A Clinical Decision Rule to Aid Ordering of Serum and Urine Protein Electrophoresis for Case-Finding of Paraproteins in Hospitalized Inpatients

Ammarin Thakkestian, PhD^{1,2}, Huy Tran, MB BS, FRACP³, Glenn Reeves, MB BS, FRACP³, Stuart Murch, B Med⁴, and John Attia, PhD, FRCPC, FRACP^{2,4}

¹Clinical Epidemiology Unit, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; ²Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, Newcastle, New South Wales, Australia; ³HRMC, Locked Bag 1, Hunter Area Pathology Service, Newcastle, New South Wales, Australia; ⁴Division of Medicine, HRMC, Locked Bag 1, John Hunter Hospital, Newcastle, New South Wales, Australia.

OBJECTIVE: To develop a simple clinical decision rule that could increase the yield of serum and urine protein electrophoresis (SPE/UPE) without loss of sensitivity.

DESIGN: A cross-sectional study of inpatients with a SPE/UPE performed over a 5-year period (2001–2006) with complete data on electrolytes, globulins, full blood count, creatinine, age, and gender.

SETTING: A tertiary-care general teaching hospital serving the Hunter Valley in New South Wales, with a referral population of over 1 million.

PARTICIPANTS: A total of 14,374 adult patients admitted between January 2001–November 2006.

MAIN OUTCOME MEASURES: Paraprotein on serum and/or urine protein electrophoresis (SPE/UPE).

RESULTS: Five points were assigned for globulin >41 g/l, 3 points for age ≥60, 2 points for each of hemoglobin <121 and male gender, and 1 point for estimated glomerular filtration rate (eGFR) <60. Total scores of 0–5, 6–10, and ≥11 corresponded to positive likelihood ratios of an abnormal SPE/UPE of 1, 2.5, and 6.6, respectively. The predictive ability of this model was strong, with an area under the curve of ~0.8. Results in the validation set were almost identical.

CONCLUSION: A clinical decision rule using simple clinical variables has the potential to improve the yield of SPE/UPE. This rule however needs to be verified prospectively.

KEY WORDS: clinical decision rule; protein electrophoresis; predictive score; paraprotein.

J Gen Intern Med 23(10):1688–92

DOI: 10.1007/s11606-008-0712-z

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INTRODUCTION

A number of conditions may be linked to paraproteinemia, including multiple myeloma, macroglobulinemia, chronic lymphocytic leukemia, lymphoma, primary amyloidosis, transient inflammation, and plasmacytoma. In current clinical practice, a high total protein or a high globulin level without obvious explanation, e.g., dehydration, may trigger serum and urine protein electrophoresis (SPE/UPE) for case-finding for paraproteins, a subject that has been discussed in the literature¹. Although there are not many data in this regard, what studies do exist indicate a low yield for detecting paraproteinemia. For example, Hughes et al.² found that of 8,339 blood samples over 1 year with globulins greater than 45 g/l, 1,332 had discretionary SPE added, and 72 of these had paraproteins identified, for a yield, although potentially incomplete, of 0.9%. Similarly, in over 10-years, screening of 102,000 subjects in a district hospital with SPE, 730 cases of paraproteinemia were identified, a yield of 0.7%³. Likewise, using raised globulins as a trigger for SPE, McKenna et al.⁴ found 15/2,656 with multiple myeloma, a yield of 0.6%. These data suggest that general screening and even case-finding using discretionary SPE triggered by high globulins or high total protein are very inefficient and costly.

A number of common factors have traditionally been associated with paraproteins, such as hypercalcemia, renal disease, and anemia. Less common findings include a low anion gap⁵; this is because IgG and IgM paraproteins may have isoelectric points higher than the physiological pH, thereby becoming positively charged in serum and behaving as cations. This excess positive charge then needs to be counterbalanced by an increase in anions, mainly chloride, thereby leading to a decrease in the calculated anion gap. Hypercalcemia (by increasing unmeasured cations) and hypoalbuminemia (by decreasing unmeasured anions) may also contribute to the low anion gap in multiple myeloma⁶ and other paraproteinemic conditions. Although these findings have been confirmed multiple times, e.g.^{7,8}, the value of a low anion gap in isolation for case-finding has been debated, partly using a Bayesian framework to argue that pre-test probabilities are so low that a low anion gap is not sufficient to increase the post-test probability to any clinically significant degree⁹, and partly on the argument that a low anion gap is much more likely to be due to lab error, variability, hyponatremia, and hypoalbuminemia¹⁰, although this has been disputed^{11–13}.

