



# Derivation and Validation of a Novel Risk Score to Predict Overcorrection of Severe Hyponatremia

## The Severe Hyponatremia Overcorrection Risk (SHOR) Score

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### Abstract

**Background and objectives** Osmotic demyelination syndrome is the most concerning complication of severe hyponatremia, occurring with an overly rapid rate of serum sodium correction. There are limited clinical tools to aid in identifying individuals at high risk of overcorrection with severe hyponatremia.

**Design, setting, participants, & measurements** We identified all patients who presented to a tertiary-care hospital emergency department in Ottawa, Canada (catchment area 1.2 million) between January 1, 2003 and December 31, 2015, with serum sodium (corrected for glucose levels) <116 mmol/L. Overcorrection was determined using 14 published criteria. Latent class analysis measured the independent association of baseline factors with a consensus overcorrection status on the basis of the 14 criteria, and was summarized as a risk score, which was validated in two cohorts.

**Results** A total of 623 patients presented with severe hyponatremia (mean initial value 112 mmol/L; SD 3.2). The prevalence of no, unlikely, possible, and definite overcorrection was 72%, 4%, 10%, and 14%, respectively. Overcorrection was independently associated with decreased level of consciousness (2 points), vomiting (2 points), severe hypokalemia (1 point), hypotonic urine (4 points), volume overload (−5 points), chest tumor (−5 points), patient age (−1 point per decade, over 50 years), and initial sodium level (<110 mmol/L: 4 points; 110–111 mmol/L: 2 points; 112–113 mmol/L: 1 point). These points were summed to create the Severe Hyponatremic Overcorrection Risk (SHOR) score, which was significantly associated with overcorrection status (Spearman correlation 0.45; 95% confidence interval, 0.36 to 0.49) and was discriminating (average dichotomized *c*-statistic 0.77; 95% confidence interval, 0.73 to 0.81). The internal (*n*=119) and external (*n*=95) validation cohorts had significantly greater use of desmopressin, which was significantly associated with the SHOR score. The SHOR score was significantly associated with overcorrection status in the internal (*P*<0.001) but not external (*P*=0.39) validation cohort.

**Conclusions** In patients presenting with severe hyponatremia, overcorrection was common and predictable using baseline information. Further external validation of the SHOR is required before generalized use.

*CJASN* 14: 975–982, 2019. doi: <https://doi.org/10.2215/CJN.12251018>

### Introduction

Hyponatremia is the most common electrolyte disorder in hospitalized patients with a prevalence of approximately 20% (1). Its rapid correction may result in osmotic demyelination syndrome (ODS). Unfortunately, no consensus exists regarding criteria for hyponatremic overcorrection with discordance among practice guidelines regarding the actual definition of overcorrection (2,3). We recently completed a systematic review of the published literature that identified nine methods to calculate sodium correction rates and 14 distinct criteria for overcorrection (4). Such variability in criteria for hyponatremic overcorrection likely reflects a lack of definitive studies correlating sodium correction rates with ODS risk.

However, latent variable models can be used in the absence of accepted definition for hyponatremic overcorrection (5). Such models could identify factors potentially influencing the risk of hyponatremic overcorrection. Knowing these factors could help clinicians stratify hyponatremic patients by their overcorrection risk to help determine the intensity of patient monitoring and treatment. In this study, we used latent class analysis (LCA) to create a risk score for hyponatremic overcorrection.

### Materials and Methods

#### Study Setting

This study took place at a 1000-bed publicly funded teaching hospital. We used our hospital's admission

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registry to identify all patients who presented to its emergency department between January 1, 2003 (the first date that data were complete) and December 31, 2015 (the last date for which long-term follow-up was complete). We identified the initial serum sodium measurement of each person's emergency department encounter and used concurrent serum glucose measures to calculate the corrected serum sodium using a modification of the correction equation from Katz (6):

$$\text{Corrected(Na)} = \text{Na} + 2 \times \frac{\text{Glucose}(\text{mmol}) - 5.5}{5.5}$$

We increased the coefficient in the Katz (6) equation from 1.6 to 2 to ensure that patients included in our study truly had hypotonic hyponatremia. Those without a serum glucose measure (2% of patients) were imputed a normal value for this calculation.

