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Predictive value of uroflowmetry in the early diagnosis of urinary symptoms in Transthyretin-related familial amyloidotic polyneuropathy carriers

Maria João Castro de Passos

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“Predictive value of uroflowmetry in the early diagnosis of urinary symptoms in Transthyretin-related familial amyloidotic polyneuropathy carriers”

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Estudante:

Maria João Castro de Passos

up201906975@up.pt

Master Degree in Medicine

Instituto de Ciências Biomédicas Abel Salazar
Student number: 201906975

Orientador:

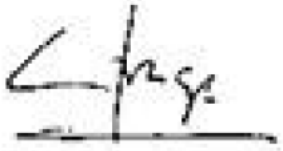
Professor Doutor Avelino Manuel Fraga Ferreira
Assistente Hospitalar de Urologia na Unidade Local de Saúde Santo António
Professor Catedrático Convidado no Instituto de Ciências Biomédicas Abel Salazar

Coorientadora:

Dra. Ana Isabel Coelho Lopes
TSDT Neurofisiologia na Unidade Local de Saúde Santo António
Docente convidada da Escola Superior de Saúde, Politécnico do Porto

Maria João Castro de Passos

Professor Doutor Avelino Manuel Fraga Ferreira



Professora Ana Isabel Coelho Lopes

Declaration of Scientific Integrity

I, Maria João Castro de Passos, a student of the Integrated Master's Degree in Medicine at the Institute of Biomedical Sciences Abel Salazar, University of Porto (student number 201906975), hereby declare that I have acted in accordance with the principles of academic integrity set forth by the University of Porto in the preparation of this dissertation.

Accordingly, I confirm that throughout the entirety of this work, I did not engage in plagiarism, data falsification, or manipulation of results, and that I acted with due care and respect toward all individuals included in the study.

Dedicatória

Aos meus pais, que sempre acreditaram em mim — em especial à minha mãe, cuja presença constante e apoio incondicional tornaram possível cada etapa deste percurso.
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Resumo

Introdução:

A polineuropatia amiloidótica familiar relacionada com transtirretina (PAF-TTR) é uma doença hereditária multissistémica, com envolvimento frequente do sistema nervoso autónomo. Embora as escalas neurológicas de Coutinho e PND sejam amplamente utilizadas, avaliam sobretudo o comprometimento motor. A evidência atual sugere que a disfunção urinária autonómica pode preceder o aparecimento de sintomas neurológicos em portadores geneticamente confirmados. A urofluxometria, exame urodinâmico não invasivo, poderá fornecer dados objetivos precoces, mas continua subutilizada de forma sistemática.

Objetivos:

Avaliar a capacidade da urofluxometria para detetar disfunção neurogénica precoce da bexiga em portadores de PAF-TTR clinicamente assintomáticos (Coutinho 0 e/ou PND 0) e explorar associações com sintomas urinários e estadio clínico.

Métodos:

Estudo observacional retrospetivo incluindo 54 doentes com mutação Val30Met, seguidos numa unidade nacional de referência em Portugal. Foram analisados os parâmetros urodinâmicos (Qmax, Qave, volume residual pós-miccional, volume urinado) e morfologia da curva de fluxo, em articulação com sintomas urinários, estádio clínico e análise de agrupamento (clusters). Aplicaram-se testes estatísticos apropriados (Mann–Whitney, qui-quadrado, correlação de Spearman, regressão logística e curvas ROC), segundo a checklist STROBE.

Resultados:

Foram identificadas curvas alteradas em 48,1% dos doentes. Entre os classificados como Coutinho 0 e PND 0, respetivamente 26,7% e 46,7% já apresentavam alterações objetivas. Estas alterações associaram-se significativamente a valores reduzidos de Qmax e Qave, aumento do volume residual e maior carga sintomática do tipo esvaziamento. A Qave correlacionou-se negativamente com o volume residual ($\rho = -0.531$, $p < 0.001$). A análise por clusters revelou um subgrupo com perfil urodinâmico mais grave e sintomatologia urinária mais marcada. A urofluxometria demonstrou boa capacidade discriminativa (AUC = 0.789) para curvas alteradas com base no volume residual.

Conclusões:

A urofluxometria revelou sinais precoces de disfunção vesical autonómica em portadores de PAF-TTR, mesmo antes da manifestação de sintomas motores ou urinários evidentes. Estes dados apoiam a sua integração em estratégias de vigilância precoce, permitindo reclassificação clínica atempada e potencial início antecipado de intervenções terapêuticas, com impacto favorável no prognóstico.

Abstract

Background:

Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is a hereditary multisystem disorder with frequent involvement of the autonomic nervous system. While neurological staging tools such as the Coutinho scale and the Polyneuropathy Disability (PND) score are widely used, they primarily assess motor impairment. Emerging evidence suggests that autonomic urinary dysfunction may precede neurological symptoms in genetically confirmed carriers. Uroflowmetry, a non-invasive urodynamic test, could offer an early window into subclinical involvement, yet its systematic application remains uncommon.

Objectives:

To evaluate the ability of uroflowmetry to detect early neurogenic bladder dysfunction in clinically asymptomatic TTR-FAP carriers (Coutinho stage 0 and/or PND 0), and to explore associations with urinary symptoms and clinical staging.

Methods:

This retrospective observational study included 54 genetically confirmed TTR-FAP patients (Val30Met mutation), followed at a national reference center in Portugal. Uroflowmetric parameters (Qmax, Qave, post-void residual volume, voided volume) and flow curve morphology were analyzed in relation to urinary symptoms, clinical stage, and unsupervised cluster grouping. Statistical methods included Mann–Whitney tests, chi-square, Spearman's correlation, logistic regression, and ROC curve analysis, in accordance with STROBE guidelines.

Results:

Altered flow curves were observed in 48.1% of patients. Notably, 26.7% of Coutinho 0 and 46.7% of PND 0 individuals already exhibited objective abnormalities. Curve alterations were significantly associated with reduced Qmax and Qave, elevated residual volume, and a higher burden of voiding symptoms. A moderate negative correlation emerged between Qave and post-void residual volume ($\rho = -0.531$, $p < 0.001$). Cluster analysis identified a subgroup with worse urodynamic profiles and more pronounced symptomatology. Uroflowmetry demonstrated good discriminative accuracy (AUC = 0.789) for identifying abnormal curves based on residual volume.

Conclusions:

Uroflowmetry revealed early signs of autonomic bladder dysfunction in TTR-FAP carriers even before the emergence of motor or overt urinary symptoms. These findings support the integration of uroflowmetry into early surveillance strategies, enabling timely clinical reclassification and potentially improving long-term outcomes through earlier therapeutic intervention.