We therefore set out to see if globulins, anion gap, and a number of other simple variables, combined in the form of a

Received October 31, 2007

Revised February 8, 2008

Accepted June 16, 2008

Published online July 30, 2008

clinical decision rule, could assist in ordering SPE/UPE more effectively in terms of cost and yield of positives. The focus was not to diagnose a specific paraproteinemic condition, e.g., myeloma, but to increase the yield of abnormal tests and potentially cut down the number of negative tests ordered without compromising sensitivity.

METHODS

We retrieved basic biochemical data on all inpatients admitted to John Hunter Hospital between January 2001 and November 2006 with a serum and/or urine protein electrophoresis; John Hunter is a tertiary-care general teaching hospital serving the Hunter Valley in New South Wales, with a referral population of over 1 million. Data included gender, age, electrolytes (sodium, potassium, chloride, bicarbonate), anion gap, urea, creatinine, estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation¹⁴, ionized calcium, globulins, total protein, albumin, liver function tests (AST, ALT, ALP, GGT), LDH, and full blood count (hemoglobin, white count, lymphocyte count, platelet count). Anion gap was defined as $[\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$; globulins were defined as $[\text{total protein}] - [\text{albumin}]$.

Laboratory Analysis

Serum sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, total protein, albumin, AST, ALT, ALP, GGT, and LDH were assayed using the automated Dade RXL platform (Dade Behring Pty Ltd., Deerfield, IL). The hemoglobin and lymphocyte count were measured using the automated Beckmann Coulter platform (Beckman Coulter, Inc., Fullerton, CA). The ionized calcium was calculated as previously published¹⁵.

Serum and Urine Electrophoresis

Serum electrophoresis was performed using the Capillarys 2 automated capillary electrophoresis system (Sebia, France). In the event of an abnormal band being detected, the capillary immunotyping (immunosubtraction) procedure was used to identify the protein using specific antisera to IgG, IgA, IgM, kappa (free and bound), and lambda (free and bound). Specific IgD antiserum testing was performed before a band was called "light-chain" only. Urine electrophoresis was performed after urine concentration using the SPIFE-3000 system (Helena Laboratories, Beaumont, TX) with proteins being detected by visible staining in agarose gel after automated electrophoretic separation. "Positive SPE/UPE" was based on the presence of a paraprotein.

Analysis

We reviewed all SPE/UPE records on the hospital's pathology database from 2001 to 2006. After excluding those records coming from hematology and oncology departments, where most patients with a diagnosed paraproteinemic condition are followed up, 29,607 SPE/UPE records, representing 14,374 subjects, remained. Of these subjects, 10,875 (75.7%) had SPE/UPE performed only once, and 3,499 (24.3%) had SPE/UPE performed multiple times (range 2–74, median 32); for the latter, only the first record was selected as this was the most relevant to initial screening/case-finding. Between 10–13% of subjects were

missing data for other variables of interest (e.g., serum sodium, potassium, creatinine, etc.), except calcium, for which about 41% of subjects were missing data. Data imputation was applied using regression methods¹⁶ to replace missing values based on available data. This resulted in 14,374 individuals with all variables for analysis.

The outcome of interest was a paraprotein identified either on serum or urine protein electrophoresis, or both. Data were randomly split into two sets with ratio 70:30 using STATA version 9.20, i.e., derivation ($n=10,062$) and validation ($n=4,312$)¹⁷. The seed number was set, and simple random sampling was used to split the data. Mean and standard deviation, and frequencies (%) were used to describe characteristics for continuous and categorical data, respectively. Independent t tests and chi-square tests were applied to compare means and proportions, respectively.

For the derivation analysis, multiple logistic regression analysis was applied to determine predictors of an abnormal SPE/UPE, i.e., presence of a paraprotein. The likelihood ratio test (LR) with backward elimination was used to select variables in the model. Receiver-operating characteristic (ROC) analysis was applied to calibrate cut-off values for variables of interest, to assess model predictability, and to simplify the model. Cut-off values were identified as those that optimized the sum of sensitivity and specificity. To simplify the model, the area under the curve (AUC) of models with/without a particular variable was estimated and compared; if dropping that variable did not significantly reduce the power of the model, that variable was omitted in the final, parsimonious model.