Patients were included in our study if their initial corrected serum sodium was <116 mmol/L and their sodium was repeated at least once in the emergency department and subsequent hospitalization. We chose this threshold of 116 mmol/L because cases of ODS are exceedingly rare in patients with a higher baseline serum sodium (3), and we were primarily interested in risk stratifying patients for whom this outcome was possible. We included only the patient's first encounter with our hospital for severe hyponatremia and excluded patients transferred to our emergency department.

### Covariates

From our hospital's data warehouse, we determined patient age and sex, ambulance status, and baseline laboratory investigations. J.D.W. used standard data abstraction methods (7) to manually abstract from each patient's medical record all other covariates that we hypothesized might influence or indicate the cause or the severity of hyponatremia (Supplemental Table 1) as defined in the literature. Variables were defined and strict inclusion and exclusion criteria were determined *a priori* (Supplemental Table 1). A standardized abstraction form was developed and used for each chart. We also recorded the type and volume of intravenously administered fluids given during the first 24 hours of the encounter.

### Analysis and Model Validation

We recently completed a systematic review of all peer-reviewed studies in which sodium correction rate methods were detailed and rate thresholds defining overcorrection were described (4). We identified a total of 14 distinct criteria for overcorrection (Supplemental Table 2). These criteria were applied to the cohort resulting in, for each patient, up to 14 binomial indicators for hyponatremic overcorrection status.

We used LCA to measure the prevalence of hyponatremic overcorrection and to measure the association of baseline covariates on its risk. LCA can be used when a categorical outcome cannot be measured (*i.e.*, it is "latent") but its status is indicated by two or more observed categorical variables. True hyponatremic overcorrection is a latent variable because it has no accepted definition. The 14 published criteria for overcorrection (Supplemental Table 2)

were used in our LCA model as the observed variables. The outcome for this LCA model can be perceived as "consensus hyponatremic overcorrection status" on the basis of the 14 overcorrection criteria.

PROC LCA (SAS version 9.4) was used for all modeling (8). This procedure estimates parameters by maximum likelihood using the *expectation-maximization* algorithm, which assumes that absent observed variables are missing at random. LCA also assumes local independence (*i.e.*, observed variables are independent of each other conditional upon the latent variable class) (5). This would not be the case for criteria having the same hyponatremic correction rate formula but different thresholds defining overcorrection. Of the 14 published criteria in Supplemental Table 2, these include criteria B (with two overcorrection thresholds), criteria E (two overcorrection thresholds), criteria G (three overcorrection thresholds), and criteria I (two overcorrection thresholds). To maintain local independence with these criteria, we created 1000 bootstrap datasets that varied only by a randomly selected subtype for criteria B, E, G, and I. Values for all other criteria and covariates remained the same. All analyses were conducted on these 1000 bootstrap datasets with mean results and 95% confidence intervals (95% CI; using the percentile method [9]) calculated and presented.

LCA modeling started by determining the ideal number of latent classes by fitting models (without covariates) having between one and six classes and then identifying the simplest model having the lowest mean Akaike or Bayesian information criterion values (10). We then used a variable selection strategy that was influenced by three factors: we had many potential covariates; there is a lack of consensus in the literature regarding factors influencing the likelihood of overcorrection; and we wanted to create a parsimonious and accurate method to predict overcorrection risk. Therefore, in our multinomial logistic regression model, we used forward variable selection starting with factors having the strongest univariate association with overcorrection. Variables were kept in the multivariable model if the 95% CI for its parameter estimate (determined using the mean value of 1000 bootstrap samples) excluded 0. This model was summarized as a point system using methods from Sullivan *et al.* (11). This point system was clustered into five similarly sized groups. The association between the point system and overcorrection status was measured with the Spearman rank correlation coefficient; discrimination was measured using the average dichotomized *c*-statistic (12). All percentages (except those <1%) are rounded to the nearest whole number.

