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A novel diagnostic score for diagnosing arginine vasopressin deficiency (central diabetes insipidus) or primary polydipsia with basal laboratory and clinical parameters: results from two international multicentre prospective diagnostic studies

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Summary

Background Distinguishing arginine vasopressin deficiency (central diabetes insipidus) from primary polydipsia is challenging. There is no validated initial laboratory assessment or diagnostic score to rule-in or rule-out arginine vasopressin deficiency during the first consultation. Therefore, this study aimed to evaluate the diagnostic potential of basal laboratory parameters and to develop a practical diagnostic score.

Methods Data from two international multicentre studies of patients with arginine vasopressin deficiency and primary polydipsia undergoing the hypertonic saline test were used to evaluate the diagnostic potential of basal laboratory tests and to develop a score incorporating laboratory results, symptoms, and medical history. CODDI was a non-randomised, controlled, diagnostic, international, multicentre non-inferiority study in 11 tertiary medical centres in Switzerland, Germany, and Brazil. CARGOx was a randomised, controlled, cross-over, diagnostic, international, multicentre non-inferiority study across seven tertiary medical centres in Switzerland, Germany, the Netherlands, Italy, the UK, and Brazil. Participants were adult patients with polydipsia (>3 L per day) and hypotonic polyuria (>50 mL/kg bodyweight in 24 h and urine osmolality <800 mOsm/kg) and adult patients with a previous diagnosis of arginine vasopressin deficiency. Data were derived from the initial consultation and a basal laboratory test. For each laboratory parameter, the cutoffs resulting in the highest specificity at 100% sensitivity and the highest sensitivity at 100% specificity were identified. For the diagnostic score, the overall best cutoff, high-sensitivity cutoff (≥95% sensitivity), and high-specificity cutoff (≥95% specificity) were identified. Each cutoff was derived from the first study (development), and their performance was determined in the second study (validation). The final score included the sum of: basal plasma sodium multiplied by plasma osmolality, divided by 100; –50 points for plasma copeptin more than 4·9 pmol/L; +30 points for nycturia (≥3 times per night) or +20 points for nycturia (2 times per night); +20 points for sudden polyuria or polydipsia onset; +30 points for drinking more than 1 L per night; +50 points for anterior pituitary dysfunction and +50 points for pituitary surgery history. The diagnostic performance in predicting arginine vasopressin deficiency was examined by the receiver operating characteristic (ROC) area under the curve (AUC) and by sensitivity and specificity. The studies were registered with ClinicalTrials.gov (NCT01940614 and NCT03572166).

Findings 299 patients who underwent the hypertonic saline test from July 1, 2013, to Sept 30, 2022 were included in this analysis. 141 patients were in the development cohort (59 [42%] had arginine vasopressin deficiency; 82 [58%] had primary polydipsia) and 158 patients were in the validation cohort (69 [44%] had arginine vasopressin deficiency; 89 [56%] had primary polydipsia). In the development cohort, the median age of patients with arginine vasopressin deficiency was 45 years (IQR 33–53), with 38 (64%) of 59 being female and 21 (36%) male, compared with a median age of 32 years (IQR 24–44) and 55 (67%) of 82 being female and 27 (33%) male in the group of patients with primary polydipsia. In the validation cohort, patients with arginine vasopressin deficiency had a median age of 42 years (IQR 32–54), with 38 (55%) of 69 being female and 31 (45%) male, compared with a median age of 37 years (IQR 28–50) and 68 (76%) of 89 being female and 21 (24%) male for patients with primary polydipsia. In the validation cohort, basal plasma sodium of more than 145 mmol/L identified arginine vasopressin deficiency with 100% specificity (95% CI 61–100), whereas primary polydipsia was identified by sodium less than 135 mmol/L with 100% specificity (34–100) and by copeptin more than 5·6 pmol/L with 100% specificity (74–100). In the validation cohort, the clinical score had an AUC of 91% (87–96), a cutoff of more than 441 points provided an overall accuracy of 86% (80–91) for diagnosing arginine vasopressin deficiency. In the validation cohort, the high-specificity cutoff of less than 415 points had 93% specificity (87–99) for diagnosing primary polydipsia, and the high-specificity cutoff of more than 461 points had 93% specificity (88–98) for diagnosing arginine vasopressin deficiency. This stepwise approach enabled diagnosis in 223 (75%) of 299 patients.

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For the German translation of the abstract see Online for appendix 1

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Interpretation **We introduce a stepwise diagnostic approach, starting with basal laboratory tests and rule-in and rule-out criteria for immediate treatment. For intermediate cases, the novel score aids in identifying arginine vasopressin deficiency or primary polydipsia with high accuracy. This approach could lead to shortening the diagnostic timeline and reducing dependence on stimulation or dynamic tests.**

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Introduction

Disruptions in the hypothalamic–posterior pituitary axis can result in arginine vasopressin deficiency (formerly known as central diabetes insipidus), which clinically manifests as hypotonic polyuria and polydipsia.[1,2] The main differential diagnosis is primary polydipsia, characterised by excessive fluid intake despite adequate arginine vasopressin secretion or renal function.[1,3] Accurate differentiation between arginine vasopressin deficiency and primary polydipsia is crucial due to the distinct treatment strategies required and the complications that can arise from misdiagnosis.[4–6]

Historically, the indirect water deprivation test was the gold standard for distinguishing between both conditions,[7–10] but it has low accuracy and imposes a burden on patients. Copeptin-based tests have shown higher accuracy.[9,11–15] Two independent multicentre trials have validated the diagnostic performance of hypertonic saline-stimulated copeptin in identifying arginine vasopressin deficiency.[9,12,16] However, hypertonic saline stimulation tests are often limited to specialised centres, which can delay diagnosis or lead physicians to use less accurate tests.[17,18] Furthermore, the availability of frequent rapid sodium monitoring is mandatory during the testing, and patients can experience discomfort from the induced hypernatraemia.[9,12]

There is no standardised and validated stepwise assessment or diagnostic score available for the initial evaluation of patients presenting with hypotonic polyuria and polydipsia. Unlike other endocrine conditions (eg, in suspected adrenal insufficiency), in which precise screening tools (basal morning plasma cortisol)[19] are available to rule in or rule out patients and avoid further stimulation testing, no such validated tool or basal laboratory cutoffs are available for arginine vasopressin deficiency. As a result, most patients with suspected arginine vasopressin deficiency are referred to a specialised centre for diagnostic testing without previous selection.