Abbreviations and Acronyms

TTR-FAP – Transthyretin-related familial amyloidotic polyneuropathy

ULSSA – Unidade Local de Saúde de Santo António

RPM – Residual post-miccional (Post-void residual)

Qmax – Maximum flow rate

Qave – Average flow rate

PND – Polyneuropathy Disability

ROC – Receiver Operating Characteristic

AUC – Area Under the Curve

PVR – Post-void residual

CNS – Central nervous system

V – Cramér's V (effect size)

χ^2 – Chi-square

U – Mann–Whitney U test

ρ – Spearman's rank correlation coefficient

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Introduction

Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is a rare, inherited, autosomal dominant systemic disease caused by mutations in the *TTR* gene. The most prevalent mutation in Portugal is Val30Met, and the disease is classically characterized by a progressive sensorimotor and autonomic polyneuropathy. However, there is growing evidence that autonomic dysfunction, particularly affecting the urinary and gastrointestinal systems, may precede the onset of motor symptoms.[1-3]

The clinical progression of TTR-FAP has traditionally been staged using classifications such as the Coutinho staging system and the Polyneuropathy Disability (PND) score, which focus mainly on motor impairment. Nonetheless, several studies have suggested that urinary symptoms—resulting from early autonomic involvement—may occur before overt neurological deficits. These symptoms include hesitancy, weak stream, incomplete emptying, retention, and nocturia, which are often underrecognized in the early stages.[4]

Simple, non-invasive, generally available uroflowmetry offers objective analysis of bladder function and detrusor activity. Although uroflowmetry has diagnostic value, it is not routinely used as a screening tool for TTR-FAP carriers judged clinically asymptomatic. Referrals to the Urodynamics Unit come from the national reference centre, Unidade Corino de Andrade, which tracks genetically confirmed TTR-FAP patients and at-risk relatives under a multidisciplinary approach. However, referral for uroflowmetry remains heterogeneous and largely dependent on individual physician judgment, leading to inconsistent application. Despite its diagnostic potential, urinary dysfunction remains underrecognized by clinicians in the early stages of TTR-FAP. [5,6]

This study aimed to evaluate the predictive value of uroflowmetry in detecting early signs of neurogenic bladder dysfunction among genetically confirmed TTR-FAP carriers, with special focus on those considered clinically asymptomatic (Coutinho stage 0 and PND 0). We hypothesized that abnormalities in flow curve morphology or urodynamic parameters may be present even before the onset of subjective urinary complaints or motor deficits.[7]

Uroflowmetry tests performed between January 2015 and May 2025 were reviewed. Although many clinically asymptomatic carriers did not undergo uroflowmetry within the study window, our findings underscore the urgent need to implement systematic urodynamic screening protocols in this population. Our findings suggest that uroflowmetry may reveal early, otherwise undetected autonomic impairment—therefore enabling earlier reclassification of disease stage and justifying timely initiation of disease-modifying therapies, such as tafamidis or gene-silencing agents. Since these treatments demonstrate greater efficacy when introduced in the early stages of the disease, systematic identification of urinary dysfunction could potentially improve long-term outcomes and modify the prognosis of patients.[8]

Objectives

The **primary objective** of this study was to assess the diagnostic value of uroflowmetry in identifying early signs of urinary dysfunction in carriers of Transthyretin-related familial amyloidotic polyneuropathy (TTR-FAP). In particular, we aimed to determine whether autonomic involvement—potentially preceding overt neurological symptoms—could be detected through this non-invasive functional assessment tool.

The **secondary objectives** were to:

- Characterize uroflowmetric parameters across different clinical stages of TTR-FAP.
- Investigate the relationship between uroflowmetry curve morphology and the presence of lower urinary tract symptoms.
- Evaluate the association between abnormal uroflowmetry patterns and clinical staging systems (PND and Coutinho scores).
- Compare urodynamic findings between clinically asymptomatic and symptomatic individuals.
- Use clustering analysis to find patterns in traits among the group and see if changes in uroflowmetry match certain symptom profiles.

Methods

This was a restrospective observational study conducted at the Unidade Corino de Andrade, part of the Local Health Unit of Santo António (ULSSA), Portugal. The Unidade Corino de Andrade is a national reference center for the management of transthyretin-related familial amyloid polyneuropathy (TTR-FAP), following both symptomatic patients and asymptomatic carriers through a multidisciplinary team including neurology, cardiology, nephrology, and urology. The Urodynamics Unit of the Urology Department maintains a screening protocol with the Unidade Corino de Andrade and performs uroflowmetry exams at the discretion of the attending clinicians. However, uroflowmetry is not applied uniformly and its indication remains heterogeneous among physicians.

Prior to analysis, all data were obtained retrospectively and anonymised. Uroflowmetry tests performed between January 2015 and May 2025 were examined. The study was approved by the institutional ethics committee. Due to institutional restrictions regarding data anonymization and ethical compliance, patient records were made available for analysis only after the inclusion and exclusion criteria had been applied by the clinical team. As a result, particular pre-selection statistics and the overall number of screened patients were unavailable.

Inclusion Criteria

Participants were included in the study if they met all of the following conditions:

- Age ≥18 years at the time of clinical evaluation
- Genetically confirmed pathogenic mutation in the transthyretin (TTR) gene
- Followed at the Unidade Corino de Andrade, an expert multidisciplinary center integrated within ULSSA, Portugal
- Availability of sufficient clinical documentation to assess neurological and urinary status

Exclusion Criteria

Patients were excluded if they presented with any of the following conditions:

- Current symptomatic urinary tract infection (UTI) at the time of the urological assessment
- Pregnancy, due to physiological changes in urinary dynamics
- Benign prostatic hyperplasia (BPH) or other non-TTR-related prostatic pathology in male patients
- Previous urological surgeries unrelated to TTR-FAP, including transurethral resection of the prostate, bladder neck surgery, or prior urethral instrumentation
- Neurological disorders unrelated to amyloid neuropathy, such as diabetic neuropathy, spinal cord compression, or multiple sclerosis
- Had a history of pelvic radiation
- Were using urinary catheters at the time of data collection
- Significant cognitive impairment interfering with clinical evaluation or symptom reporting

Uroflowmetry Protocol

All uroflowmetry exams were performed by trained personnel in the Urodynamics Unit using standardized non-invasive equipment. Patients were instructed to void with a comfortably full bladder under quiet and private conditions. Post-void residual volume (PVR) was measured immediately after voiding using transabdominal bladder ultrasound. Trained staff conducted all uroflowmetry procedures, adhering to standardized institutional protocols to ensure consistency and reproducibility.

Flow curve morphology was classified by trained technicians according to international standards. Two main variables were derived from flow curve analysis:

- Curve classification: normal vs abnormal
- Curve shape/type: plateaued, intermittent, flattened, or prolonged emptying

These morphological features were interpreted following ICS (International Continence Society) guidelines and internal urodynamic criteria.

