30$) and non-inflammatory ($n = 70$) conditions. Using the COMPASS-31 cut-off of 28.67, dysautonomia was present in 22 of 30 (73%) participants with inflammatory conditions and 50 of 70 (71%) with non-inflammatory conditions (Fisher's exact $p = 1.00$). A positive 10 min Lean Test occurred in eight (27%) and 20 (29%) respectively ($p = 1.00$). Median COMPASS-31 total score was 38.9 (IQR 28.3–46.0) in the inflammatory group and 42.7 (IQR 25.5–59.1) in the non-inflammatory group ($p = 0.16$).

3.4. COMPASS-31 and 10 Min Lean Test Association

Linear regression was used to examine the ability of COMPASS-31 score to predict heart-rate changes during the 10 min Lean Test. COMPASS-31 total score did not significantly predict maximum, average or sustained heart-rate change in the full sample, in both the CMP group or within pain-free controls (all $p > 0.18$, $R^2 < 0.03$). For binary orthostatic

outcomes, a weak but statistically significant association was observed in the full sample between COMPASS-31 and delayed orthostatic hypotension (OR 1.02, 95% CI 1.00–1.04, $p = 0.023$) and a positive 10 min Lean Test (OR 1.02, 95% CI 1.01–1.04, $p = 0.004$). When stratified by group, associations in the CMP group were essentially unchanged (delayed OH OR 1.01, positive 10 min Lean Test OR 1.01) but lost statistical significance, and estimates in controls had very wide confidence intervals (Table 7). The full sample associations therefore appear partly driven by between-group differences.

Table 7. COMPASS-31 total score as a predictor of orthostatic outcomes by group.

Outcome	Sample	*n*	OR (95% CI) per 1-Point Increase	*p*-Value
Orthostatic hypotension	Full sample	156	1.02 (1.00–1.04)	0.113
	CMP	100	1.00 (0.97–1.03)	0.973
	Pain-free controls	56	1.02 (0.85–1.23)	0.847
Delayed OH	Full sample	156	1.02 (1.00–1.04)	0.023
	CMP	100	1.01 (0.98–1.03)	0.548
	Pain-free controls	56	0.98 (0.82–1.17)	0.801
Positive 10 min Lean Test	Full sample	156	1.02 (1.01–1.04)	0.004
	CMP	100	1.01 (0.99–1.03)	0.422
	Pain-free controls	56	0.97 (0.80–1.17)	0.731

The COMPASS-31 score showed poor discriminatory ability within CMP participants alone (AUC = 0.55, 95% CI 0.42–0.67), improving to moderate in the full sample (AUC = 0.67, 95% CI 0.56–0.77). The enhanced model, including all six COMPASS-31 domain scores, age and sex, showed an AUC of 0.75 (95% CI 0.65–0.84) (Table 8). Because the model was developed and evaluated in the same sample, with 31 positive Lean Tests across eight predictors (3.9 events per predictor), we performed bootstrap optimism adjustment (1000 replications). The apparent AUC of 0.75 reduced to an optimism-adjusted AUC of 0.67 (bootstrap 95% CI 0.58–0.76; calibration slope 0.66), consistent with overfitting. This model is therefore exploratory and requires external validation. The within-CMP estimate (AUC 0.55) is more clinically informative, given that discrimination observed in the full sample may partly be influenced by separation between patients and controls and may not represent discrimination of orthostatic abnormalities among patients.

Table 8. ROC analysis.

Model	*N*	AUC (CI 95%)	*p*	AUC (CI 95%) without OI Domain
COMPASS-31 total, CMP patient only	100	0.55 (0.42–0.67)	0.42	0.51 (0.39–0.64)
COMPASS-31 total, full sample	156	0.67 (0.56–0.77)	0.004	0.65 (0.54–0.75)
COMPASS-31 domains + age + sex, full sample	156	0.75 (0.65–0.84)	0.014	0.72 (0.63–0.82)

Three models are presented examining the discriminatory ability of COMPASS-31 to predict a positive 10 min Lean Test. AUC = area under the curve; OI, orthostatic intolerance. The final column shows the AUC with COMPASS-31 orthostatic domain excluded, given its overlap with the Lean Test outcome. Apparent AUC 0.75; optimism-adjusted AUC 0.67 (bootstrap 95% CI 0.58–0.76; 1000 replications).

We conducted a sensitivity analysis that excluded the orthostatic-intolerance domain of COMPASS-31, given its overlap with the Lean Test outcome, with both investigating the same orthostatic abnormality. The analysis showed that the discrimination was essentially

unchanged (enhanced model AUC 0.72, COMPASS-31 total AUC 0.65 in the full sample and 0.51 within CMP), indicating that our results were not influenced by overlap between the predictor and outcome (Table 8).