Research in context

Evidence before the study

Arginine vasopressin deficiency is a rare neuroendocrine condition that presents a diagnostic challenge, underscoring the need for clear, accessible diagnostic algorithms to aid in the initial assessment of suspected cases, as patients often endure lengthy referral processes before undergoing stimulation tests for a definitive diagnosis. We conducted a PubMed search from database inception to Oct 1, 2024, using terms such as "diabetes insipidus", "arginine vasopressin deficiency", "primary polydipsia", "polyuria polydipsia", "copeptin", "provocation test", "stimulation test", "water deprivation test", "hypertonic saline", "arginine", and "diagnosis". Data on arginine vasopressin resistance were excluded. The gold standard for diagnosis is the hypertonic saline stimulation test, with a diagnostic accuracy of 95%. However, it is invasive and requires close monitoring, thereby restricting its availability. The absence of accessible, standardised, and simplified diagnostic tools results in diagnostic delays. Studies show that patients have delays in initial diagnosis that range between 6 and 12 months from symptom onset to diagnosis. This delay can defer treatment initiation, leaving patients symptomatic and susceptible to complications such as dehydration.

Added value of this study

Our findings provide an efficient and practical tool, derived from routine measurements, to prioritise suspected cases for more complex testing. Specifically, we show that a basal plasma sodium concentration of less than 135 mmol/L or a plasma copeptin concentration of more than 5·6 pmol/L can rule out arginine vasopressin deficiency, and a plasma sodium concentration of more than 145 mmol/L is a reliable criterion for the diagnosis. We developed and validated a score incorporating basal laboratory parameters, symptoms, and medical history, showing a high diagnostic accuracy of 86% for identifying arginine vasopressin deficiency without the need for further dynamic testing.

Implications of all available evidence

This new evidence supports a more accessible diagnostic approach for arginine vasopressin deficiency, reducing dependence on stimulation tests. For clinical practice, physicians can start with routine basal laboratory tests—plasma sodium and copeptin—using rule-in and rule-out criteria to guide immediate treatment initiation. For intermediate cases, the clinical score provides further guidance, identifying arginine vasopressin deficiency or primary polydipsia with high likelihood, ensuring that only unclear cases proceed to invasive testing. This approach could lead to shortening the diagnostic timeline and reducing the burden on health-care systems.

Therefore, this study aimed, first, to assess the diagnostic potential of basal laboratory tests and, second, to develop a novel diagnostic score based on routine basal laboratory tests, symptoms, and medical history for clinical practice.

Methods

Study design

This study includes data from independent patient cohorts from two international multicentre trials that used the hypertonic saline stimulation test for the diagnostic evaluation of patients presenting with polyuria–polydipsia syndrome. The first study (referred to as the development cohort; CODDI trial)[9], was a non-randomised, controlled, diagnostic, international, multicentre non-inferiority study conducted between July 1, 2013, and June 30, 2017, involved 11 tertiary medical centres in Switzerland, Germany, and Brazil, with a 3-month follow-up completed by Sept 30, 2017. The second study (referred to as the validation cohort, CARGOx trial)[12] was a randomised, controlled, cross-over, diagnostic, international, multicentre non-inferiority study conducted from Sept 1, 2018 to Sept 30, 2022, across seven tertiary medical centres in Switzerland, Germany, the Netherlands, Italy, the UK, and Brazil, with follow-up concluding in Dec 31, 2022. Both studies received approval from the local ethics committees of all centres. The studies were preregistered on ClinicalTrials.gov (CODDI NCT01940614; CARGOx NCT03572166).[9,12]

Participants

Adult patients with polydipsia (exceeding 3 L per day) and hypotonic polyuria (more than 50 mL/kg bodyweight in a 24 h urine collection and urine osmolality less than 800 mOsm/kg) and adult patients with a previous diagnosis of arginine vasopressin deficiency were recruited. Exclusion criteria were patients with arginine vasopressin resistance or polyuria and polydipsia secondary to other causes (eg, type 1 and type 2 diabetes, hypercalcaemia, or hypokalaemia); acute or terminal illness; epilepsy requiring treatment; uncontrolled arterial hypertension (blood pressure >160/100 mm Hg); heart failure (New York Heart Association Functional Classification III–IV); liver cirrhosis (Child B–C); uncorrected adrenal or thyroidal deficiency; and pregnancy or breastfeeding. All patients referred or presented to the outpatient clinic with polyuria and polydipsia syndrome were recruited. Written informed consent was obtained from all patients before any study procedures.

Procedures

At enrolment, a standardised assessment was conducted to evaluate symptoms and concomitant diseases. This assessment included measuring polyuria through a 24 h urine collection, reporting polydipsia with a 24 h drink protocol (in case of pretreatment with desmopressin, polydipsia volume recorded before desmopressin initiation was used), recording the frequency of nycturia, and noting whether the onset of polyuria or polydipsia was sudden (within days to a few weeks) or gradual (over several weeks to months). Additionally, the amount and frequency of nighttime drinking were assessed, previous pituitary surgery was documented, and the presence of anterior pituitary deficiencies was either prerecorded or tested after the diagnostic procedure and recorded retrospectively.

Participants presented in the morning after overnight meal fasting. They were permitted to drink water until 6 am (2 h before the first basal blood sample was taken). Patients under desmopressin treatment were instructed to cease the medication 24 h before testing. However, local investigators could reduce this withdrawal period to a minimum of 12 h for patients with severe symptoms of arginine vasopressin deficiency. Patients on hydrocortisone therapy received an individualised stress dose. The first standardised blood sample (a 2 h fasting sample for basal plasma sodium, plasma osmolality, and plasma copeptin) was used for this analysis. The diagnosis was based on stimulated copeptin concentration at a sodium concentration of more than 149 mmol/L, with 4·9 pmol/L or lower of copeptin indicating arginine vasopressin deficiency and more than 4·9 pmol/L of copeptin indicating primary polydipsia.

Samples were immediately centrifuged at 4°C and 1500×g for 10 min, then stored at less than –70°C until batch analysis. Laboratory measurements were performed by automated biochemical analyses. Plasma sodium concentrations were analysed with the indirect ion selective electrode method. Plasma osmolality was measured by freezing point depression. All copeptin measurements were conducted with the BRAHMS Copeptin proAVP automated immunoassay (Thermo Scientific Biomarkers, Hennigsdorf, Germany). The lower detection limit was 0·4 pmol/L, the interassay coefficient of variation was 7·0%, and the intra-assay coefficient of variation was 9·8%. All previously published copeptin cutoffs—including cutoffs from this analysis—must be considered in the context of measurements with the BRAHMS Copeptin proAVP assay; other copeptin assays will not result in the same cutoffs.

Development of the scoring scheme

In the initial phase, machine learning-based feature selection was used to identify the five most relevant predictors from a total of 56 available laboratory measures and medical history components in the development cohort: urine osmolality, plasma sodium, glucose concentrations, pituitary surgery, and anterior pituitary dysfunction.[20] However, urine osmolality was excluded as it was not consistently assessed in the validation cohort, and glucose was omitted as it is not directly linked to arginine vasopressin physiology. In addition, clinically relevant variables related to the disease itself and considered to be important for arginine vasopressin

deficiency or primary polydipsia diagnosis were included based on the authors' consensus, all of which were involved in conducting both trials: nycturia and nighttime fluid intake, onset of symptoms, and MRI findings. All variables were collected in a standardised manner in both trials. Overall, this resulted in a set of ten predictors: plasma sodium, osmolality, copeptin, nycturia frequency, onset of polyuria or polydipsia, nighttime fluid intake, presence of anterior pituitary dysfunction, history of pituitary surgery, pituitary stalk thickening (MRI), and absence of a posterior bright spot (MRI). Based on these, the scoring system was designed as a stepwise model, starting with key laboratory parameters before integrating clinical and imaging features (ie, that starts simple and increases in complexity).