Uroflowmetric parameters analyzed were:

- Maximum flow rate (Qmax) in mL/s
- Average flow rate (Qave) in mL/s
- Post-void residual (PVR) in mL
- Voided volume in mL
- Curve pattern and morphology

Variables Collected

The following data were systematically extracted:

- Demographics: age, sex
- Clinical variables: presence of neurological and/or urinary symptoms, documented date of symptom onset
- Urinary symptoms: hesitancy, intermittency, weak stream, straining, incomplete emptying, urinary retention, dysuria, urgency, nocturia, incontinence, and absence of bladder sensation
- Uroflowmetric variables: Qmax, Qave, PVR, voided volume, and curve morphology

- Coutinho stage and PND (polyneuropathy disability) score were retrospectively assigned by the investigator based on available neurology records, using standardized classification criteria.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics v29.0. Normality of continuous variables was assessed using the Shapiro-Wilk test. Non-normally distributed variables were presented as medians and interquartile ranges (IQR). Comparisons were made using:

- Mann-Whitney U test for independent two-group comparisons
- Kruskal-Wallis test for comparisons involving more than two groups
- Chi-square test or Fisher's exact test for categorical variables

Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. Multivariate analysis was carried out using binary logistic regression, both with ENTER and backward stepwise (Wald) methods. Variables with p-values <0.10 in univariate analysis were considered for multivariable models. Model calibration and goodness-of-fit were assessed using the Hosmer-Lemeshow test. The number of covariates included in each model was constrained according to the number of observed outcomes, in accordance with recommended standards to prevent model overfitting.

ROC curves were created to assess the accuracy of continuous variables (like RPM, Qmax, Qave, and symptom count) in detecting unusual curve patterns. The area under the curve (AUC), best cutoff points (Youden Index), sensitivity, and specificity were all reported.

A k-means cluster analysis was performed to identify natural subgroups of patients based on uroflowmetric variables, urinary symptoms, clinical stage, and sex. The optimal number of clusters was determined using the Elbow method. K-means clustering was selected for its robustness in partitioning continuous variables and clinically relevant features. Clusters were then analyzed in terms of demographic and clinical characteristics.

A p-value < 0.05 was considered statistically significant in all analyses. The reporting follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies.

Results

Sample Characterization

Fifty-four patients with genetically confirmed TTR-FAP were included, of whom 28 were male (51.9%) and 26 were female (48.1%) (Figure 1). Uroflowmetry revealed that 26 individuals (48.1%) exhibited an altered flow curve pattern, whereas 28 (51.9%) maintained a normal bell-shaped curve (Figure 2). There was no statistically significant difference in age between groups with normal and altered curves (Mann–Whitney U test, $p = 0.752$), and no correlation was observed between age and uroflowmetric parameters (Spearman's $\rho > 0.8$ for all). However, female sex was more frequent among those with normal curves ($\chi^2 = 4.267$, $p = 0.039$), suggesting a possible sex-related trend (Figure 1).

Uroflowmetry Parameters and Curve Pattern

Participants with altered flow curves showed significantly lower maximum flow rate (Qmax; $p = 0.003$) and average flow rate (Qave; $p = 0.002$), as well as higher post-void residual (PVR; $p = 0.001$), with no difference in voided volume ($p = 0.706$). These findings align with our primary hypothesis that early neurogenic dysfunction may be captured by uroflowmetric changes before overt symptoms emerge. Strong positive correlation was found between Qmax and Qave ($\rho = 0.854$, $p < 0.001$), and moderate negative correlation between Qave and PVR ($\rho = –0.531$, $p < 0.001$) (Figure 3).

Urinary Symptoms and Curve Pattern

Several voiding symptoms were significantly associated with an altered flow curve, including difficulty emptying the bladder ($\chi^2 = 5.103$, $p = 0.024$; Cramér's $V = 0.341$), incomplete emptying ($\chi^2 = 6.138$, $p = 0.013$; $V = 0.373$), hesitation ($\chi^2 = 5.789$ $p = 0.016$) and urinary retention ($\chi^2 = 7.827$, $p = 0.005$; $V = 0.422$) (Table II).These findings suggest that flow curve alterations mirror voiding-phase dysfunction (Figure 4). Storage symptoms, including urgency ($p = 0.720$), frequency ($p = 0.416$), nocturia ($p = 0.246$), urinary tract infection ($p = 0.533$), urinary incontinence ($p = 0.111$) and absence of bladder sensation ($p = 0.773$), showed no significant associations.

Composite Symptom Burden

A composite score summing 11 urinary symptoms was significantly higher in patients with altered curves (Mann–Whitney $U = 238.0$, $p = 0.018$), reinforcing that uroflowmetry abnormalities are not isolated findings but occur alongside greater clinical burden (Table III).

Association with Clinical Stage

There was a significant association between curve morphology and PND stage ($\chi^2 = 11.132$, $p = 0.004$) and Coutinho stage ($\chi^2 = 10.229$, $p = 0.006$). Importantly, 8 out of 30 patients classified as Coutinho stage 0 (26.7%) and 7 out of 15 with PND stage 0 (46.7%) already exhibited altered curves—supporting our study's primary goal of detecting pre-symptomatic autonomic dysfunction via uroflowmetry (Table I).

Clinically Asymptomatic vs. Symptomatic Patients

Among patients who underwent uroflowmetry, clinically asymptomatic individuals (PND 0 and Coutinho 0; $n = 15$) showed statistically significant differences in three of the four analyzed parameters when compared to symptomatic patients ($n = 30$). Maximum flow rate (Qmax) was significantly higher in the asymptomatic group ($U = 92.000$, $p = 0.001$), as was the average flow rate (Qave) ($U = 100.000$, $p = 0.003$), consistent with preserved detrusor function (Table IV). Additionally, post-void residual volume (RPM) was significantly lower in asymptomatic individuals ($U = 129.000$, $p = 0.019$). Voided volume showed no significant difference between groups ($U = 178.500$, $p = 0.263$), though values were highly variable. Notably, a subset of clinically asymptomatic patients already exhibited altered flow curve morphology.

Symptom Comparison Across Groups
Voiding difficulty was significantly more frequent in symptomatic than asymptomatic patients (35.3% vs. 10.0%, p = 0.041). No significant differences were found in incontinence (p = 0.517), frequency (p = 0.445), nocturia (p = 0.439), or absence of bladder sensation (p = 0.885). These findings support the interpretation that voiding-phase symptoms emerge earlier and more prominently in disease progression (Table V).