Once the final regression model was obtained, the odds ratios of the final model were rounded off in order to simplify the scores and were used to construct the scoring scheme. Individuals were allocated the scores relevant to each variable and summed to get a total score. Characteristics such as sensitivity, specificity, and positive and negative likelihood ratios (LR+/LR-) were calculated according to each possible total score. The total scores were then trichotomized according to the strength of the LR+¹⁸.

The scoring scheme was then applied to the validation dataset. The AUC and diagnostic test characteristics were estimated and compared with the values in the derivation set. All analyses were performed using STATA version 9.20.

RESULTS

Out of all inpatients admitted between January 2001–November 2006, 14,374 subjects with complete data were available for final analysis. Mean age in this group was 60 years ($SD=19$), and 61% were females. One hundred thirty-seven (1.0%) had a paraprotein on both SPE and UPE, 979 (6.7%) on serum only, and 40 (0.3%) on urine only.

Derivation Phase

Ten-thousand sixty-two subjects were used for derivation of a score model to predict the presence of a paraprotein on SPE/UPE. Among them, 808 subjects (8.0%) had a positive SPE and/or UPE, i.e., a paraprotein was detected.

The variables that were found to be significant predictors for detection of a paraprotein in univariate analysis are listed in Table 1. The cut-offs for each variable were determined using

Table 1. Characteristics of positive and negative serum or urine protein electrophoresis (SPE/UPE) groups

Characteristics	SPE/UPE		P value	OR (95% CI)
	Positive n=834	Negative n=9,228		
Age, years				
≥60	653 (78%)	4,721 (51%)	<0.001	4.1 (3.5–5.0)
Sex				
Male	420 (50%)	3,546 (38%)	<0.001	1.8 (1.5–2.0)
Globulin, g/l				
>41	514 (61%)	1,791 (19%)	<0.001	7.3 (6.2–8.5)
Hemoglobin, g/l				
<120	478 (57%)	2,301 (25%)	<0.001	4.4 (3.7–5.0)
eGFR, ml/min/1.73 m ²				
<60	448 (54%)	2,504 (27%)	<0.001	3.4 (2.9–3.9)
Lymphocyte, × 10 ⁹ /l				
<1.88	420 (50%)	4,345 (47%)	0.56	1.0 (0.9–1.2)
Anion gap, mmol/l				
<11	591 (71%)	5,495 (60%)	<0.001	1.9 (1.6–2.1)
Ca ²⁺ , mmol/l				
<1.21	401 (48%)	5,212 (56%)	<0.001	0.5 (0.4–0.6)

ROC analysis; we found that all variables except lower lymphocyte count (i.e., older age, male gender, higher globulin, lower hemoglobin, lower eGFR, high calcium, and low anion gap) were associated with presence of a paraprotein.

These variables were combined in a full multivariate model and then dropped one by one to test whether their contribution in the model remained significant. Comparison of the AUCs suggested that ionized calcium (AUC=0.814 vs 0.808; $p=0.09$) and anion gap (AUC=0.814 vs 0.814; $p=0.83$) contributed least to the model and could be omitted. The final model therefore contained five variables, and their ORs are listed in Table 2, along with the full multivariate regression equation.

The factor with the most impact was globulin, i.e., those with a globulin level higher than 41 g/l had roughly five-fold higher odds of having a paraprotein than those with lower globulin levels. The other four factors had a lower magnitude of risk (OR=1.3–2.9).

Table 2. Multivariate logistic regression model results for predicting a positive serum or urine protein electrophoresis and associated point scores

Variables	OR (95% CI)	Scores
Globulin, g/l		
>41	4.5 (3.8, 5.4)	5
≤41		0
Age, years		
≥60	2.9 (2.4, 3.7)	3
<60		0
Hemoglobin, g/l		
<121	1.9 (1.5, 2.3)	2
≥121		0
Sex		
Male	1.6 (1.4, 1.9)	2
Female		0
eGFR, ml/min/1.73 m ²		
<60	1.3 (1.1, 1.5)	1
≥60		0
Total scores		0–13

Logistic equation: $\text{Logit}[SPE/UPE^+ / SPE/UPE^-] = -4.4 + 1.5x_{\text{globulin}} + 1.1x_{\text{age}} + 0.6x_{\text{hgb}} + 0.4x_{\text{sex}} + .2x_{\text{gfr}}$

Figure 1. Receiver-operator characteristic (ROC) curve (plotting sensitivity versus 1- specificity) for predicting the presence of a paraprotein according to point scores in the derivation data set. By choosing different thresholds for the point score, one can maximize sensitivity or specificity. Area under the curve=0.8024