Domain-level predictors of positive 10 min Lean Test are presented in Table 9. In the full sample, orthostatic intolerance was a significant predictor (OR = 1.05, 95% CI 1.00–1.11, $p = 0.046$). The vasomotor domain showed an inverse association in both the full sample (OR = 0.70, $p = 0.026$) and within CMP patients only (OR = 0.72, $p = 0.033$), possibly reflecting the fact that vasomotor symptoms occur early in dysautonomia (more common in milder cases), though this is speculative given the exploratory nature of the analysis, or due to the different weighting given to orthostatic intolerance and vasomotor domains while calculating the total score. No other domain predicted positive 10 min Lean Test within CMP patients (all $p > 0.11$) with poor overall model fit (pseudo $R^2 = 0.09$). Given the number of comparisons and the small number of positive outcomes, results were not corrected for multiple testing. The borderline orthostatic-intolerance and vasomotor associations are therefore hypothesis-generating rather than confirmed predictors.

Table 9. Domain-level logistic regression predicting positive 10 min Lean Test.

Domain	Weighted Score Range	Full Sample ($n = 156$)		CMP Only ($n = 100$)	
		OR (95% CI)	p	OR (95% CI)	p
Orthostatic intolerance	(0–40)	1.05 (1.00–1.11)	0.046	1.04 (0.99–1.10)	0.117
Vasomotor	(0–5)	0.70 (0.51–0.96)	0.026	0.72 (0.53–0.97)	0.033
Secretomotor	(0–15)	1.06 (0.92–1.21)	0.411	1.07 (0.93–1.23)	0.379
Gastrointestinal	(0–22)	1.05 (0.94–1.17)	0.374	1.03 (0.91–1.17)	0.612
Bladder	(0–10)	1.07 (0.82–1.39)	0.634	1.07 (0.81–1.42)	0.615
Pupillomotor	(0–5)	0.93 (0.60–1.46)	0.761	0.82 (0.51–1.32)	0.412

Both models adjusted for age and sex. OR = odds ratio per one unit increase in weighted domain score. Overall model fit was poor in both the full sample ($p = 0.014$, pseudo $R^2 = 0.12$) and CMP-only model ($p = 0.259$, pseudo $R^2 = 0.09$). Domain-level analyses are exploratory and uncorrected for multiple comparisons.

3.5. Relationship Between Autonomic Measures and Pain, Anxiety, and Depression

We examined whether pain severity, anxiety and depression contributed to the elevated COMPASS-31 scores in the CMP group, given that these were also substantially higher compared to the pain-free group. COMPASS-31 correlated moderately with BPI pain severity (Spearman rho = 0.48), HADS anxiety (rho = 0.55) and HADS depression (rho = 0.61) within the CMP group. Given the cross-sectional design, the causal relationship between these variables and COMPASS-31 cannot be determined, and any adjustment for them is of limited interpretative value. In unadjusted linear regression, CMP participants scored substantially higher on COMPASS-31 than pain-free controls ($\beta = +34.3$, 95% CI 28.6–40.0, $p < 0.001$). This difference remained significant after individual adjustment for pain severity ($\beta = +9.9$, 95% CI 0.8–19.0, $p = 0.034$), HADS anxiety ($\beta = +18.0$, 95% CI 11.9–24.1, $p < 0.001$), or HADS depression ($\beta = +18.0$, 95% CI 11.8–24.2, $p < 0.001$), but was reduced to non-significance after simultaneous adjustment for all three factors ($\beta = +3.8$, 95% CI −4.2–11.9, $p = 0.35$).

In contrast, objective 10 min Lean Test positivity showed no significant association with pain severity, anxiety or depression within the CMP group, whether examined individually (all $p \geq 0.41$) or in a combined logistic model (overall model $p = 0.32$, no covariate reaching significance, all $p \geq 0.08$). Unlike COMPASS-31 score, no statistically significant association was detected between the objective haemodynamic outcome and the overlapping pain and psychological symptom burden in this sample, although residual confounding and limited precision cannot be excluded.

4. Discussion

This study compared subjective autonomic symptom burden and objective haemodynamic responses to the 10 min Lean Test in patients with CMP and pain-free controls. CMP patients reported substantially greater subjective autonomic symptoms than controls, with 83% of them scoring above the COMPASS-31 threshold of 17, compared with 11% of pain-free controls. At the higher cut-off of 28.67, 72% of CMP patients remained above the threshold, compared to none of the controls. This difference narrowed when the 10 min Lean Test was applied, detecting orthostatic intolerance in 28% of chronic pain patients and 5% of pain-free controls. The burden of dysautonomia has been demonstrated using both subjective and objective measures of dysautonomia captured in a diverse CMP group compared with pain-free controls. No statistically significant difference was detected between inflammatory and non-inflammatory conditions in this sample on either subjective or objective assessments, although the study was not designed to test this comparison.