Receiver Operating Characteristic (ROC) Analysis
To evaluate the diagnostic accuracy of uroflowmetric parameters in predicting curve abnormalities, ROC curves were generated for Qmax, Qave and RPM. Among the parameters analyzed, RPM showed the highest discriminatory power with an AUC of 0.789 (p = 0.001), suggesting good predictive ability for detecting altered curves. Qave and Qmax also demonstrated statistically significant but inverse associations, with AUC values of 0.234 (p = 0.002) and 0.217 (p = 0.003), respectively. These findings support the value of RPM as a non-invasive indicator of subclinical dysfunction, whereas lower Qmax and Qave were inversely associated with curve abnormality (Figure 6).

Cluster Analysis
Two-step cluster analysis identified two subgroups with distinct uroflowmetric profiles. Cluster 2, representing patients with more severe dysfunction, exhibited significantly lower Qmax (24.3 vs. 31.9 mL/s), lower Qave (10.4 vs. 37.6 mL/s), higher RPM (81.4 vs. 13.7 mL), and comparable voided volume (355.9 vs. 375.2 mL). These results suggest that Cluster 2 is characterized by impaired voiding efficiency and higher post-void residuals. The significant association between Cluster 2 and altered flow curve morphology ($\chi^2 = 18.269$, $p < 0.001$), along with higher prevalence of voiding symptoms such as hesitation (p = 0.002), retention (p = 0.003), intermittency (p = 0.008), and incomplete emptying (p = 0.001), reinforces the clinical value of flow curve analysis in early detection of dysfunction (Table VI, Figure 5).

Discussion

This study aimed to evaluate whether uroflowmetry could detect early signs of autonomic urinary dysfunction in genetically confirmed carriers of transthyretin-related familial amyloid polyneuropathy (TTR-FAP), particularly among those classified as clinically asymptomatic. Our findings back up this hypothesis, revealing significant changes in uroflowmetric parameters and flow curve morphology even in the absence of obvious neurological or urinary complaints.[7,9]

We classified a large proportion of patients with altered flow curves as either Coutinho stage 0 or PND stage 0. Specifically, 26.7% of Coutinho 0 and 46.7% of PND 0 patients already presented with abnormal uroflowmetry curves. These findings are consistent with previous observations suggesting that autonomic dysfunction may precede the appearance of sensorimotor symptoms in TTR-FAP. The identification of abnormal flow curves in clinically asymptomatic carriers emphasizes the importance of uroflowmetry as a sensitive and objective screening tool.[6,9,10] Among patients who underwent uroflowmetry, clinically asymptomatic individuals (PND 0 and Coutinho 0) showed statistically significant differences in uroflowmetric parameters when compared to symptomatic patients. Specifically, maximum flow rate (Qmax) and average flow rate (Qave) were significantly higher, while post-void residual volume (PVR) was significantly lower in the asymptomatic group. Voided volume did not differ significantly between the groups. These objective differences support the claim that early bladder dysfunction can be present before overt neurological symptoms, and may be detected by uroflowmetric analysis even in clinically silent stages.

Physiologically, the observed reductions in maximum (Qmax) and average flow rate (Qave), together with elevated post-void residual (PVR), are suggestive of detrusor underactivity or impaired coordination between bladder contraction and sphincter relaxation. These changes are consistent with early amyloid deposition in the autonomic fibers innervating the bladder, as evidenced by histopathological studies. Interestingly, despite significant changes in flow rate and residual volume, voided volume remained consistent across groups, suggesting preserved sensation and voluntary initiation of voiding in the early stages.[11]

The strong positive correlation between Qmax and Qave (Spearman's $\rho = 0.854$, $p < 0.001$) was expected given their shared physiological basis. More importantly, the moderate inverse correlation between Qave and PVR ($\rho = –0.531$, $p < 0.001$) highlights the potential of average flow rate to serve as a surrogate marker for voiding efficiency. In this context, Qave may outperform Qmax in predicting functional bladder emptying, because it takes into account detrusor contractility over time.[4,12,13]

Notably, voiding-phase symptoms such as hesitancy, urinary retention, and incomplete emptying were significantly more frequent in patients with altered flow curves. Conversely, storage-phase symptoms—including urgency, nocturia, and frequency—did not show significant associations. This pattern supports previous work suggesting that parasympathetic denervation, which impairs detrusor contraction, is a dominant mechanism in the early autonomic dysfunction of TTR-FAP.[2]

The total burden of urinary symptoms was also significantly higher in patients with abnormal flow curves ($p = 0.018$), suggesting a cumulative effect of subclinical dysfunction. Importantly, even among individuals classified as clinically asymptomatic (stage 0 in both Coutinho and PND), some showed abnormal flow curves and mildly elevated PVR. These cases illustrate the dissociation between subjective perception and objective urodynamic impairment, and underline the limitations of relying solely on clinical staging to detect early disease.[9,10,14]

The cluster analysis identified two clinically meaningful subgroups of TTR-FAP carriers, as distinguished by objective uroflowmetric parameters. Cluster 2, characterized by significantly lower Qmax and Qave, elevated post-void residual volumes, and a greater prevalence of urinary symptoms, was strongly associated with altered flow curve morphology. These findings show that even among genetically confirmed carriers—many of whom are clinically asymptomatic or in the earliest disease stages—subclinical autonomic bladder dysfunction can be objectively detected through uroflowmetry and phenotypic clustering. These findings support the clinical validity of uroflowmetry-based phenotyping, and suggest that machine learning models could be developed

to automatically stratify patients based on objective parameters. In future work, these models could be enhanced using longitudinal data to predict progression risk.[15,16]

Clinically, these findings have immediate relevance, as disease-modifying therapies such as tafamidis, patisiran and inotersen are more effective when initiated in early stages, before irreversible nerve damage occurs. Current staging systems, however, rely predominantly on motor deficits, thereby underestimating the true burden of autonomic dysfunction. Our study supports the inclusion of uroflowmetry in routine screening protocols for TTR-FAP carriers, as an addition to neurological assessments.[6]

Nevertheless, limitations must be acknowledged. First, the study was conducted in a single national referral center in Portugal, where the Val30Met mutation is highly prevalent (100% in our sample), potentially limiting its applicability to other genotypes with more aggressive phenotypes. Second, the retrospective design and anonymized dataset restricted access to pre-inclusion data, limiting the ability to account for referral bias. Third, because uroflowmetry was not systematically prescribed, asymptomatic individuals may have been referred based on subtle clinical suspicion, introducing potential selection bias. Future prospective studies using systematic screening would help to validate these findings.[17]

In conclusion, our findings suggest that uroflowmetry is an effective, non-invasive method for detecting early bladder dysfunction in TTR-FAP. The presence of abnormal curves and altered flow parameters in stage 0 patients indicates that neurogenic bladder involvement may precede motor symptoms and justify earlier initiation of therapy. We thus advocate for the incorporation of uroflowmetry into standard clinical pathways for TTR-FAP monitoring, particularly in asymptomatic carriers, in order to improve diagnostic accuracy and treatment timing.[7,18]