A point score for each variable was obtained by rounding off the ORs and assigning 0 to the reference category. Five points were assigned for globulin >41 g/l; 3 points for age ≥60, 2 points for each of hemoglobin <120 g/l and male gender, and 1 point for eGFR <60 ml/min/1.73 m². Total scores ranged from 0–13, and diagnostic probabilities for each score are shown in Figure 1. For ease of use and simplicity, the range of scores was trichotomized; scores of 0–5, 6–10, and ≥11 correspond to low, medium, and high probabilities of finding a paraprotein and to positive likelihood ratios of 1, 2.5, and 6.7, respectively.

Validation Phase

Four thousand three-hundred twelve subjects were used for validation. Scores for each subject were calculated by applying the scoring scheme from Table 2. We found that the diagnostic characteristics of the scoring scheme in the validation set were virtually identical to the derivation set, i.e., the AUCs were 0.806 versus 0.795 ($p=0.44$), and the positive likelihood ratios of having a paraprotein were 1, 2.5, and 6.6 for scores 0–5, 6–10, and ≥11, respectively (see Table 3). The trichotomized scheme retains most of the power of the full model with an AUC of 0.755 (95% CI: 0.728–0.782), down slightly from 0.806. Positive predictive values were calculated to be 3.1%, 12.1%, and 36.5% for the low, medium, and high risk groups, respectively, in the validation dataset. Conversely, the low-risk group could be seen as having a very high negative predictive value of 96.9%. The results are robust to sensitivity analysis in the outcomes; restricting the analyses to those who had a paraprotein only in serum and not urine did not change the likelihood ratios or the AUCs significantly (data not shown).

DISCUSSION

To our knowledge, this is the first attempt to derive a clinical decision rule to help guide the ordering of SPE/UPE. The scoring system uses easily available clinical and laboratory values and is simple to use. The most powerful variable in predicting a paraprotein was total serum globulin, which was

Table 3. Simplified score for estimating risk of an abnormal serum or urine protein electrophoresis

Score (prob. of para-protein)	Derivation set				Validation set			
	SPE/UPE		LR* (95% CI)	PPV (%)	SPE/UPE		LR* (95% CI)	PPV(%)
	Positive	Negative			Positive	Negative		
0-5(Low)	207	6,537	1.0	3.1	91	2,797	1.0	3.1
6-10(Med)	303	2,205	2.5(2.4-2.7)	12.1	129	941	2.5(2.3-2.7)	12.1
≥11(High)	294	506	6.7(5.9-7.6)	36.8	127	221	6.6(5.4-7.9)	36.5

somewhat surprising; despite the fact that many instances of raised globulins reflect polyclonal rather than monoclonal hyperglobulinemias, the discriminatory power of globulins in our model was remarkable (OR=4.5).

This study does have a number of caveats. This is a retrospective cross-sectional study and suffers from the limitations of such studies in that the triggers that lead to the request of SPE/UPE are not clear. Potential bias is evidenced by the fact that the yield in our study was ten-fold higher than previously reported, i.e., approximately 8% versus 0.8%. This may be due to a number of reasons:

- We focused on abnormal SPE/UPE rather than a pathological diagnosis, e.g., myeloma, which included potential transient, non-specific rises in paraproteins. However, our main aim was to increase the yield of abnormal tests;
- physicians may have ordered SPE/UPE based implicitly on characteristics that increase the probability of a paraprotein;
- this may reflect referral bias inherent in being a tertiary referral center and seeing a more severe spectrum of patients;
- there may be a truly increased prevalence of myeloma in our setting (the Hunter Valley in New South Wales Australia)^{19,20}

Secondly, clinical follow-up was not obtained for this study, and the presence of a paraprotein does not necessarily mean a clinical condition necessitating intervention. In fact, most of these positives are likely to be transient rises and monoclonal gammopathies of unknown significance (MGUS), and clinical management would consist of monitoring²¹. Nevertheless, follow-up of these patients is important, and the few cases with overt myeloma or lymphoma will benefit from earlier identification. Thirdly, the data are also based only on hospitalized inpatients and would need to be verified in an outpatient setting if the rule were to be used in that population.

The study, however, does have several strengths. We have obtained a very large number of samples and have tested the clinical decision rule in a separate validation set. The included variables are easily obtained and are objective; hence, the rule can be used regardless of the degree of experience. The AUC of the simplified rule is also high, close to 0.8.