The relationships between the subjective and objective measures are not linear [19], suggesting that subjective dysautonomia symptoms are complex and cannot be fully captured by objective tests of orthostatic intolerance alone. This discrepancy between the 72% classified as having a high dysautonomia symptom burden by COMPASS-31 and the 28% with a positive 10 min Lean Test (AUC 0.55, within-CMP) is likely attributable to several factors. First, the two instruments measure different constructs: COMPASS-31 captures perceived multi-system symptom burden over the preceding year, while the 10 min Lean test captures a single-timepoint haemodynamic response. Second, the Lean Test assesses only the orthostatic intolerance-aspects of dysautonomia, not the vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor domains captured by COMPASS-31. Third, autonomic symptoms may vary over time, so a single Lean Test may overlook transient orthostatic intolerance. Fourth, COMPASS-31 symptoms overlap with pain, anxiety, and depression, which may inflate reported symptom burden. These factors collectively suggest that the two measures (COMPASS-31 and 10 min Lean Test) are complementary rather than interchangeable, and that elevated symptom burden should not be taken as evidence of objectively confirmed orthostatic intolerance. This is in keeping with the existing literature, which suggests only modest correlation between symptoms and joint radiographic changes seen in musculoskeletal conditions [20]. These findings suggest that subjective and objective tests provide complementary information for assessing autonomic function in CMP.

COMPASS-31 has been validated as a reliable tool for capturing autonomic symptom burden in CMP populations [21,22]. Building on this evidence, our findings extend the use of COMPASS-31 to a broader CMP population, including both inflammatory and non-inflammatory conditions. We observed a high symptom burden with a median COMPASS-31 score of 41.8 (IQR 25.8–54.8) in the CMP population, which exceeded values reported in conditions traditionally recognised for autonomic involvement, including long COVID (median 26.8) [23], Parkinson's disease (mean 22.0) [24], and type 2 diabetes with confirmed cardiovascular autonomic neuropathy (mean 23.7) [25]. In contrast, our pain-free controls had a median COMPASS-31 score of 2.9 (IQR 0.4–10.8), well below the established dysautonomia threshold of 17 [14]. This suggests a substantial burden of self-reported autonomic symptoms in CMP, consistent with the central sensitisation recognised in CMP [6,26]; however, this reflects self-reported symptom burden, which overlaps with concurrent pain and psychological symptoms (Section 3.5).

Beyond autonomic symptoms, our cohort also reported marked burden across pain, anxiety and depression measures. Chronic pain patients scored markedly higher than pain-free controls on both pain severity and interference on the Brief Pain Inventory (median 6.3 vs. 0.0 and 6.7 vs. 0.0 respectively). Anxiety and depression scores on the Hospital Anxiety and Depression Scale were also elevated, with a difference in median of 8 points between

groups for both subscales. The co-occurrence of elevated pain, anxiety, and depression in our cohort is consistent with established evidence that mental health burden in CMP scales with pain intensity [27] and reflects shared neurobiological pathways linking these domains [28]. It is difficult to predict the direction of this relationship, as CMP could also be leading to greater anxiety and depression rather than the other way round.

These observations warrant cautious interpretation of the subjective autonomic findings. Because pain, anxiety and depression are closely interrelated with the CMP state, their causal relationship cannot be determined in this cross-sectional design. The between- group difference in COMPASS-31 was no longer statistically significant after simultaneous adjustment for pain, anxiety and depression; this reduction may reflect the substantial overlap between these self-reported measures rather than the absence of a true difference, although the study design cannot establish which. This does not reduce the clinical relevance of COMPASS-31 as a marker of symptom burden, but it does underline why the objective 10 min Lean Test, for which no statistically significant association with pain, anxiety, or depression was detected, provides complementary information.

Objective tests showed a positive 10 min Lean Test in 28% of CMP patients under standard criteria, compared to 5% of pain-free controls (OR 6.80, 95% CI 1.94–36.8, $p = 0.001$) comprising OH in 16% and PoTS at the 30 bpm threshold in 12%. This is a significant finding of this study, as this test is currently not a routine test undertaken in musculoskeletal clinics. The association does not indicate causality or direction of the relationship but does suggest that assessment for dysautonomia may warrant consideration as part of the comprehensive assessment of patients in MSK clinics, given such a high prevalence.