We validated the final prediction model in two sites, including (1) the derivation site ("internal validation") and (2) the University Health Network, a teaching hospital located at two sites in Toronto, Canada ("external validation"). The former included all patients presenting to the emergency room between January 1, 2016 and December 31, 2018 with a corrected serum sodium level <116 mmol/L. The latter was on the basis of a previous study (13) and included consecutive patients admitted from the emergency room with an initial uncorrected serum sodium <116 mmol/L between April 1, 2004 and March 30, 2014, excluding patients treated immediately with desmopressin to prevent hyponatremic overcorrection (*n*=13), with subsequent

encounters after already being included in the study ( $n=16$ ), with severe hyperglycemia ( $n=9$ ), with non-numeric sodium values (*i.e.*,  $<100$  mmol/L) ( $n=4$ ), transferred from another service ( $n=4$ ), with diabetes insipidus ( $n=1$ ), and with only one serum sodium measured ( $n=1$ ). At each site, J.D.W. reviewed the hospital's data repository (blinded to patient sodium levels or their overcorrection status) to retrieve data required to calculate the Severe Hyponatremic Overcorrection Risk (SHOR) score and record administration of desmopressin during the early hospitalization. All serum sodium measures were used to determine overcorrection status as per each criterion, which were used to classify each patient's overcorrection status using criteria response patterns of the original LCA model. Desmopressin administration and the consensus overcorrection status was compared with the final prediction model.

## Results

We identified 623 patients who were seen in the emergency department between March 1, 2003 and December 12, 2015 with an initial corrected serum sodium value  $<116$  mmol/L and at least one repeat sodium measurement (Table 1). All patients except eight (1%) were admitted to hospital (presenting corrected sodium 110.8–115.8 mmol/L; one death).

The 14 hyponatremic overcorrection criteria identified in our systematic review (Supplemental Table 2) returned notably different results (Table 2). By these criteria, a median of 25% patients (interquartile range, 19%–45%) were classified as overcorrected, but this varied more than 11-fold, from a low of 8% (criterion D) to a maximum of 90% (criterion A). Agreement between the criteria (measured using the prevalence-adjusted bias-adjusted  $\kappa$ -statistic [14–30]) also varied extensively from 0.13 (for criterion D) to 0.56 (for criteria B5 and I5).

We found that a four-class model fit the data best (Supplemental Table 3). Overall, the latent class model showed excellent homogeneity within, and separation between, the classes (Supplemental Table 4). The prevalence of each criterion increased progressively between the four classes (that we labeled “no overcorrection,” “unlikely overcorrection,” “possible overcorrection,” and “definite overcorrection”). Within the no overcorrection class, the prevalence of each criterion was  $<8\%$  (except for criterion A), whereas the prevalence was  $\geq 90\%$  within the definite overcorrection class for all except criterion D. The no overcorrection and unlikely overcorrection classes were statistically distinct from each other (*i.e.*, their 95% CIs did not overlap) for all except criteria A and I. The possible overcorrection and definite overcorrection classes were statistically distinct from each other for all except criteria C and I. Overlap between unlikely overcorrection and possible overcorrection classes was common. There were 2177 distinct criteria patterns in our cohort, of which 2010 (92%) were classified into a single overcorrection class more than 95% of the time (Supplemental Table 5).