First, plasma sodium, osmolality, and copeptin were prioritised, as they are directly linked to arginine vasopressin physiology: osmolality triggers arginine vasopressin release, sodium regulates osmolality, and copeptin serves as a direct biomarker of arginine vasopressin secretion. The distribution of plasma sodium and plasma osmolality concentrations was assessed in both conditions. High-normal concentrations of plasma sodium and osmolality were indicative of arginine vasopressin deficiency, while low-normal concentrations suggested primary polydipsia. To enhance the differentiation between these two conditions, an index combining both parameters was created (figure 1). This index formed the core of the diagnostic score. Previous diagnostic studies showed that a hypertonic saline stimulated copeptin concentration more than 4·9 pmol/L substantially reduces the likelihood of arginine vasopressin deficiency, making this cutoff an additional key component in our scoring system (figure 1).

See Online for appendix 2

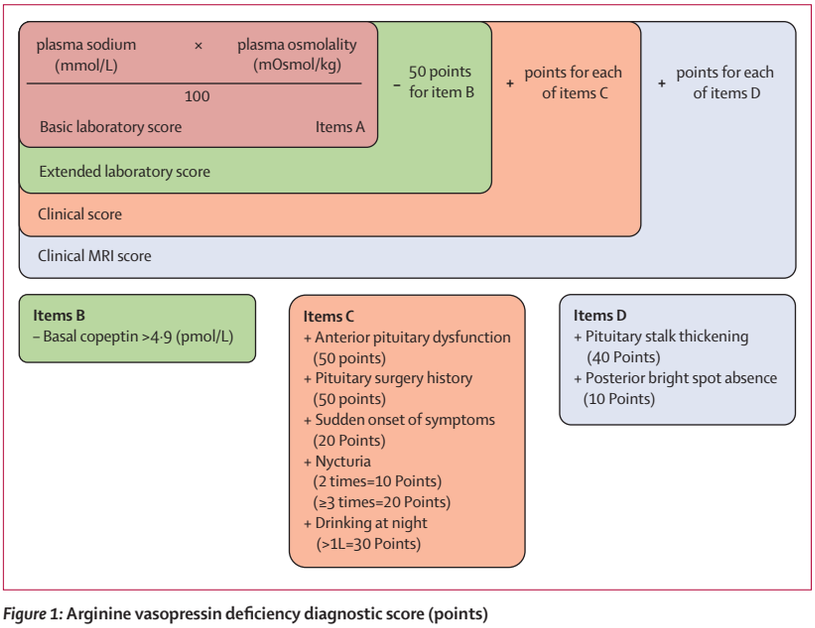

Figure 1: **Arginine vasopressin deficiency diagnostic score (points)**

Next, a multivariable logistic regression model was developed with the diagnosis as the binary outcome variable (arginine vasopressin deficiency *vs* primary polydipsia). The model incorporated basal copeptin more than 4·9 pmol/L (yes or no), nycturia frequency (≤1, 2, or ≥3 times per night), sudden onset of polyuria or polydipsia (yes or no), nighttime fluid intake more than 1 L (yes or no), presence of anterior pituitary dysfunction (yes or no), and history of pituitary surgery (yes or no). For the MRI data, presence of pituitary stalk thickening (yes or no) and the absence of a posterior bright spot (yes or no) was included.

To ensure clinical applicability, we did not use the estimated regression coefficients per se for scoring. Instead, we pursued a more pragmatic approach and assigned a weight with a score ranging from ten points (least important) to 50 points (most important) to each predictor. The importance of each predictor was based on the order or rank of the regression coefficient and clinical relevance based on the authors' assessment. To summarise, the score development was based on a hybrid approach combining (1) machine learning-based predictor selection (data-driven variable selection), (2) estimation of regression coefficients (data-informed weighting), and (3) expert consensus (weighting by relative importance in a real-world clinical setting). This scoring system was developed with data from the first study (development cohort) and validated with data from the second study (validation cohort). To maintain independence between the study populations, patients from the first trial were not included in the second trial. Since regression coefficients were not directly incorporated into the score, no additional internal model validation was performed. The complete procedure in selecting variables and developing the scoring scheme is visualised and described in appendix 2 (p 14).

The final scoring scheme is a combination of the basic laboratory score, the extended laboratory score, the clinical score, and the clinical MRI score (figure 1). The basic laboratory score scheme uses the formula: basal plasma sodium (in mmol/L) multiplied by plasma osmolality (in mOsm/kg), divided by 100. The extended laboratory score scheme is based on basal plasma copeptin: deduct 50 points if copeptin is more than 4·9 pmol/L. The clinical score uses additional data from symptoms and clinical history at presentation: add 50 points for the presence of additional anterior pituitary deficiencies, add 50 points for previous pituitary surgery, add 30 points if nycturia 3 times per night or more or 20 points if nycturia twice per night, add 30 points for night-time drinking exceeding 1 L, and add 20 points for a sudden onset of polyuria or polydipsia. The clinical MRI score uses additional data from MRI findings: add 40 points if pituitary stalk thickening is present and add 10 points if the posterior bright spot is absent.

Statistical analysis

Demographic information and laboratory parameters were summarised with median (IQR) for continuous variables and absolute (relative) frequency for categorical variables. The diagnostic performance in predicting arginine vasopressin deficiency of each laboratory parameter was examined separately by the receiver operating characteristic (ROC) area under the curve (AUC), with sensitivity and specificity reported with 95% CIs. In addition, for each laboratory parameter, the cutoffs resulting in the highest specificity at 100% sensitivity and the highest sensitivity at 100% specificity were identified. For each score (variant), the AUC, overall best cutoff, high-sensitivity cutoff (defined as ≥95% sensitivity), and high-specificity cutoff (defined as ≥95% specificity) were derived in the development cohort. Best cutoffs were identified with Youden's J statistic, which is the threshold that maximises the distance to the identity (diagonal) line. The optimality criterion is the maximum of sensitivity plus specificity.

