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Background

A protein gap, defined as [total protein] – [albumin] in serum, has traditionally been associated with conditions that result in hypergammaglobulinemia or hypogammaglobulinemia. Although the protein gap is thought to reflect hyper- or hypogammaglobulinemia, this has never been validated in patients with suspected paraproteinemia, such as multiple myeloma, or in patients with suspected immunodeficiencies.

A study by Thakkinstian et. al defined a gap of >41g/L to represent a high protein gap in their clinical decision model to order a SPE (1). A study by Juraschek et. al determined that a protein gap of >31g/L is associated with all-cause mortality (2).

We set out to determine the relationship between a protein gap and a paraproteinemia, specifically looking at values that have been reported in the literature as representing a high or low gap.

Methods

Biochemical data was obtained for all patients at The Ottawa Hospital who had received a serum protein electrophoresis (SPE) test between March 2014 and June 2017. When patients had more than one SPE, the first SPE record was used for the analysis as this reflects the initial presentation that prompted the test.

Receiver-operating characteristic (ROC) curves were created to assess the sensitivity and specificity of using a protein gap to predict a SPE result. Sensitivity, specificity, PPV, NPV and LR tests were specifically performed for protein gap values that have previously been defined in literature as being representative of hypergammaglobulinemia. Univariate and multivariate regression analyses were performed for a pre-determined set of variables to predict the presence of a positive SPE value. The likelihood ratio test with forward elimination was used to select variables in the model.

The second outcome of interest was hypogammaglobulinemia as identified on total gamma globulin laboratory results, which was used as the reference standard. Receiver-operating characteristic (ROC) curves were created to assess the sensitivity and specificity of using a protein gap to predict total gamma globulin results.