The LCA model found a prevalence for no, unlikely, possible, or definite overcorrection of 72%, 4%, 10%, and 14%, respectively. Eight baseline factors were independently associated with overcorrection (Table 3). Increased

**Table 1. Description of study cohort ( $n=623$ )**

Characteristic	<i>n</i> (%)
<b>Demographics</b>	
Mean age (SD)	68 ± 16
Male	245 (39%)
Arrived by ambulance	389 (62%)
<b>Past Medical History</b>	
Stroke	77 (12%)
Dementia	70 (11%)
Parkinson disease	4 (0.6%)
Alcoholism	120 (19%)
Cancer	114 (18%)
Cirrhosis	52 (8%)
Hemodialysis	3 (0.5%)
Adrenal insufficiency	20 (3%)
<b>Active disease</b>	
Low serum albumin/total protein	40 (6%)
Clinical diagnosis malnutrition	131 (21%)
<b>Drug exposure</b>	
HCTZ	215 (34%)
Furosemide	107 (17%)
Anticonvulsant	55 (9%)
SSRI	85 (14%)
SNRI	32 (5%)
MDMA	1 (0.2%)
<b>History</b>	
Vomiting	227 (36%)
<b>Physical examination</b>	
Mean Systolic BP (SD)	137 ± 66
Baseline LOC: normal	230 (37%)
Confused	232 (37%)
Decreased	129 (21%)
Comatose	9 (1.4%)
Not documented	23 (4%)
Baseline volume status: normal	131 (21%)
Hypovolemic	455 (73%)
Overloaded	37 (6%)
<b>Baseline investigations</b>	
Mean (SD) corrected sodium (mmol/L)	112 ± 3
Serum K+ $<3$ mmol/L	144 (23%)
Urine osmolality	
$<150$ mosm/kg	62 (10%)
150–300 mosm/kg	173 (28%)
$>300$ mosm/kg	261 (42%)
Not measured	127 (20%)
Median eGFR (IQR)	77 (50–114)
eGFR $<30$ ml/min per 1.73 m <sup>2</sup>	79 (13%)
CNS bleed	3 (0.5%)
Significant chest tumor	63 (10%)
Significant chest infection	114 (18%)
<b>Outcomes</b>	
Median length of stay (IQR)	6 (3–13)
Disposition: community	454 (73%)
Rehabilitation	17 (3%)
Assisted living	101 (16%)
Dead	51 (8%)

HCTZ, hydrochlorothiazide; SSRI, sustained serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; MDMA, 3,4-methylenedioxy-methamphetamine; LOC, level of consciousness; K+, potassium; IQR, interquartile range; CNS, central nervous system.

patient age, volume overload, and significant chest tumor were each associated with a decreased risk of overcorrection. Vomiting, decreased level of consciousness or coma, hypokalemia, and a low urine osmolality were independently associated with an increased risk of overcorrection. Overcorrection risk was also greater as the baseline sodium

Table 2. Prevalence of hyponatremic overcorrection by 14 different published criteria

Criterion	Overcorrection Threshold	Patients without Missing Values	Patients Meeting Criteria for Overcorrection	% Patients with Hyponatremic Overcorrection (95% CI)	Mean (Range) Agreement with Other Criteria
A	0.5 mmol/L per hour	623	561	90 (87 to 92)	-0.25 (-0.74 to 0.22)
B3	8 mmol/L per day	623	310	50 (46 to 54)	0.44 (-0.04 to 0.87)
B5	12 mmol/L per day	623	152	24 (21 to 28)	0.56 (-0.31 to 0.92)
C	18 mmol/L per 2 days	623	102	16 (13 to 19)	0.49 (-0.47 to 0.94)
D	8 mmol/L per day	520	44	8 (6 to 11)	0.13 (-0.74 to 0.39)
E3	8 mmol/L per day	622	292	47 (43 to 51)	0.44 (-0.02 to 0.79)
E4	10 mmol/L per day	622	193	31 (27 to 35)	0.54 (-0.18 to 0.80)
E5	12 mmol/L per day	622	125	20 (17 to 23)	0.53 (-0.40 to 0.86)
F	18 mmol/L per 2 days	623	109	18 (14 to 20)	0.50 (-0.45 to 0.86)
G3	8 mmol/L per day	613	326	53 (49 to 57)	0.39 (-0.12 to 0.87)
G4	10 mmol/L per day	613	245	40 (36 to 44)	0.51 (-0.02 to 0.75)
H	18 mmol/L per 2 days	552	110	20 (17 to 23)	0.37 (-0.47 to 0.74)
I5	12 mmol/L per day	623	159	26 (22 to 29)	0.56 (-0.29 to 0.92)
I6	18 mmol/L per day	623	111	18 (15 to 21)	0.51 (-0.44 to 0.94)