We conducted a sensitivity analysis of the optimal cutoffs with the closest to (0,1) method, which identifies the cutoff closest to a perfect classifier (sensitivity=1, specificity=1) by minimising the Euclidean distance to the top-left corner of the ROC curve (appendix 2 p 17). The diagnostic performance of these cutoffs was subsequently identified in the validation cohort. To account for cases in which the default pROC package function in R applies bootstrapping for 100% sensitivity or specificity—resampling only within the affected group—Wilson's CI for a single proportion was used instead (PropCIs package). There were no missing data for the clinical and laboratory variables used in both studies. MRI evaluations were performed only in a subset of patients, and data were available accordingly. Sensitivity was defined as the proportion of true positive cases correctly identified, calculated as true positives divided by (true positives plus false negatives). Specificity was defined as the proportion of true negative cases correctly classified, calculated as true negatives divided by (true negatives plus false positives). All analyses were conducted with the statistical software R (version 4.2.3; pROC, epiR, and PropCIs packages).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 299 patients underwent the hypertonic saline test from July 1, 2013, to Sept 30, 2022 (figure 2). The development cohort comprised 141 patients: 59 (42%) were diagnosed with arginine vasopressin deficiency and 82 (58%) with primary polydipsia. The median age for patients with arginine vasopressin deficiency was 45 years (IQR 33–53), with 38 (64%) of 59 patients being female and 21 (36%) male, compared with a median age of 32 years (IQR 24–44) and 55 (67%) of 82 patients with primary polydipsia being female and 27 (33%) male (table 1). Among the 59 patients with arginine vasopressin deficiency, 22 (37%) had isolated posterior pituitary dysfunction, and 37 (63%) had combined anterior and posterior pituitary dysfunction.

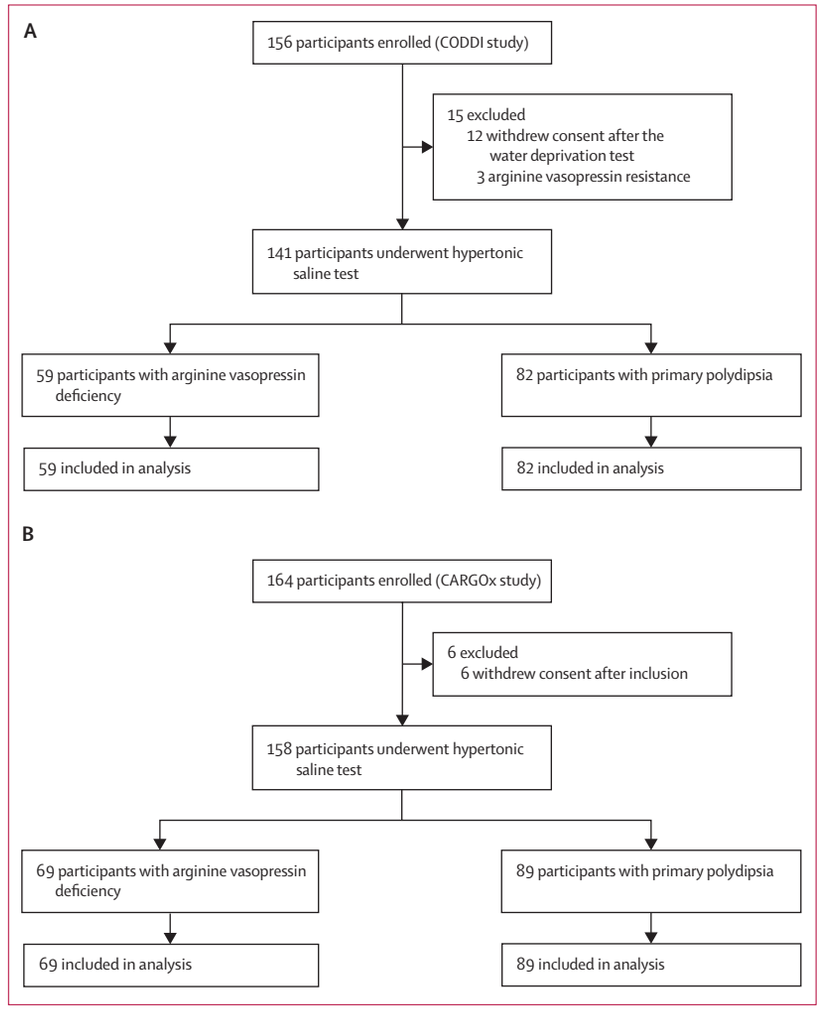

Figure 2: **Study profile**
Summary of inclusion and participation of patients with arginine vasopressin deficiency and primary polydipsia in the (A) development (CODDI) and (B) validation (CARGOx) cohorts.

The validation cohort comprised 158 patients: 69 (44%) patients were diagnosed with arginine vasopressin deficiency and 89 (56%) patients with primary polydipsia. Among 69 patients with arginine vasopressin deficiency, the median age was 42 years (IQR 32–54), with 38 (55%) being female and 31 (45%) being male. By comparison, among 89 patients with primary polydipsia, the median age was 37 years (IQR 28–50), with 68 (76%) being female and 21 (24%) being male (table 1). In this cohort, of 69 patients with arginine vasopressin deficiency, 40 (58%) had isolated posterior pituitary dysfunction, and

	Development cohort (n=141; CODDI)		Validation cohort (n=158; CARGOx)	
	Arginine vasopressin deficiency (n=59)	Primary polydipsia (n=82)	Arginine vasopressin deficiency (n=69)	Primary polydipsia (n=89)
Sex				
Female	38 (64%)	55 (67%)	38 (55%)	68 (76%)
Male	21 (36%)	27 (33%)	31 (45%)	21 (24%)
Age, years	45 (33–53)	32 (24–44)	42 (32–54)	37 (28–50)
BMI	27·6 (23·7–31·4)	23·9 (21·2–26·0)	27·6 (24·5–33·0)	23·8 (21·0–28·5)
Race				
White	55 (93%)	79 (96%)	62 (90%)	86 (97%)
Other	4 (7%)	3 (4%)	7 (10%)	3 (3%)
Clinical symptoms				
Polyuria, mL urine per day	5500 (4000–8000)	4500 (4000–6000)	6000 (4000–8125)	5000 (4000–6000)
Polydipsia, mL consumed per day	6000 (4800–8000)	5000 (4500–6900)	6000 (4000–8000)	5000 (4000–7000)
Any nighttime fluid intake	54 (92%)	51 (62%)	51 (74%)	60 (67%)
Nighttime fluid intake, mL per night	1500 (1000–2000)	500 (300–1000)	1000 (500–2000)	650 (475–1000)
Any nycturia	56 (95%)	56 (68%)	56 (81%)	68 (76%)
Nycturia, times per night	3 (2–5)	2 (1–3)	4 (3–5)	3 (2–3)
Sudden onset of symptoms	37 (63%)	18 (22%)	40 (58%)	15 (17%)
Laboratory data				
Plasma sodium, mmol/L	142 (3·5)	140 (2·4)	143 (3·0)	139 (1·9)
Plasma osmolality, mOsmol/kg	293 (5·2)	284 (11·2)	293 (10·2)	286 (6·4)
Plasma copeptin, pmol/L	2·4 (1·8–3·2)	3·9 (2·5–5·9)	2·2 (1·6–2·4)	2·6 (2·0–3·9)
Medical history				
History of pituitary surgery	30 (51%)	2 (2%)	22 (32%)	6 (7%)
Hypothalamic–pituitary or pituitary tumour or lesion	29 (49%)	5 (6%)	23 (33%)	10 (11%)
Anterior pituitary deficiency	37 (63%)	2 (2%)	29 (42%)	5 (6%)
Previous diagnosis of arginine vasopressin deficiency	31 (53%)	7 (9%)*	35 (51%)	2 (2%)*
Established desmopressin treatment at enrolment	26 (44%)	6 (7%)*	35 (51%)	2 (2%)*
MRI characteristics				
Hyperintense signal in posterior pituitary absent	33/47 (70%)	14/36 (39%)	43/64 (67%)	6/44 (14%)
Pituitary stalk enlarged	9/52 (17%)	1/39 (3%)	13/64 (20%)	2/44 (5%)