Results

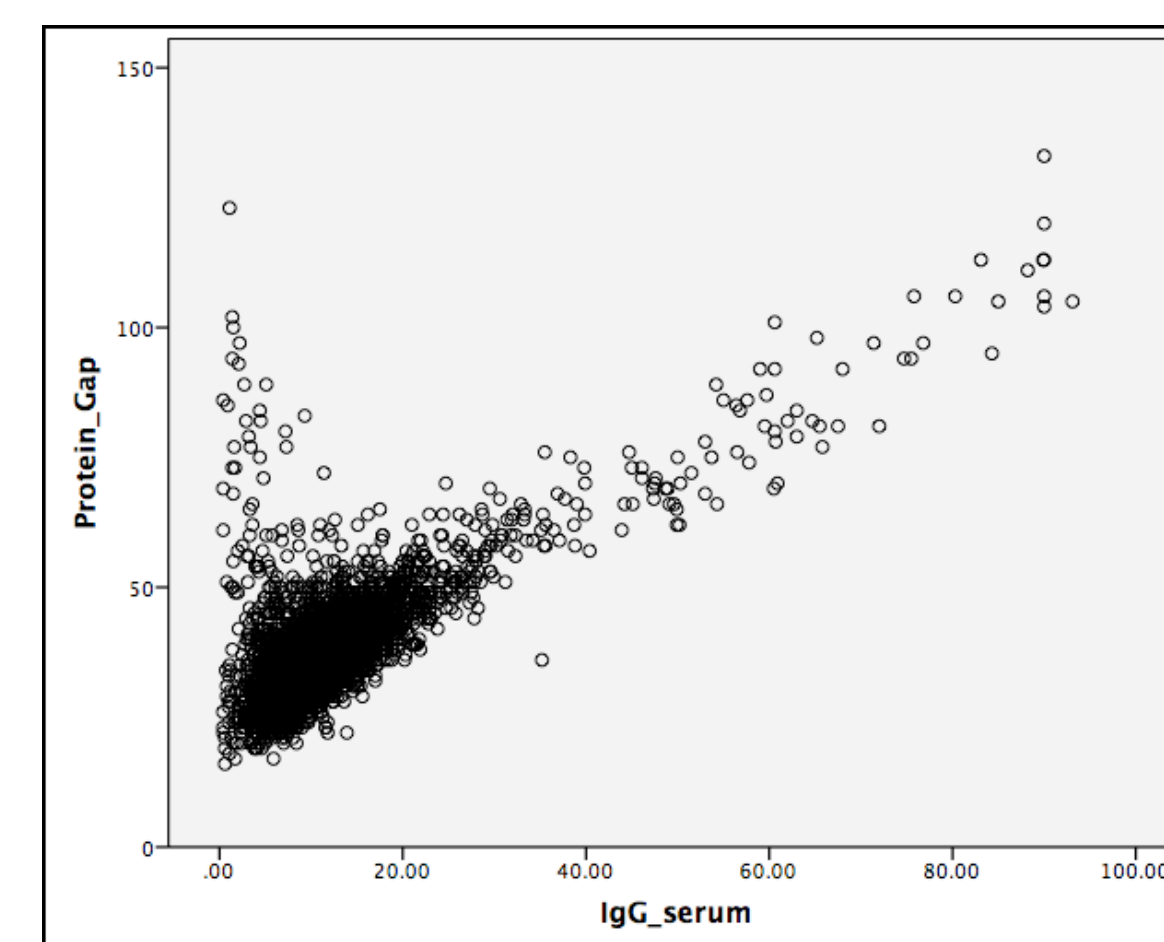


Figure 1. Relationship of the protein gap with serum IgG levels.

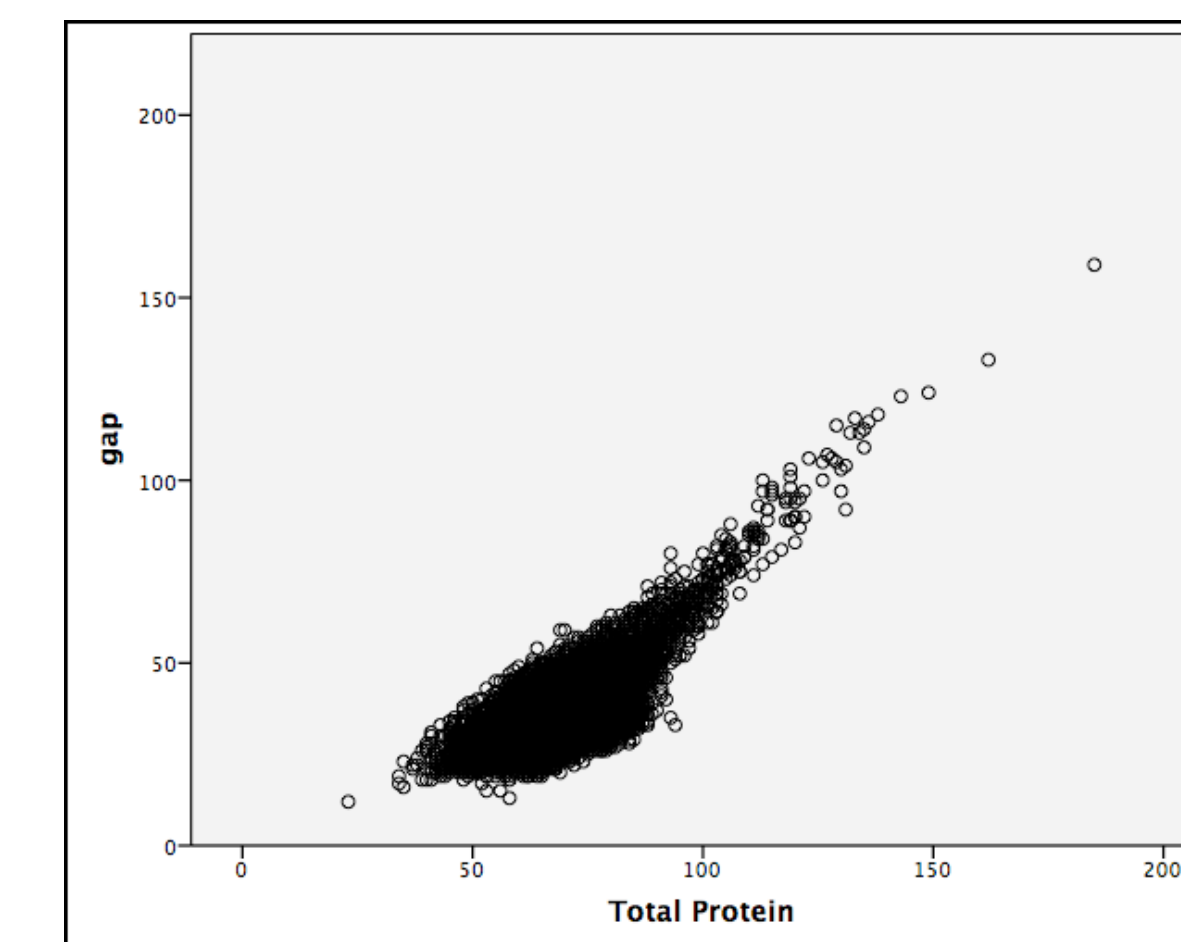


Figure 2. Relationship of the protein gap with total protein levels.