Details regarding the criteria and overcorrection thresholds are described in Supplemental Table 2. Agreement with other criteria was measured using prevalence-adjusted and bias-adjusted  $\kappa$ -statistic (14). 95% CI, 95% confidence interval.

level decreased. For all variables except hypokalemia, association measures were most extreme for the definite overcorrection group; considerable overlap existed for association measures between unlikely and possible overcorrection groups.

The final model was summarized as the SHOR score (Table 3). Chest tumor was most protective (-5 points); baseline corrected sodium <110 mmol/L and urine osmolality <150 mosm/kg were associated with the greatest risk of overcorrection (+4 points). Observed SHOR scores ranged from -10 to 11 (mean -0.06, SD 3.7). There was only a slight decrease in fit from the full model containing all covariates (log-likelihood -1507.0) with that containing SHOR only (log-likelihood -1515.2) despite 21 fewer degrees of freedom (df) in the latter model.

The SHOR score significantly predicted overcorrection risk (Table 4). As the SHOR score increased, the probability of no overcorrection decreased (< -3 points: 96%; 5+ points: 27%) and the probability of definite overcorrection increased (< -3 points: 0%; 5+ points: 55%) (chi-squared value 156.8;  $P$ <0.001; Spearman correlation 0.45; 95% CI, 0.36 to 0.49). The SHOR score was significantly discriminative (average dichotomized  $c$ -statistic 0.77; 95% CI, 0.73 to 0.81).

SHOR scores were also significantly associated with both the volume of intravenously administered fluid and the amount of sodium ( $P$ <0.001, Wilcoxon test, for both). Only nine patients (1.4%) were given desmopressin but the likelihood of administration increased significantly with the SHOR score ( $P$ =0.002). Two patients were diagnosed with ODS. Both were males with alcoholism with decreased level of consciousness and initial corrected sodium levels <104 mmol/L. ODS was diagnosed approximately 2 weeks after presentation with confusion, tremor, and (in one patient) bilateral spasticity. The mean sodium correction rate (calculated using the methods presented in Supplemental Table 2) was 24.1 and 16.4 mmol/d. SHOR scores were very high in both patients (6 and 8 points).

**Validation.** The internal and external validation group originally included 149 and 301 patients, respectively. Eight (5%) and 100 patients (32%), respectively, were excluded because they had an overcorrection criteria pattern not seen in the derivation group (and therefore could be by the LCA model into an overcorrection category; Supplemental Table 5). A total of 59 patients (20%) were excluded from the external validation because their corrected sodium exceeded 116 mmol/L. This left the internal and external validation cohorts with 141 and 142 patients, respectively (Supplemental Table 6). Overall, they were similar to the derivation cohort (Table 1) except that the external validation group was slightly older (Supplemental Table 6). Desmopressin was significantly more likely to be given in both the internal (16%) and the external validation groups (33%; chi-squared value 158;  $df$ =2,  $P$ <0.001), with the SHOR score significantly associated with desmopressin use in both the internal (Spearman correlation coefficient 0.18;  $P$ =0.03) and external groups (chi-squared value 40.3;  $df$ =4;  $P$ <0.001). In external validation patients who received no desmopressin (Table 5), hyponatremic overcorrection was significantly less likely than in the derivation group (probability of possible or definite overcorrection: derivation 24%, internal validation 25%, external validation 14%; chi-squared value 46.3;  $df$ =6;  $P$ <0.001). In the internal validation, the SHOR score (Table 3)

**Table 3. Baseline factors associated with hyponatremic overcorrection and the Severe Hyponatremic Overcorrection Risk score**