Data are n (%), median (IQR), mean (SD), or n/N (%). *These patients were reclassified as patients with primary polydipsia after the diagnostic procedure (ie, were misdiagnosed before enrolment).

Table 1: **Baseline characteristics**

29 (42%) had combined anterior and posterior pituitary dysfunction.

Patient characteristics are summarised in table 1. Patients with arginine vasopressin deficiency and patients with primary polydipsia had similar total volumes of polyuria and polydipsia across cohorts. Basal plasma sodium, osmolality, and copeptin concentrations were similar, though patients with arginine vasopressin deficiency had a slightly higher frequency of nycturia and increased nighttime fluid intake than patients with primary polydipsia.

For both cohorts, basal plasma sodium, plasma osmolality, and plasma copeptin concentrations are shown in figure 3 and summarised in table 2. To identify the clear (ie, extreme) cases with certainty, 100% sensitivity and 100% specificity for each laboratory parameter were assessed. For diagnosing arginine vasopressin deficiency in the development cohort, a basal plasma sodium concentration of more than 145 mmol/L provided a 100% specificity (95% CI 68–100), and plasma osmolality of more than 300 mOsmol/kg provided 100% specificity (72–100). A basal plasma sodium concentration of 135 mmol/L or more provided 100% sensitivity (95% CI 44–100), plasma osmolality of 274 mOsmol/kg or more provided 100% sensitivity (34–100), and plasma copeptin of 5·6 pmol/L or less provided 100% sensitivity (85–100; figure 3; table 2). Conversely, for diagnosing primary polydipsia, a basal plasma sodium concentration of 145 mmol/L or less provided 100% sensitivity (95% CI 68–100) and plasma osmolality of 300 mOsmol/kg or less provided 100% sensitivity (72–100). A basal plasma sodium concentration of less than 135 mmol/L provided 100% specificity (44–100), plasma osmolality of less than 274 mOsmol/kg provided 100% specificity (34–100), and plasma copeptin of more than 5·6 pmol/L provided 100% specificity (85–100).

In the validation cohort, these diagnostic cutoffs showed similar accuracy: for diagnosing arginine vasopressin deficiency, basal plasma sodium concentration of more than 145 mmol/L had 100% specificity (95% CI 61–100) and plasma osmolality of more than 300 mOsmol/kg had 100% specificity (51–100). A basal plasma sodium concentration of 135 mmol/L or more had 100% sensitivity (34–100), plasma osmolality of 274 mOsmol/kg or more had 100% sensitivity (34–100), and plasma copeptin of 5·6 pmol/L or less had 100% sensitivity (74–100; figure 3; table 2). Conversely, for diagnosing primary polydipsia, a basal plasma sodium concentration of 145 mmol/L or less provided 100% sensitivity (95% CI 61–100) and plasma osmolality of 300 mOsmol/kg or less provided 100% sensitivity (51–100). A basal plasma sodium concentration of less than 135 mmol/L provided 100% specificity (34–100), plasma osmolality of less than 274 mOsmol/kg provided 100% specificity (34–100), and plasma copeptin of more than 5·6 pmol/L provided 100% specificity (74–100). Applying these cutoffs in both directions resulted in an accurate diagnosis in 61 (20%) of 299 patients (40 [28%] of 141 patients in the development cohort and 21 [13%] of 158 patients in the validation cohort).

For both cohorts, the distribution of the clinical score is shown in figure 4. The basic laboratory score, extended laboratory score, clinical score, and clinical MRI score are summarised in table 2 and shown in appendix 2 (pp 3–5).

In the development cohort, the laboratory score had an AUC of 75% (95% CI 66–83), and the threshold of more than 414 points had the best diagnostic performance for diagnosing arginine vasopressin deficiency. In the validation cohort, the laboratory score had an AUC of 91% (87–95), and the threshold of more than 414 points had 91% specificity (84–97) and 64% sensitivity (52–75) for diagnosing arginine vasopressin deficiency. The diagnostic performance of the high-sensitivity and high-specificity cutoffs for diagnosing arginine vasopressin deficiency are summarised in table 2 and for diagnosing primary polydipsia in appendix 2 (pp 13).

In the development cohort, the extended laboratory score had an AUC of 78% (95% CI 70–86), and the threshold of more than 409 points had the best diagnostic performance for diagnosing arginine vasopressin deficiency. In the validation cohort, the extended laboratory score had an AUC of 91% (86–95), and the threshold of more than 409 points had 89% specificity (82–94) and 74% sensitivity (64–84) for diagnosing arginine vasopressin deficiency. The diagnostic performance of the high-sensitivity and high-specificity cutoffs are summarised in table 2 for diagnosing arginine vasopressin deficiency and appendix 2 (p 13) for diagnosing primary polydipsia.

In the development cohort, the clinical score had an AUC of 94% (95% CI 90–99), and the threshold of more than 441 points provided the highest diagnostic performance with an overall diagnostic accuracy of 90% (85–95) for diagnosing arginine vasopressin deficiency. The high-sensitivity cutoff of 415 points or more provided 95% sensitivity (92–100), and the high-specificity cutoff of more than 461 points provided 95% specificity (90–99) for diagnosing arginine vasopressin deficiency. Conversely, the high-specificity cutoff of less than 415 provided 95% specificity (92–100), and the high-sensitivity cutoff of 461 or less provided 95% sensitivity (90–99) for diagnosing primary polydipsia.

In the validation cohort, the clinical score maintained this performance, with an AUC of 91% (95% CI 87–96), and the threshold of more than 441 points had an overall diagnostic accuracy of 86% (80–91) for diagnosing arginine vasopressin deficiency. The high-sensitivity cutoff of 415 points or more had 93% sensitivity (95% CI 87–99), and the high-specificity cutoff of more than 461 points had 93% specificity (95% CI 88–98) for diagnosing arginine vasopressin deficiency. Conversely, the high-specificity cutoff had 93% specificity (87–99), and the high-sensitivity cutoff had 93% sensitivity (88–98) for diagnosing primary polydipsia. The distribution and performance of the clinical score in patients without a history of pituitary surgery or those already excluded based on the basal laboratory test are shown and summarised in appendix 2 (pp 6, 8–9).