Conclusion

This study illustrates the importance of proactively identifying early autonomic dysfunction in transthyretin-related familial amyloid polyneuropathy (TTR-FAP), even before the onset of overt neurological symptoms emerge. Our findings demonstrate that nearly half of clinically asymptomatic carriers (Coutinho stage 0 or PND 0) already exhibit abnormal uroflowmetry patterns and significant deviations in urodynamic parameters—suggesting that the disease process is progressing despite apparent clinical silence.[7,18,19]

The observed reduction in Qmax and Qave, combined with increased post-void residual volumes and higher overall symptom burden, points toward subclinical detrusor underactivity and early impairment of voiding-phase coordination. These functional disturbances are most likely due to early amyloid infiltration of autonomic pathways that innervate the lower urinary tract, preceding sensory or motor deficits traditionally used to define disease progression.[9,20]

By capturing these subtle changes, uroflowmetry emerges as a sensitive, accessible, and underutilized tool for detecting early-stage dysfunction. Its routine application could enable earlier staging reclassification and timely initiation of disease-modifying therapies at a point when their effectiveness is at its peak.[11,13,21]

Although additional prospective studies are required to validate these findings and quantify the long-term predictive value of uroflowmetric alterations, our results strongly advocate for the incorporation of uroflowmetry into standard surveillance protocols for TTR-FAP carriers. Recognizing dysfunction before it becomes symptomatic not only enhances diagnostic precision, but may also redefine the therapeutic window—transforming early detection into early protection.[7,22,23]

Appendix

Table I. Demographic and clinical characteristics of the study population.

Variable	n	%	Mean ± SD
Age (years)	54		45.6 ± 10.0
Qmax (mL/s)	45		26.5 ± 27.0
Qave (mL/s)	45		18.8 ± 39.0
Voided volume (mL)	45		359.7 ± 200.8
Post-void residual (RPM, mL)	45		59.8 ± 99.1
Sex (Male)	28	51.9	
Sex (Female)	26	48.1	
Clinical stage (PND 0)	20	37.0	
Clinical stage (PND 1)	19	35.2	
Clinical stage (PND 2)	14	25.9	
Clinical stage (PND 3)	1	1.9	
Curve morphology (normal)	22	40.7	
Curve morphology (altered)	32	59.3	

Table II. Frequency of individual urinary symptoms among TTR-FAP carriers.

Symptom	n (Yes)	n (No)	% (Yes)	% (No)
Urinary tract infection	32	22	59.26	40.74
Increased urinary frequency	8	46	14.81	85.19
Nocturia	1	53	1.85	98.15
Absent bladder sensation	5	49	9.26	90.74
Urinary retention	9	45	16.67	83.33
Urinary urgency	8	46	14.81	85.19
Dysuria	0	54	0.0	100.0
Intermittency	4	50	7.41	92.59
Straining to void	12	42	22.22	77.78
Feeling of incomplete emptying	8	46	14.81	85.19
Weak urinary stream	2	52	3.7	96.3
Hesitancy	5	49	9.26	90.74
Urinary incontinence	11	43	20.37	79.63

Table III. Comparison of uroflowmetric parameters by curve morphology

Parameter	Median (IQR) - Normal Curve	Median (IQR) - Altered Curve	p-value
Qmax	27.00 (21.0)	14.59 (11.0)	0.001
Qave	12.50 (7.7)	6.50 (6.5)	0.002
Post-void residual (RPM)	10.0 (30.0)	55.0 (201.0)	0.001
Voided volume	310.0 (235.0)	380.0 (324.0)	0.715

Table IV. Comparison of uroflowmetric parameters between clinically asymptomatic (PND 0 and symptomatic patients

Parameter	PND 0 Mean ± SD	PND ≥ 1 Mean ± SD	p-value (t-test)	p-value (Mann–Whitney)	Interpretation
Qmax (mL/s)	31.87 ± 11.70	25.41 ± 33.22	0.473	0.004	Higher in PND 0
Qave (mL/s)	37.63 ± 64.05	8.78 ± 4.61	0.024	0.002	Higher in PND 0
RPM (mL)	13.67 ± 15.63	76.81 ± 114.82	0.043	0.033	Lower in PND 0
Voided Volume (mL)	375.20 ± 156.97	370.22 ± 225.89	0.938	0.446	No significant difference

Table V. Association between urinary symptoms and uroflowmetry curve morphology in TTR-FAP patients.

Parameter	Normal curve	Altered curve	p-value
Absent bladder sensation	2	2	0.773
Hesitation	0	4	0.016
Incomplete emptying	1	6	0.013
Increase in urinary frequency	3	4	0.416
Intermittency	2	2	0.773
Nocturia	0	1	0.246
Straining (difficulty emptying the bladder)	4	9	0.024
Urinary incontinence	3	6	0.111
Urinary retention	1	7	0.005
Urinary tract infection	7	7	0.533
Urinary urgency	5	3	0.720

Table VI. Comparison of uroflowmetric parameters between Cluster 1 and Cluster 2 identified through two-step clustering.

Parameter	Cluster 1 – Mean (SD)	Cluster 2 – Mean (SD)	Cluster 1 – Median	Cluster 2 – Median	Cluster 1 – 95% CI	Cluster 2 – 95% CI
Qmax (mL/s)	31.87 (11.70)	24.34 (32.26)	34.0	18.0	25.39–38.34	12.07–36.62
Qave (mL/s)	37.63 (64.05)	10.38 (4.70)	15.5	8.0	2.16–73.10	6.59–10.16
Voided volume (mL)	375.20 (156.97)	355.90 (224.40)	340.0	270.0	288.27–462.13	270.54–441.25
RPM (mL)	13.67 (15.64)	81.41 (116.31)	5.0	30.0	5.01–22.33	37.17–125.65

Table VII. Clinical staging systems used for TTR-FAP classification.

Staging System	Stage	Definition
Coutinho Score	0	Genetically confirmed carrier with no neurological symptoms or clinical signs of peripheral neuropathy.
Coutinho Score	1	Sensory-motor symptoms present but patient is able to walk unaided.
Coutinho Score	2	Patient requires one or two walking aids (e.g., crutches or canes) to walk.
Coutinho Score	3	Patient is wheelchair-bound or bedridden.
Polyneuropathy Disability (PND) Score	0	No neurological symptoms or signs of functional impairment.
Polyneuropathy Disability (PND) Score	1	Sensory-motor symptoms without walking limitations.
Polyneuropathy Disability (PND) Score	2	Patient can walk unaided but has some gait disturbances.
Polyneuropathy Disability (PND) Score	3	Patient requires walking support (one or two canes/crutches).
Polyneuropathy Disability (PND) Score	4	Patient is confined to a wheelchair or bed, unable to walk.