Factor	Parameter Estimate (SEM)			Adjusted Odds Ratio (95% CI)			Points
	Unlikely	Possible	Definite	Unlikely	Possible	Definite	
Intercept	5.09 (1.31)	7.14 (0.189)	19.37 (1.278)	N/A	N/A	N/A	N/A
<b>Patient age, yr</b>	−0.1 (0.024)	−0.1 (0.004)	−0.39 (0.028)	0.9 (0.86 to 0.95)	0.9 (0.89 to 0.91)	0.68 (0.64 to 0.72)	N/A
40–50							0
50–60							−1
60–70							−2
70–80							−3
80–90							−4
Vomiting	0.07 (0.075)	0.37 (0.011)	0.63 (0.091)	1.07 (0.92 to 1.24)	1.45 (1.41 to 1.47)	1.88 (1.57 to 2.25)	2
Somnolent	0.12 (0.086)	0.13 (−0.002)	0.68 (0.092)	1.13 (0.96 to 1.34)	1.14 (1.14 to 1.14)	1.97 (1.66 to 2.37)	2
Volume overloaded	−1.05 (0.202)	−1.23 (0.022)	−1.8 (0.409)	0.35 (0.24 to 0.52)	0.29 (0.28 to 0.31)	0.17 (0.07 to 0.37)	−5
<b>Corrected sodium, mmol/L</b>	−0.05 (0.012)	−0.07 (0.002)	−0.17 (0.011)	0.95 (0.93 to 0.98)	0.93 (0.93 to 0.93)	0.84 (0.83 to 0.87)	N/A
<110							4
110 to <112							2
112 to <114							1
114–116							0
K+ <3.0 mmol	0.72 (0.08)	0.77 (0.009)	0.49 (0.106)	2.05 (1.76 to 2.41)	2.16 (2.12 to 2.2)	1.63 (1.32 to 2)	1
Uosm <150 mosm/kg	0.76 (0.119)	0.42 (0.081)	1.39 (0.108)	2.14 (1.7 to 2.71)	1.52 (1.29 to 1.78)	4.01 (3.27 to 4.98)	4
Chest tumor	−0.8 (0.131)	−0.81 (0.029)	−1.85 (0.29)	0.45 (0.35 to 0.58)	0.44 (0.42 to 0.47)	0.16 (0.09 to 0.28)	−5

Parameter estimates and adjusted odds ratios are compared with the no overcorrection group. Presented values are the mean of 1000 bootstrap samples. 95% CI, 95% confidence interval; N/A, not applicable; K+, potassium; Uosm, urinary osmolarity.

**Table 4. Hyponatremic overcorrection status and treatment during the first 24 hours by SHOR score**

SHOR Score	No. of Patients (N=623)	Hyponatremic Overcorrection <sup>a</sup>				IV Fluids (L)		IV Sodium (mEq)		Desmopressin Given, n (%)
		No, n=449 (72%)	Unlikely, n=25 (4%)	Possible, n=64 (10%)	Definite, n=85 (14%)	Mean (95% CI)	Median (IQR)	Mean (95% CI)	Median (IQR)	
<-3	98	94 (96%)	3 (3%)	1 (1%)	0 (0%)	0.6 (0.5 to 0.8)	0.3 (0-1.0)	95.4 (71.3 to 119.5)	47.3 (0-154.0)	0 (0%)
-3 to -1	167	141 (84%)	5 (3%)	12 (7%)	9 (5%)	1.1 (1.0 to 1.3)	1.0 (0.3-1.6)	176.3 (151.8 to 200.7)	154 (45.7-261.8)	0 (0%)
0-2	191	138 (72%)	10 (5%)	25 (13%)	18 (9%)	1.3 (1.2 to 1.5)	1.2 (0.5-2.0)	206.3 (180.9 to 231.6)	188.6 (74.4-308)	2 (1%)
3-4	107	60 (56%)	4 (4%)	18 (17%)	25 (29%)	1.5 (1.2 to 1.7)	1.2 (0.6-2.1)	219.0 (185.2 to 252.8)	175.2 (100.1-326)	6 (6%)
5+	60	16 (27%)	3 (5%)	8 (13%)	33 (55%)	1.8 (1.4 to 2.1)	1.6 (0.9-2.8)	262.7 (216.5 to 309.0)	232.7 (128.5-398.8)	1 (2%)