Adding further MRI data showed no major improvement in the diagnostic performance. In the development cohort, a clinical MRI score had an AUC of 94% (95% CI 90–99), and the threshold of more than 440 points provided the highest diagnostic performance. In the validation cohort, the clinical MRI score maintained this performance, archiving an AUC of 93% (89–97) and the threshold of more than 440 points had 76% specificity (67–84) and 91% sensitivity (84–97) for diagnosing arginine vasopressin deficiency. The diagnostic performance of the high-sensitivity and high-specificity cutoffs for diagnosing arginine vasopressin deficiency is summarised in table 2, and performance of cutoffs for diagnosing primary polydipsia is summarised in appendix 2 (p 13).

A full algorithm is provided in appendix 2 (p 2). Overall, using the 100% specificity cutoffs in the basal laboratory and the 95% high-specificity cutoffs for both conditions in the clinical score combined enabled diagnosis in 223 (75%) of 299 patients (112 [79%] of 141 patients in the development cohort [3 false negative and 4 false positive] and 111 [70%] of 158 patients in the validation cohort [5 false negative and 6 false positive]). The clinical score without copeptin enabled diagnosis in 249 (83%) of 299 patients (118 [84%] of 141 patients in the development cohort [3 false negative and 5 false positive] and 131 [83%] of 158 in the validation cohort [7 false negative and 8 false positive]).

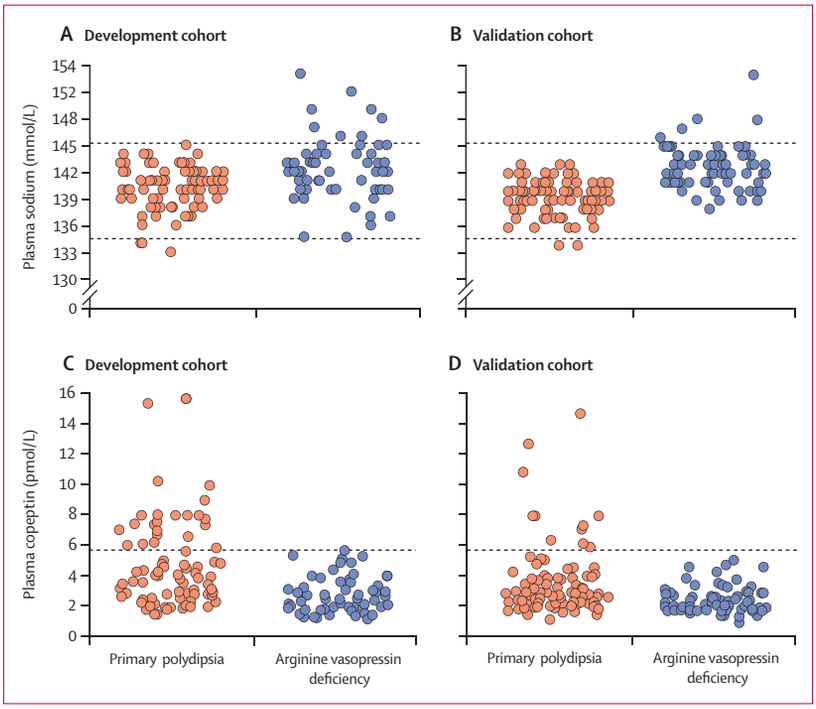

Figure 3: **Basal plasma sodium and copeptin**
Basal plasma sodium concentrations in the (A) development cohort and (B) validation cohort. Basal plasma copeptin concentrations in the (C) development cohort and (D) validation cohort. Data are expressed as individual points for each patient with arginine vasopressin deficiency (in blue) and primary polydipsia (in orange). The dashed lines represent the 100% sensitivity cutoffs derived from the development cohort for diagnosing arginine vasopressin deficiency.

Discussion

This study presents two key findings with important clinical implications for diagnosing arginine vasopressin

	Cutoff	Development cohort			Validation cohort		
		ROC–AUC	Specificity	Sensitivity	ROC–AUC	Specificity	Sensitivity
Plasma sodium, mmol/L	..	68% (59–78)	..	..	88% (82–93)	..	..
100% specificity threshold	>145	..	100% (68–100*)	14% (5–22)	..	100% (61–100*)	9% (3–16)
100% sensitivity threshold	≥135	..	4% (0–9)	100% (44–100*)	..	2% (0–7)	100% (34–100*)
Plasma osmolality, mOsm/kg	..	72% (63–81)	..	..	87% (81–92)	..	..
100% specificity threshold	>300	..	100% (72–100*)	17% (8–27)	..	100% (51–100*)	6% (1–12)
100% sensitivity threshold	≥274	..	2% (0–6)	100% (34–100*)	..	2% (0–6)	100% (34–100*)
Plasma copeptin, pmol/L	..	74% (66–82)	..	..	69% (60–77)	..	..
100% sensitivity threshold	≤5·6	..	27% (18–37)	100% (85–100*)	..	12% (6–20)	100% (74–100*)
Laboratory score	..	75% (66–83)	..	..	91% (87–95)	..	..
Overall best threshold	>414	..	87% (79–94)	54% (42–68)	..	91% (84–97)	64% (52–75)
High specificity threshold	>426	..	95% (88–99)	22% (12–34)	..	100% (80–100*)	12% (4–19)
100% specificity threshold	>431	..	100% (74–100*)	19% (8–29)	..	100% (68–100*)	13% (6–22)
High sensitivity threshold	≥389	..	13% (6–21)	95% (88–100)	..	21% (13–30)	100% (83–100*)
100% sensitivity threshold	≥369	..	2% (1–6)	100% (34–100*)	..	1% (0–3)	100% (21–100*)
Extended laboratory score	..	78% (70–86)	..	..	91% (86–95)	..	..
Overall best threshold	>409	..	78% (68–87)	68% (56–80)	..	89% (82–94)	74% (64–84)
High specificity threshold	>425	..	95% (88–99)	25% (15–37)	..	98% (94–100)	30% (19–42)
100% specificity threshold	>431	..	100% (74–100*)	19% (8–31)	..	100% (68–100*)	13% (6–22)
High sensitivity threshold	≥360	..	20% (12–29)	95% (86–98)	..	9% (3–16)	99% (96–100)
100% sensitivity threshold	≥349	..	11% (5–18)	100% (70–100*)	..	8% (2–13)	100% (65–100*)
Clinical score	..	94% (90–99)	..	..	91% (87–96)	..	..
Overall best threshold	>441	..	90% (83–95)	90% (81–97)	..	87% (79–93)	86% (77–93)
High specificity threshold	>461	..	95% (90–99)	83% (73–92)	..	93% (88–98)	70% (58–80)
100% specificity threshold	>567	..	100% (74–100*)	19% (8–29)	..	100% (61–100*)	3% (1–8)
High sensitivity threshold	≥415	..	66% (56–76)	95% (92–100)	..	53% (43–63)	93% (87–99)
100% sensitivity threshold	≥364	..	17% (10–26)	100% (78–100*)	..	9% (3–16)	100% (44–100*)
Clinical score (without copeptin)	..	95% (92–98)	..	..	90% (85–95)	..	..
Overall best threshold	>447	..	90% (84–96)	88% (80–95)	..	84% (76–91)	87% (78–94)
High specificity threshold	>461	..	95% (88–99)	83% (73–92)	..	91% (84–97)	71% (59–83)
100% specificity threshold	>567	..	100% (74–100*)	19% (10–31)	..	100% (61–100*)	9% (3–16)
High sensitivity threshold	≥429	..	72% (62–82)	95% (88–100)	..	74% (65–83)	90% (83–97)
100% sensitivity threshold	≥413	..	50% (40–61)	100% (91–100*)	..	46% (36–56)	94% (88–99)
Clinical MRI score	..	94% (90–99)	..	..	93% (89–97)	..	..
Overall best threshold	>440	..	89% (82–95)	92% (83–98)	..	76% (67–84)	91% (84–97)
High specificity threshold	>465	..	95% (89–99)	83% (73–92)	..	90% (83–96)	77% (67–86)
100% specificity threshold	>577	..	100% (76–100*)	20% (10–31)	..	100% (61–100*)	9% (3–16)
High sensitivity threshold	≥429	..	76% (66–84)	95% (88–100)	..	65% (56–74)	93% (86–99)
100% sensitivity threshold	≥364	..	16% (9–24)	100% (77–100*)	..	3% (1–8)	100% (44–100*)