Figures

Figure 1. Distribution of the sample by sex

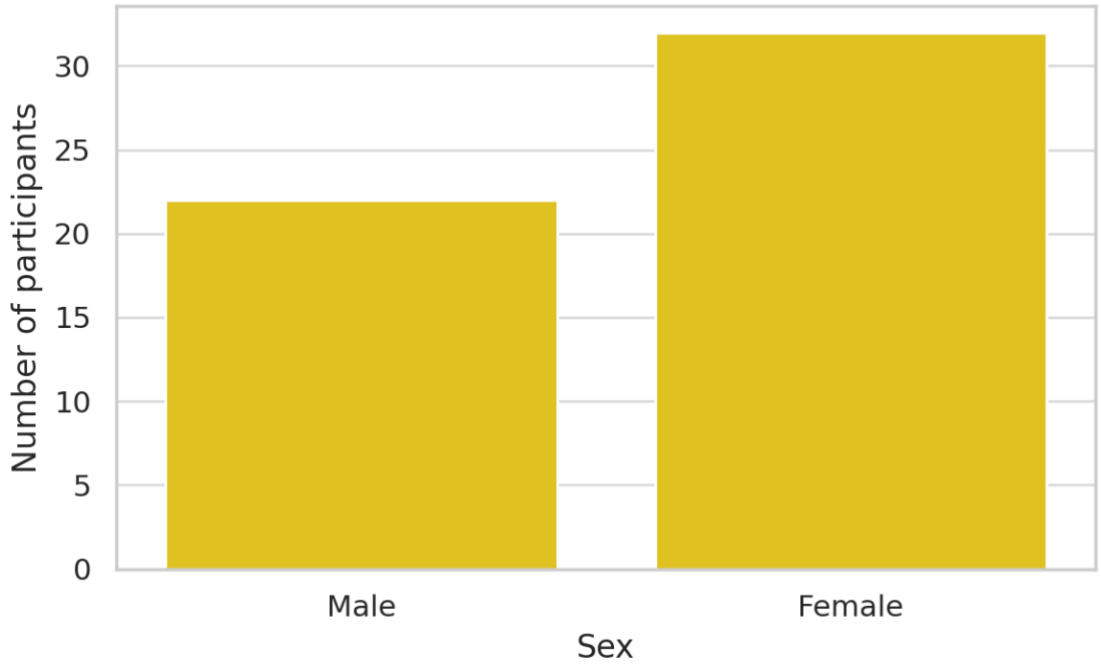


Figure 2. Flow curve morphology (normal vs altered)