The total volume of fluids and amount of sodium given intravenously during the first 24 hours after the baseline sodium measurement was determined. The SHOR score was strongly associated with hyponatremic overcorrection class (chi-squared value 156.8;  $P < 0.001$ ; Spearman correlation 0.45; 95% CI, 0.36 to 0.49). SHOR, Severe Hyponatremia Overcorrection Risk; 95% CI, IV, intravenous; 95% confidence interval; IQR, interquartile range.

<sup>a</sup>These values are on the basis of the hyponatremic overcorrection category having the highest probability (Supplemental Table 5) for each patient and is the average of 1000 bootstrap samples to account for correlated hyponatremic overcorrection criteria (Supplemental Table 2).

was significantly associated with overcorrection status (Spearman correlation coefficient 0.44;  $P$  value  $< 0.001$ ). In the external validation, this association was smaller (Spearman correlation coefficient 0.09) and did not meet standard criteria for statistical significance ( $P = 0.39$ ).

## Discussion

Overcorrection is the most controllable risk factor for ODS but has no accepted criteria nor reliable knowledge regarding how its risk is influenced by baseline patient factors. This study used LCA to incorporate all published criteria for overcorrection and measure its association with baseline covariates. This model was summarized into the SHOR score which effectively stratified our cohort by overcorrection risk. Intravenous administration of both fluids and sodium during the first 24 hours increased significantly as SHOR score increased. The SHOR score was significantly associated overcorrection risk in an internal but not external validation cohort.

George *et al.* measured the association of baseline factors with hyponatremic overcorrection in a large ( $n = 1490$ ) multicenter study of patients with hyponatremia (31). Using criterion G3 to define overcorrection (Supplemental Table 2), they found that patient age, initial sodium, and hypokalemia were all independently associated with overcorrection risk. Results changed notably when overcorrection was defined differently (using criteria E3, G4, and H; Supplemental Table 2), highlighting that measures of association between hyponatremic overcorrection and covariates can vary with the criteria used to define this outcome. In the absence of empirical data exist to determine which overcorrection criteria best predict ODS risk, we believe that incorporating all published criteria using LCA to produce a "consensus" definition of overcorrection is the least-biased method for identifying overcorrection risk factors.

Our study identifies several important points. First, we found that the risk of hyponatremic overcorrection is heavily influenced by nonmodifiable patient factors that can be measured when severe hyponatremia is identified (Table 3). On the basis of the status of these factors, a patient's expected risk of overcorrection could vary from as low 0% (for SHOR scores  $< -3$ ) to as high as 55% (for SHOR scores of  $\geq 5$ ; Table 4). This information should be kept in mind when physician treatment is reviewed for cases in which overcorrection is identified. Second, knowing an individual patient's overcorrection risk might influence the intensity of patient monitoring and their treatment. For example, desmopressin is increasingly being considered as an agent to decrease the risk of hyponatremic overcorrection. Risk stratification using the SHOR score could identify patients at a high risk of hyponatremic overcorrection and most likely to benefit from this therapy.