The 10 min Lean Test is an active stand test that recent reviews regard as sufficient for the diagnosis of PoTS in many cases when combined with chronic orthostatic symptoms and exclusion of alternative causes [29]; in our cohort, chronic orthostatic symptoms were assessed using COMPASS-31, which captures symptoms over a one-year period. In the existing literature, when the Lean Test was compared directly with Head-Up Tilt testing, it showed good agreement for systolic blood-pressure responses, supporting its validity for detecting orthostatic hypotension [30]. The Lean Test has also demonstrated high agreement with independent expert evaluation of orthostatic responses [31]. However, since extensive validation of the Lean Test against gold-standard tilt-table testing is lacking, and alternative causes were not systematically assessed, such as thyroid dysfunction and antihypertensive or beta-blocker use, we refer to participants as meeting the haemodynamic criteria for PoTS rather than as having a confirmed clinical diagnosis.

The 30 bpm increase in HR and 20 mmHg drop in systolic blood-pressure thresholds derive from standard orthostatic testing criteria, largely established using the passive Head-Up Tilt (HUT) test. Lower thresholds may be more appropriate for active stand tests such as the 10 min Lean Test, to account for the compensatory muscle-pump activity during active standing. Relaxing the heart-rate criterion for the 10 min Lean Test revealed a considerably greater prevalence of symptomatic dysautonomia, with test positivity rising from 28% under the primary definition (HR rise $\geq$ 30 bpm, or a $\geq$ 20 mmHg systolic or $\geq$ 10 mmHg diastolic drop in blood pressure) to 41% under the broader, exploratory definition (HR rise $\geq$ 20 bpm or orthostatic hypotension). As the study included no external reference standard, it cannot be determined whether this increase reflects improved sensitivity or reduced specificity.

Considering the heart-rate criterion alone, applying lower PoTS thresholds of 25 bpm and 20 bpm, as in previous orthostatic-intolerance studies [13,16], captured 18% and 25% of patients respectively. Extending observation to 10 min identified delayed OH in an additional 22% of patients, consistent with previous reports that a substantial proportion of orthostatic hypotension occurs beyond the standard three-minute window [32]. Under

this broad composite definition, the prevalence of positive 10 min Lean Tests reached 41% in CMP participants compared to 13% in pain-free controls (OR 4.82, 95% CI 1.92–13.9, $p < 0.001$). These lower thresholds are exploratory and non-standard. The additional positive cases they capture are open to two interpretations: detection of milder orthostatic-intolerance conditions overlooked by standard criteria, or reduced specificity. A single-test design without an external reference standard cannot separate these possibilities. This finding is therefore hypothesis-generating and requires prospective validation to determine whether lower thresholds improve detection of orthostatic intolerance. Although pain-free controls showed higher heart-rate changes on the 10 min Lean Test than CMP patients, this reflects baseline rather than orthostatic differences. A large proportion of pain-free controls (39.3%) started the test with a resting heart rate below 60 bpm. This lower resting baseline allowed for greater absolute heart-rate rises during orthostatic stress. In contrast, CMP participants had an already-elevated mean resting heart rate consistent with the autonomic dysfunction described in CMP conditions [33], which may have limited the absolute change in heart rate during the test. As Lean Test classifications depend on within-participant change from baseline rather than absolute values, absolute baseline heart rate and blood pressure are not used directly in the outcome; this does not, however, fully exclude the influence of baseline values. The between-group difference in Lean Test positivity remained robust after adjustment for age, sex, and BMI (Supplementary Table S6).

The lack of a linear association between subjective (COMPASS-31 score) and objective (10 min Lean Test) measures of autonomic function has been identified in the autonomic literature where COMPASS-31 correlated weakly with quantitative autonomic testing [19]. COMPASS-31 assesses symptom burden across six body systems, whereas the 10 min Lean Test measures only haemodynamic responses, making COMPASS-31 a broader screening tool. The two measures also capture different time windows. COMPASS-31 reflects cumulative symptom experience over the preceding year, while the 10 min Lean Test provides a single point-in-time haemodynamic assessment. Patients with fluctuating autonomic symptoms may therefore score highly on COMPASS-31 without demonstrating positive 10 min Lean Test findings during a single test session. In addition, central sensitisation is well-established in CMP and represents amplification of sensory input across multiple body systems [26,34], which may extend to the autonomic system abnormalities which subjective scales capture well below the threshold of objective haemodynamic dysregulation. Together these factors suggest that subjective and objective measures provide complementary information in CMP.