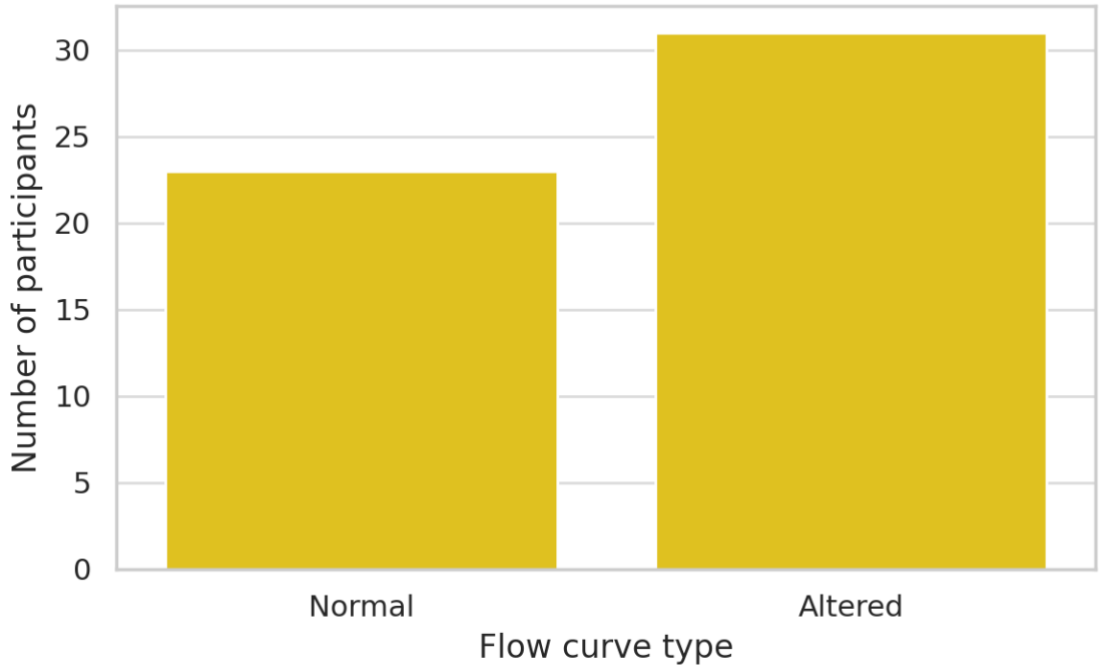


Figure 3. Coutinho clinical stage distribution

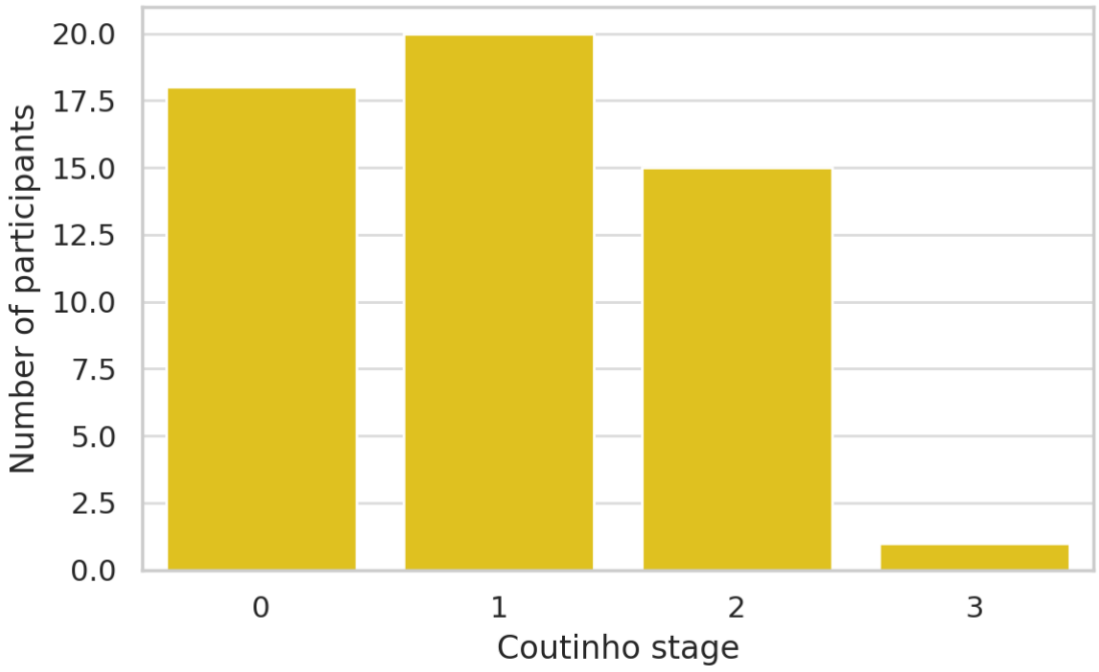


Figure 4. PND stage distribution

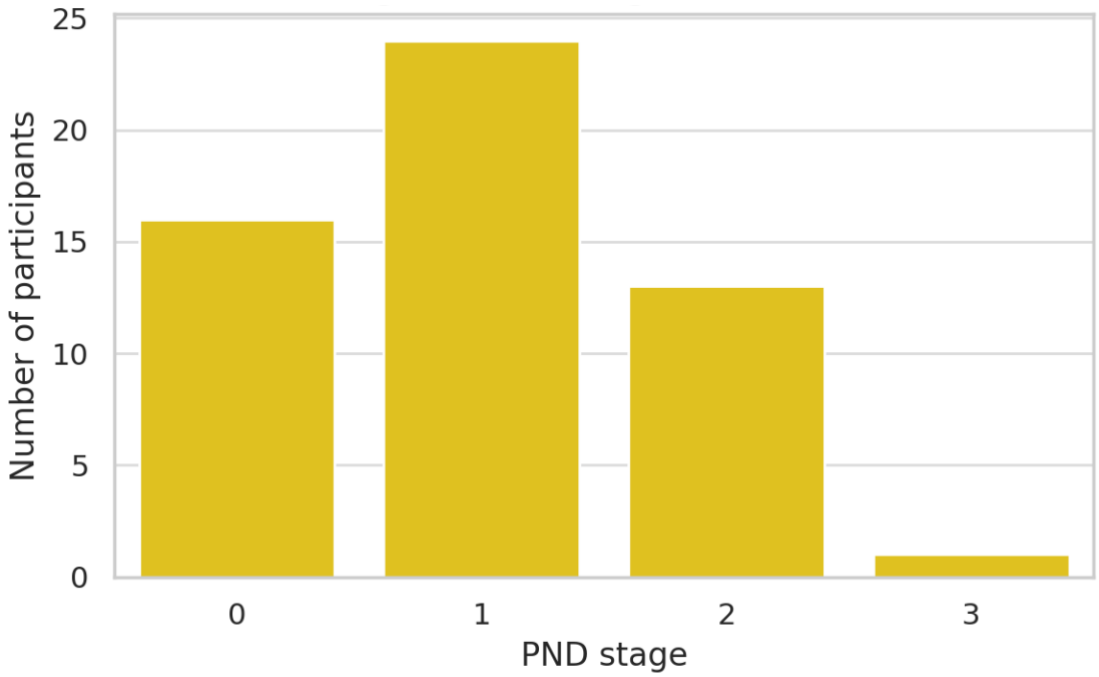


Figure 5. Frequency of urinary symptoms among TTR-FAP carriers

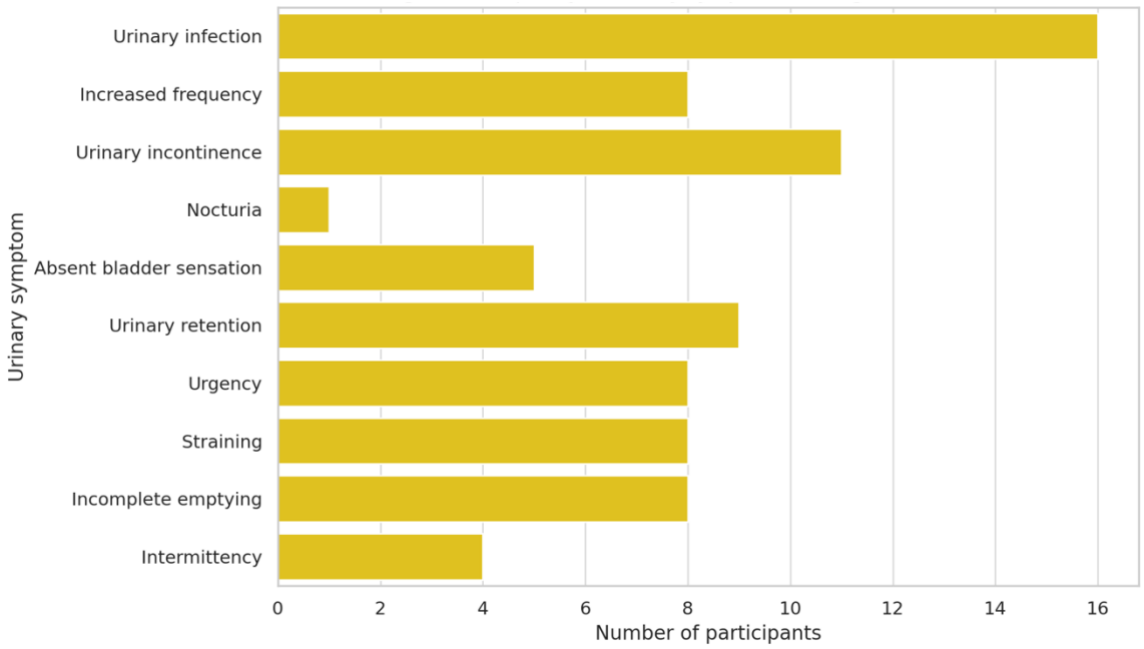


Figure 6. Frequency of urinary symptoms by uroflowmetry curve morphology