Several issues should be considered when reviewing our data. First, our study was tested in only two populations distinct from the derivation cohort. In the external population, our model was significantly associated with desmopressin administration but not with overcorrection status (possibly because of the former). Therefore, it is essential that our model be evaluated in other cohorts before physicians can confidently use it. Second, although physicians make great efforts to prevent hyponatremic

**Table 5. Performance of the SHOR index in validation groups**

SHOR Points	Consensus Overcorrection Status				Total
	No (56%)	Unlikely (18%)	Possible (19%)	Definite (9%)	
<b>Internal validation (n=119)</b>					
< -3	23	1	1	1	26
-3 to -1	17	6	3	2	28
0-2	17	6	6	2	31
3-4	6	5	6	2	19
5+	4	4	3	4	15
	No (77%)	Unlikely (8%)	Possible (5%)	Definite (9%)	
<b>External validation (n=95)</b>					
< -3	20	3	1	1	25
-3 to -1	20	2	2	3	27
0-2	24	3	0	3	30
3-4	4	2	0	0	6
5+	4	0	1	2	7

The validation patients only included patients with severe hyponatremic who did not receive desmopressin treatment. The association between the SHOR score and consensus overcorrection group was significant in the internal validation (Spearman correlation coefficient 0.41;  $P < 0.001$ ) but not the external validation (Spearman correlation coefficient 0.09;  $P = 0.39$ ). SHOR, Severe Hyponatremia Overcorrection Risk.

overcorrection, the true outcome of interest is osmotic demyelination which occurs in only a small fraction of patients who are overcorrected. Models to predict ODS risk would be much more clinically relevant. Until that model, however, we believe that the SHOR score could be helpful to clinicians (for risk stratification) and researchers (for risk adjustment when hyponatremic overcorrection is used as an outcome). Third, although we identify patient factors that predict hyponatremic overcorrection, we do not provide a mechanism explaining these associations. Some model components increasing the risk of overcorrection (e.g., vomiting) might transiently stimulate antidiuretic hormone secretion, removal of which causes a free water diuresis and rapid sodium correction. Conversely, protective factors might stem from poorly suppressed antidiuretic hormone secretion (e.g., edematous states, chest tumor, advanced age [32]). Fourth, several factors potentially influencing the likelihood of overcorrection (preadmission desmopressin use, low urine sodium or chloride without edema, high urine sodium without diuretics, serum bicarbonate concentration, hyperkalemia, high BUN-to-creatinine ratio without edema, high serum uric acid without edema, low serum uric acid) are missing from our model and could be considered in future studies. Fifth, our systematic review (4) might have missed some published criteria for overcorrection, but it is unlikely that such omissions would materially change our results. Sixth, some of the model's associations could be due to treatment. For example, associations between overcorrection risk with lower initial sodium levels or decreased level of consciousness could stem from treatment with hypertonic saline in clinically severe patients. More detailed analysis is required to determine how such treatment relates to overcorrection. Finally, although the SHOR model was significantly associated with overcorrection risk in the internal validation cohort (Spearman correlation coefficient 0.44;  $P < 0.001$ ), it was not in the external validation cohort (0.09;  $P = 0.39$ ). The latter could be owing to a small number of patients having higher SHOR scores or a large fraction of patients (37%) whose overcorrection criteria

pattern was distinct from the derivation patients (Supplemental Table 5) and therefore could not be classified into an overcorrection status. It could also be owing to a significantly more extensive use of desmopressin which itself was strongly associated with the SHOR score. If clinicians were able to identify patients having a greater likelihood of overcorrection and give them desmopressin administration, this could obscure associations between SHOR scores and overcorrection risk.

Although further validation of our model is necessary, clinicians should be aware hyponatremic overcorrection risk might be predicted by baseline patient characteristics.

#### Disclosures

Dr. Cavalcanti, Dr. MacMillan, Dr. Sood, Dr. van Walraven, and Dr. Woodfine have nothing to disclose.

#### Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12251018/-/DCSupplemental>.

Supplemental Table 1. Variables abstracted from the patient record.

Supplemental Table 2. Published formulae for sodium correction rates and criteria for hyponatremic overcorrection.

Supplemental Table 3. Summary of LCA model fit with varying number of model classes.

Supplemental Table 4. Prevalence of indicator criteria within each overcorrection group.

Supplemental Table 5. Criteria response patterns and their overcorrection classification status in bootstrap analysis.

Supplemental Table 6. Model validation populations.

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**Received:** October 16, 2018 **Accepted:** April 30, 2019

Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).