The findings of this study highlight the need to broaden the clinical assessment pathway for CMP to include autonomic symptom evaluation. Autonomic symptoms have historically received limited attention in the CMP population, and the literature has remained narrowly focused on fibromyalgia. Assessment of chronic fatigue, post-exertional malaise and other multi-system autonomic symptoms have received considerably less attention even though they account for a substantial symptom burden in CMP presentations. In our cohort, 83% of patients reported autonomic symptoms above the COMPASS-31 threshold and 41% had a positive 10 min Lean Test under broader, exploratory definitions.

Integrating a brief autonomic screen into chronic pain consultations may help identify affected patients and could inform management approaches such as positional advice, salt and fluid intake, pacing strategies and referral for further autonomic evaluation where indicated. As these management strategies were not evaluated in the present study, their benefit in CMP requires prospective assessment. A related pilot in orthostatic-intolerance populations (ME/CFS and long COVID) found such a conservative protocol feasible and associated with modest improvements in autonomic symptoms, though without a control group [35]; whether it is effective in CMP has not yet been tested. Acknowledging auto-

nomic dysfunction as part of the CMP assessment may also support patient validation and contribute to more integrated multidisciplinary care.

To our knowledge this study is the first to characterise both subjective and objective autonomic profiles across a deliberately broad CMP population, including inflammatory and non-inflammatory conditions, extending the existing evidence beyond the predominantly fibromyalgia-focused literature and establishing that the autonomic involvement is not confined to a single diagnosis. A further strength was the parallel use of validated patient-reported outcomes and an objective haemodynamic test, which allowed perceived and physiological dimensions of dysautonomia to be examined within the same cohort.

Several limitations of this study warrant consideration. Firstly, the cross-sectional design limits inference of causality and does not capture fluctuations in autonomic function over time. Our study does, however, demonstrate the existence of an association, which is a good starting point for future mechanistic and interventional studies. Secondly, recruitment from a single centre may restrict generalisability. However, the sample size is reasonably large for a single-centre study and is a good representative sample of caseload in any secondary-care musculoskeletal clinic. Thirdly, statistical power was established only for the primary group comparison; accordingly, the secondary subgroup, ROC, and regression findings are exploratory and require confirmation in larger studies. Fourthly, the CMP group comprised patients with a range of underlying musculoskeletal conditions and condition-specific differences in autonomic profile that could not be examined within the study due to small sample size for each condition. The same applies to the comparison between inflammatory and non-inflammatory conditions, where the smaller inflammatory subgroup means that the absence of a detectable difference should not be read as evidence of equivalence. Fifthly, medication use was recorded only for pain treatment; antihypertensive and cardiovascular medications, as well as measures of physical activity and fitness, were not systematically recorded. Their potential effect on the haemodynamic measures could not be evaluated, although no between-group difference was observed in the orthostatic blood-pressure responses (the systolic and diastolic drops on standing). Finally, pain-free controls were recruited through convenience sampling from hospital and university staff and patients' companions, which may have introduced selection effects, including a possible healthy-worker effect. Moreover, declining to participate was more common among patients than controls, and as non-participants did not consent to data collection, their characteristics were not recorded, and the possibility of selection or non-response bias could not be excluded.

5. Conclusions

This study demonstrates substantial autonomic symptom burden and a higher prevalence of orthostatic haemodynamic abnormalities in CMP than in controls, with limited correlation between subjective and objective measures and no significant difference detected between inflammatory and non-inflammatory conditions in this sample. Recognising autonomic dysfunction as a component of the CMP experience may support more comprehensive and patient-centred care. Longitudinal and condition-specific studies are required to characterise the patterns of autonomic dysfunction in this population and to evaluate the clinical utility of routine autonomic symptom screening and targeted intervention for orthostatic intolerance and dysautonomia.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm15228792/s1, Table S1: Medications and comorbidities by group; Table S2: Baseline characteristics by inflammatory category; Table S3: Dysautonomia profile, pain, anxiety and depression; Table S4: 10 min Lean Test outcomes for chronic musculoskeletal pain patients by inflammatory category; Table S5: Sensitivity analysis using progressively stricter

healthy control definitions; Table S6: Adjusted logistic regression for positive Lean Test, CMP versus pain-free controls.

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Abbreviations

The following abbreviations are used in this manuscript:

CMP	Chronic musculoskeletal pain
BPI	Brief Pain Inventory
HADS	Hospital Anxiety and Depression Scale
OH	Orthostatic hypotension
PoTS	Postural orthostatic tachycardia syndrome
LT	Lean Test
COMPASS-31	The Composite Autonomic Symptom Score questionnaire

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