Using the Clinical Decision Rule

The main utility of this decision rule is for case-finding for paraproteinemia. The cutoff score of 0-5 gives a sensitivity of close to 90%, whereas the cutoff score of 11 or over gives a specificity of 90%. Either of these thresholds can be used depending on whether the aim is to minimize false negatives or

false positives, respectively. Indeed, other points along the ROC curve can be selected based on the requirements needed.

Although we have calculated positive predictive values for the trichotomised score, this parameter is dependent on the prevalence of paraproteinemia (8% in our sample) and is not easily applicable across different clinical situations. Using likelihood ratios is more clinically relevant and universal. The positive likelihood ratio corresponding to scores 0-5 is 1, indicating that the likelihood of a paraprotein is not raised significantly. The incidence of a paraprotein therefore is similar to the background or baseline rate and depends on the clinical picture; the SPE/UPE does not contribute any incremental information and is not warranted unless other clinical variables indicate this possibility. Given that just over 66% of patients in this series fell in the range of 0-5, if this threshold were adopted in clinical practice, it could potentially decrease the ordering of SPE/UPE by two thirds and still detect approximately 75% of all paraproteins. Based on the Medicare rebate (in Australia) for SPE/UPE and assuming that 10% of samples need follow-up immunoelectrophoresis, we estimate an average cost of approximately \$42. Given that close to 6,000 sets of these investigations are requested every year in our center, probably typical of other large teaching centers, and that potentially half of these might be avoided, this would translate into cost savings of over \$125,000/year. This, however, still has to be seen in the clinical context, given that approximately 3% of those in this range still have a paraprotein.

We suggest that the best use of this decision rule is in the context of a Bayesian approach, using pre-test probabilities, likelihood ratios, and Bayes nomogram to arrive at post-test probabilities. This approach is explained in detail in multiple other references²²⁻²⁵ and will not be labored here except to give some clinical scenarios as examples. The Bayes nomogram is also available in electronic form for PDA (<http://www.cebm.utoronto.ca/>).

- As part of the admission blood work for a 75-year-old male hospitalized with severe heart failure, globulins are noted to be 50 g/l. His hemoglobin is 110 g/l and eGFR is 40 ml/min/1.73 m². This gives him a score of 13, corresponding to a+LR of ~7. Assuming a baseline prevalence (pre-test probability) of paraproteinemia of 5-10%, the post-test probability is ~25-40%, high enough to support ordering the SPE/UPE.
- As part of a workup for recurrent infections, fatigue, and weight loss in a 40-year-old hospitalized woman, globulins are high, but no other abnormalities are noted. Based on the history and physical exam, the clinician's estimate of the risk of a paraprotein-associated condition is 40%. Her score of 5 corresponds to a+LR of 1, leading to a post-test

probability that is the same, i.e., 40%. This is still high enough that the SPE/UPE should be ordered.

This decision rule can easily be entered in a personal digital assistant (PDA) or could be provided as part of the laboratory report or laboratory information technology support when reporting abnormal globulins. If the rule is automated, the full regression equation could be used as is, which would yield a probability of having an abnormal SPE/UPE. If the rule is applied manually by clinicians, then the trichotomized point score is simpler and does not require any calculations.

A further point of interest is that the vast majority of paraproteins were detected in serum, or serum and urine. Only 3% of paraproteins were detected in urine only. This raises the possibility that for general screening, SPE might be sufficient, whereas current recommendations suggest both serum and urine, particularly to pick up light chains that are excreted. New high sensitivity methods appear to be able to pick up light chains in the serum that were previously only detectable in urine, and this may be an alternative approach^{26,27}. Given the retrospective cross-sectional nature of our data and the possibility that physicians ordered mainly SPE thus missing positive UPE, this possibility needs to be verified systematically in a prospective study.

In conclusion, we propose a simple clinical decision rule to aid in ordering screening SPE/UPE for detecting paraproteins in hospitalized inpatients. This decision rule has the potential to avoid unnecessary testing, but still needs testing in a prospective cohort.

Acknowledgement: The authors declare that there was no conflict of interest, and there was no financial support.

Corresponding Author: John Attia, PhD, FRCP, FRACP; Division of Medicine, HRMC, Locked Bag 1, John Hunter Hospital, Newcastle, New South Wales, Australia 2310 (e-mail: john.attia@newcastle.edu.au).

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