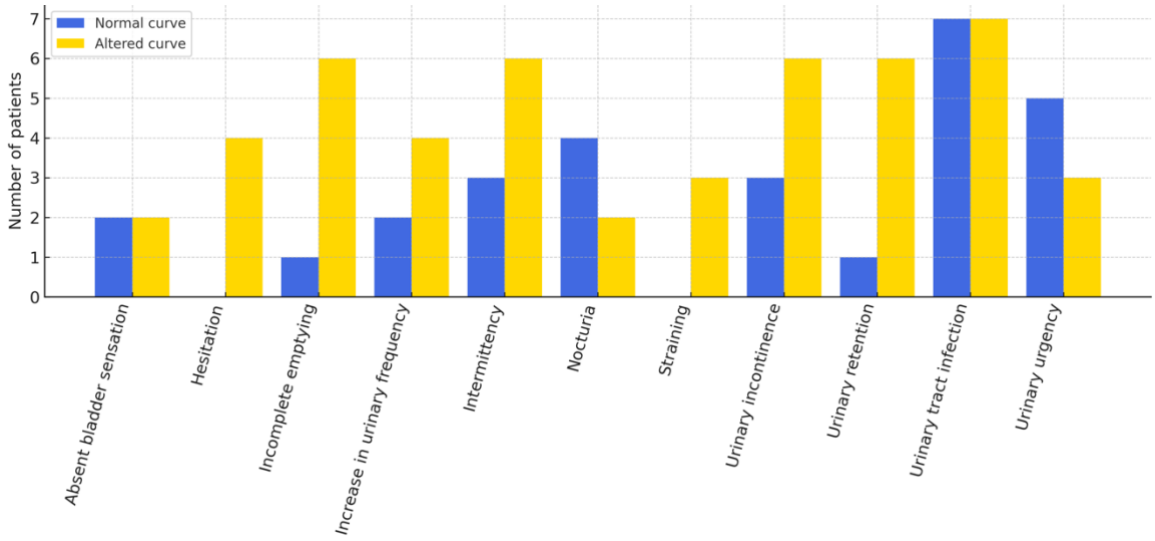


Figure 7. Comparison of Uroflowmetry Parameters by clinical status

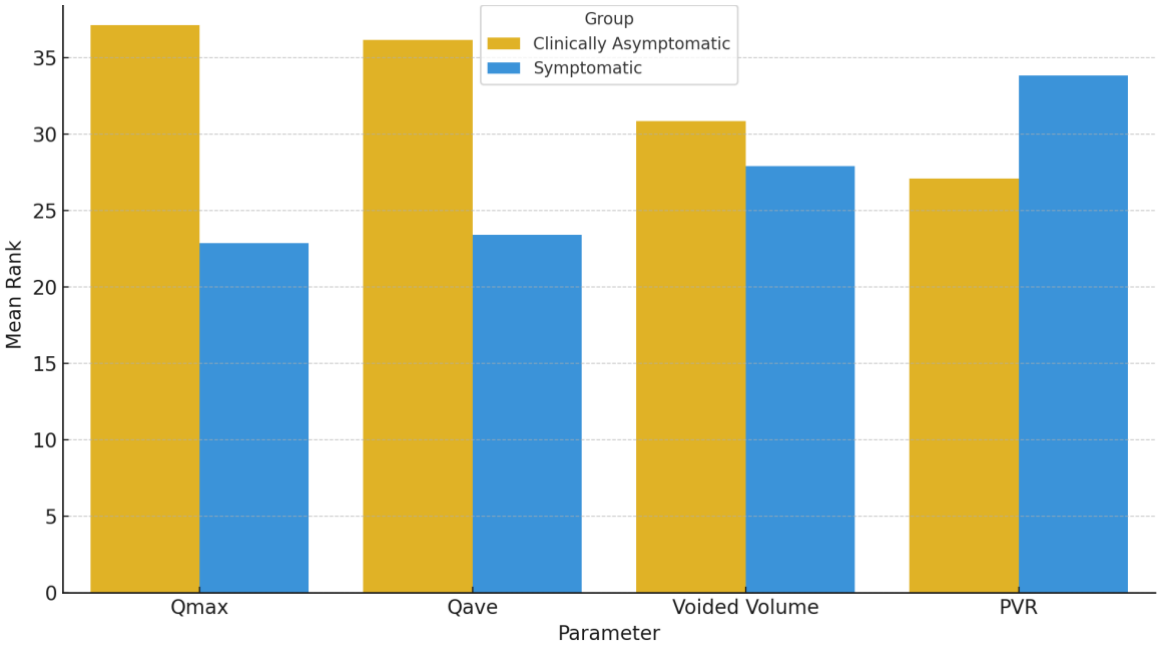
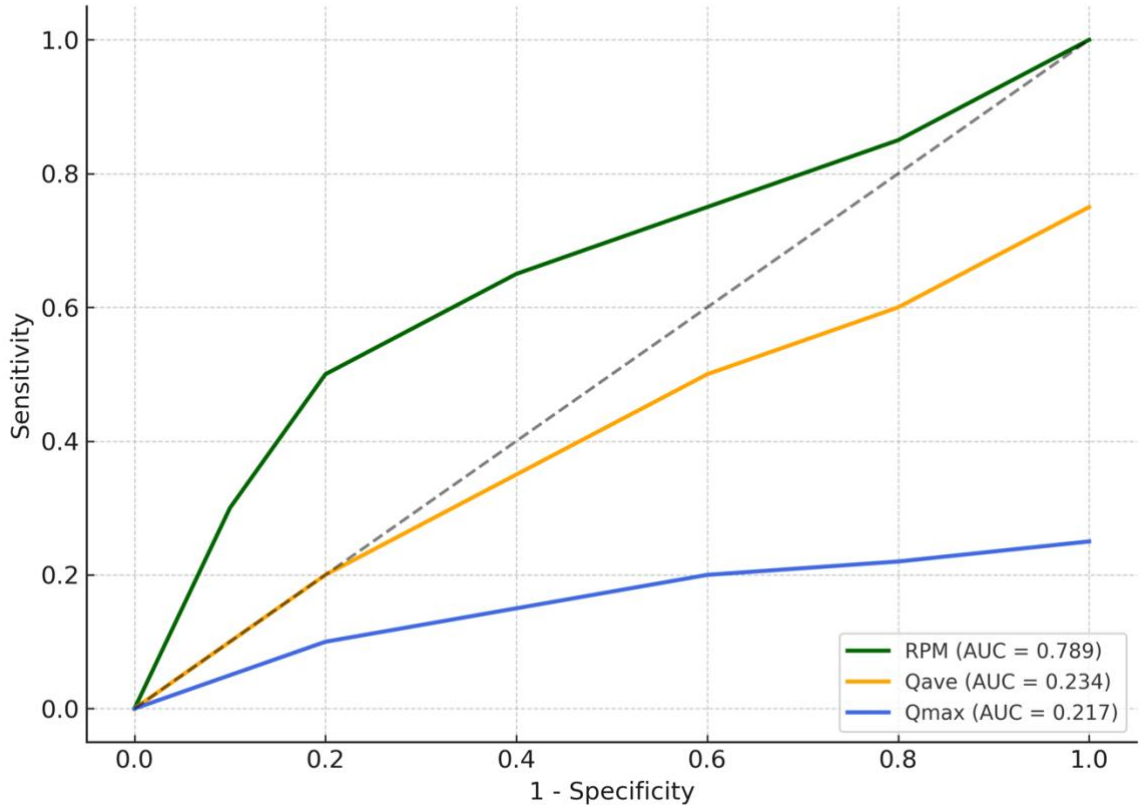


Figure 8. ROC curves for RPM, Qave, Qmax predicting altered flow rate



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INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**