Data are ROC–AUC (95% CI) or % (95% CI), unless otherwise stated. High specificity or sensitivity thresholds are defined as a specificity or sensitivity of ≥95% in the development cohort for arginine vasopressin deficiency. ROC–AUC=receiver operating characteristic area under the curve. *The default pROC function in R applies bootstrapping for 100% sensitivity or specificity, resampling only within the affected group, therefore, in these cases, Wilson's CI for a single proportion were implemented with the PropCIs package for the given cutoff.

Table 2: **Diagnostic performance of basal laboratory parameters and different scores in the diagnosis of arginine vasopressin deficiency**

deficiency. First, we show that a basal plasma sodium concentration of less than 135 mmol/L or plasma copeptin concentration of more than 5·6 pmol/L identifies patients with primary polydipsia and can rule out arginine vasopressin deficiency at the initial evaluation, whereas plasma sodium concentration of more than 145 mmol/L is a reliable criterion for confirming arginine vasopressin deficiency. Second, we developed and validated a score incorporating basal laboratory parameters, symptoms, and medical history, showing high accuracy in identifying arginine vasopressin deficiency without the need for further dynamic testing.

Arginine vasopressin deficiency is a rare condition affecting approximately 1 in 25 000 people and poses diagnostic challenges, particularly in non-specialised settings where clinicians might have insufficient disease-specific experience.[21] This challenge highlights

the importance of clear, accessible diagnostic algorithms to guide the initial assessment of suspected cases, as patients often have lengthy referral processes before reaching a specialised centre for a definitive diagnosis. Studies reveal substantial delays in the initial diagnostic investigation, with the average time from symptom onset to diagnosis ranging from 6 months to 12 months, particularly if patients do not have a history of pituitary surgery.[18,22] During this period, patients often undergo several tests for other conditions or multiple rounds of dynamic testing before the correct diagnosis is made.[18] As a result, treatment initiation can be delayed, leaving patients symptomatic and susceptible to complications such as dehydration. Basal plasma sodium concentration, copeptin, or both, as well as our score, which is derived from simple baseline measurements and patient history, provide an efficient and practical screening tool to prioritise suspected cases before more complex testing. This prioritisation is of particular importance, as timely desmopressin treatment can relieve nearly all symptoms and substantially enhance wellbeing.[23]

In clinical practice, physicians should begin with routine basal laboratory tests, including plasma sodium, osmolality, and copeptin, ideally obtained after a 2 h fasting period during the initial consultation. Measuring plasma copeptin in a non-stressed state, avoiding exercise within the past 12 h and illness within the past 2 days, is crucial. Additionally, impaired kidney function can influence plasma copeptin and sodium concentrations, making assessment of glomerular filtration rate important for accurate interpretation. Since inflammation (eg, interleukin-6) can stimulate arginine vasopressin release, measuring C-reactive protein as a marker of inflammation should also be considered.[24] Plasma sodium concentration of less than 135 mmol/L or copeptin concentrations of more than 5·6 pmol/L can exclude arginine vasopressin deficiency, suggesting primary polydipsia and enabling interventions such as controlled fluid intake reduction. Conversely, plasma sodium concentrations of more than 145 mmol/L strongly indicate arginine vasopressin deficiency, allowing desmopressin initiation after the first consultation, alongside imaging and further diagnostics to identify the underlying cause.

For intermediate cases, the point-based clinical score offers additional guidance. A high-sensitivity threshold of lower than 415 points minimises unnecessary testing in patients at low risk, confidently excluding arginine vasopressin deficiency, whereas a high-specificity threshold of higher than 461 points identifies patients with a high likelihood of arginine vasopressin deficiency (appendix 2 p 2). Only in unclear cases should more invasive stimulation tests be considered. Importantly, copeptin measurement is not universally available in all clinical settings, which could limit its applicability in routine practice. Although basal copeptin alone, or when integrated into the laboratory score, improved diagnostic accuracy, the clinical score was only slightly less precise

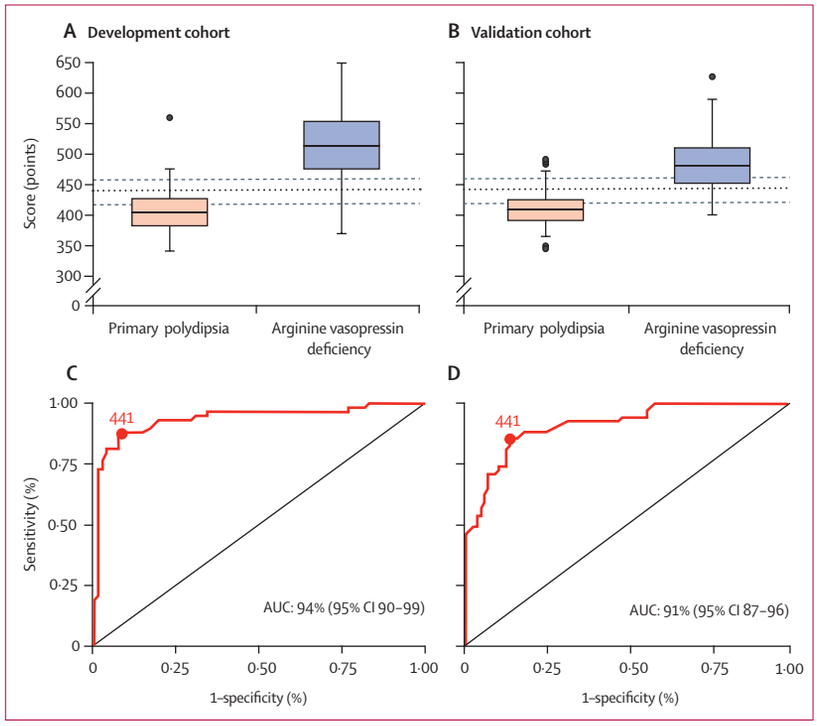

Figure 4: **Clinical score**
Clinical score in the (A) development cohort and the (B) validation cohort. Data are expressed as box plots for patients with arginine vasopressin deficiency (in blue) and primary polydipsia (in red). The horizontal line shows the median, boxes are IQR, and whiskers are the most extreme values lying within the box edge and 1·5× IQR. The dashed lines represent the high-specificity (ie, 95% specificity) and high-sensitivity (ie, 95% sensitivity) cutoff derived from the development cohort for diagnosing arginine vasopressin deficiency. The dotted line represents the overall best cutoff derived from the development cohort. The receiver-operating characteristics curve is shown with the AUC in the (C) development cohort and the (D) validation cohort. AUC=area under the curve.

even without incorporating copeptin. However, these results have to be interpreted with care, since the cohorts used were limited to patients with arginine vasopressin deficiency and primary polydipsia, as patients with arginine vasopressin resistance were excluded by measuring basal copeptin concentrations. Overall, this diagnostic score can potentially shorten the diagnostic timeline, reduce unnecessary referrals, and alleviate the burden on health-care systems.

Traditional diagnostic tests for arginine vasopressin deficiency (eg, the water deprivation test) and new copeptin-based approaches (eg, the hypertonic saline test or arginine stimulation test) require specialised expertise and are often unavailable in small health-care settings. Notably, the water deprivation test and arginine stimulation test have only around 75% diagnostic accuracy, and dynamic tests generally pose a substantial burden on patients.[9,14,25] In a 2022 survey of 1035 patients, 60% underwent initial dynamic testing, with more than 90% subjected to the water deprivation test.[18] This test was rated as highly burdensome, with an average burden score of 8 out of 10 on a visual analogue scale, mostly due to prolonged thirst and extended test duration. Although new copeptin-based tests were rated less burdensome in

clinical trials, they are associated with test-specific discomfort and side-effects (eg, nausea, mild headache, and malaise), frequent blood sampling, and logistical issues (eg, need for constant supervision).[12,14] Importantly, our clinical score, with a cutoff of 441 points, has a diagnostic accuracy close to the hypertonic saline test, outperforming both the water deprivation test and the arginine stimulation test, allowing accurate assessment in approximately 70% of cases at initial evaluation and potentially reducing the need for dynamic tests in many patients.

In the future, incorporating machine learning-based analysis could further enhance precision in diagnosing arginine vasopressin deficiency. In previous work, we identified five crucial parameters—urine osmolality, plasma sodium, glucose concentrations, and clinical history (trans-sphenoidal surgery and pituitary deficiencies)—that had a high diagnostic performance with an AUC of 0·87.[20] MRI is an additional key diagnostic tool in evaluating suspected cases. Among the findings, pituitary stalk enlargement has been identified as the most significant, but not specific, covariate for arginine vasopressin deficiency.[9,12,26–29] When these MRI data were incorporated into the algorithm, the AUC increased to 0·93. Interestingly, adding MRI findings to our score did not improve diagnostic accuracy, which is noteworthy given the high cost and limited availability of MRI. One possible explanation is that the previously considered specific posterior pituitary bright spot might not be truly specific, as it has also been observed in patients with primary polydipsia and arginine vasopressin resistance.[26,30–32] Thus, use of our algorithm as a prescreening tool could assist in identifying patients who might benefit most from undergoing MRI. Although machine learning holds promise for improving accuracy, it is underused due to the unfamiliarity and mistrust of its so-called black box nature among clinicians. By contrast, our score provides an immediate, practical, and transparent tool for clinical practice.

One of the strengths of this study is its large, well characterised cohort of nearly 300 patients combined and its international multicentre design, which enhances the generalisability of our findings. Importantly, although the validation cohort included more severe cases of primary polydipsia than the development cohort—making differentiation from arginine vasopressin deficiency particularly challenging—the scores showed robust performance. However, we acknowledge that the absence of standardised urine samples in the validation cohort is a limitation; these data could have further strengthened the performance of the score. Additionally, a key limitation of our study is the potential for model mis-specification bias, as the scores were derived from variables based on previous machine learning analysis and expert weighting. Furthermore, there is an absence of an established diagnostic gold standard for arginine vasopressin deficiency. Although diagnoses were based on a comprehensive review of patient data, they partly also incorporated the hypertonic saline stimulation test. To mitigate incorporation bias, both trials integrated the treatment response at 3 months into the final diagnosis. A potential limitation of our study is that under-represented causes, particularly genetic forms of arginine vasopressin deficiency or transient post-surgical arginine vasopressin deficiency, might not fully benefit from this algorithm and this score was not developed for other conditions with polyuria. All copeptin cutoffs, including those from this analysis, apply specifically to the BRAHMS Copeptin proAVP assay and are not transferable to other assays. Finally, we emphasise the need for further real-world validation of the score across diverse patient subpopulations and clinical settings.

In conclusion, our study introduces a stepwise diagnostic approach for arginine vasopressin deficiency that can be applied in both specialist and non-specialist settings. Physicians can start with routine basal laboratory tests—plasma sodium, osmolality, and copeptin—and rule-in and rule-out criteria to guide immediate treatment initiation. For intermediate cases, the clinical score provides further guidance, identifying arginine vasopressin deficiency or primary polydipsia with high likelihood, ensuring that only unclear cases proceed to invasive testing.

Contributors

CA contributed to data collection, covered the statistical aspects and data analysis and interpretation, did the literature search, and wrote the manuscript. MC-C and JR wrote the protocols, contributed to data analysis and interpretation, edited the manuscript, and supervised the conduct of the study. DRV supported and supervised all statistical aspects and revised the manuscript. UN provided statistical advice, data interpretation, and revised the manuscript. All other authors contributed to data collection, data analysis and interpretation, and revised the manuscript. CA, BW, JR, and MCC verified the data. All authors had access to all raw data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

We can share deidentified, individual participant data that underlie the results reported in this Article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of our main manuscript on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The steering committee of this study will discuss all requests and decide, based on the scientific rigor of the proposal, whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

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