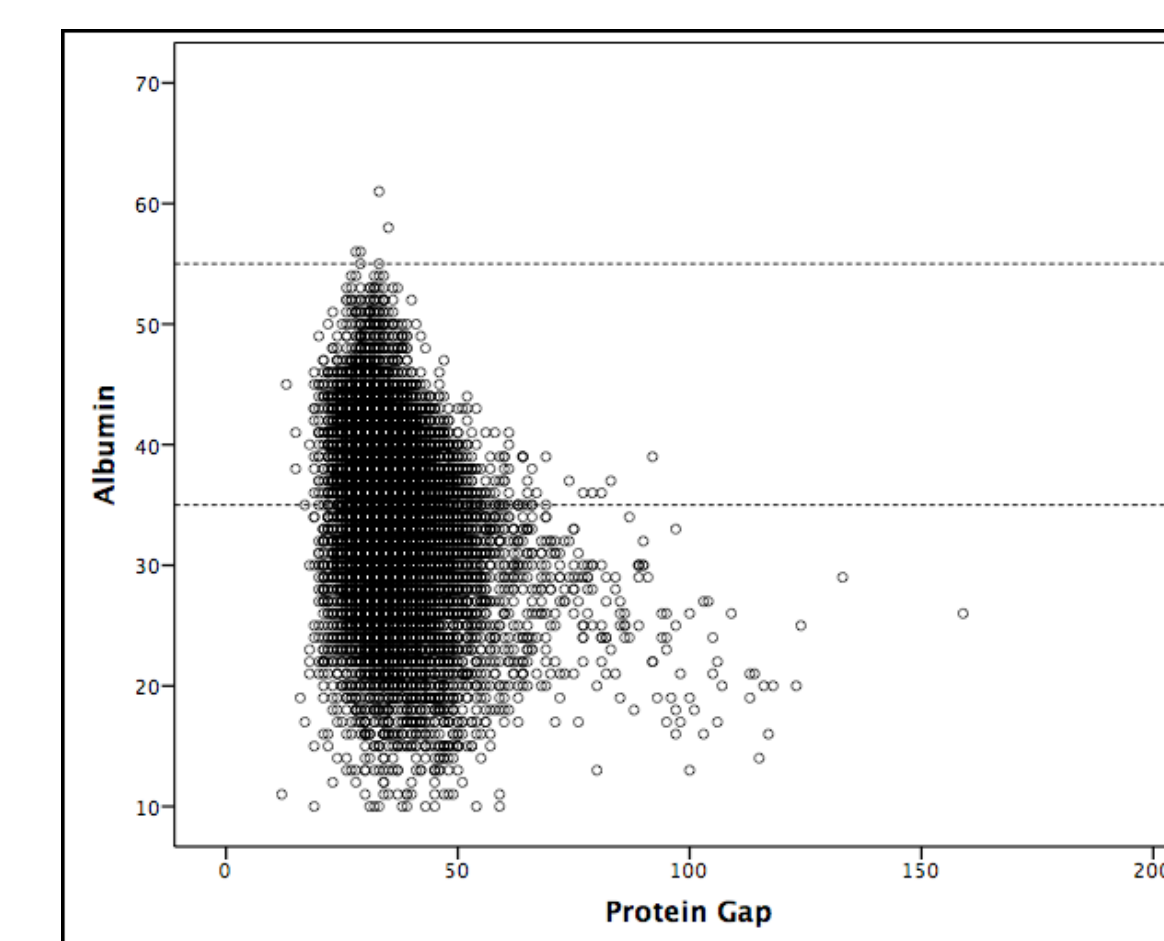


Figure 3. Relationship of the protein gap with serum albumin levels.

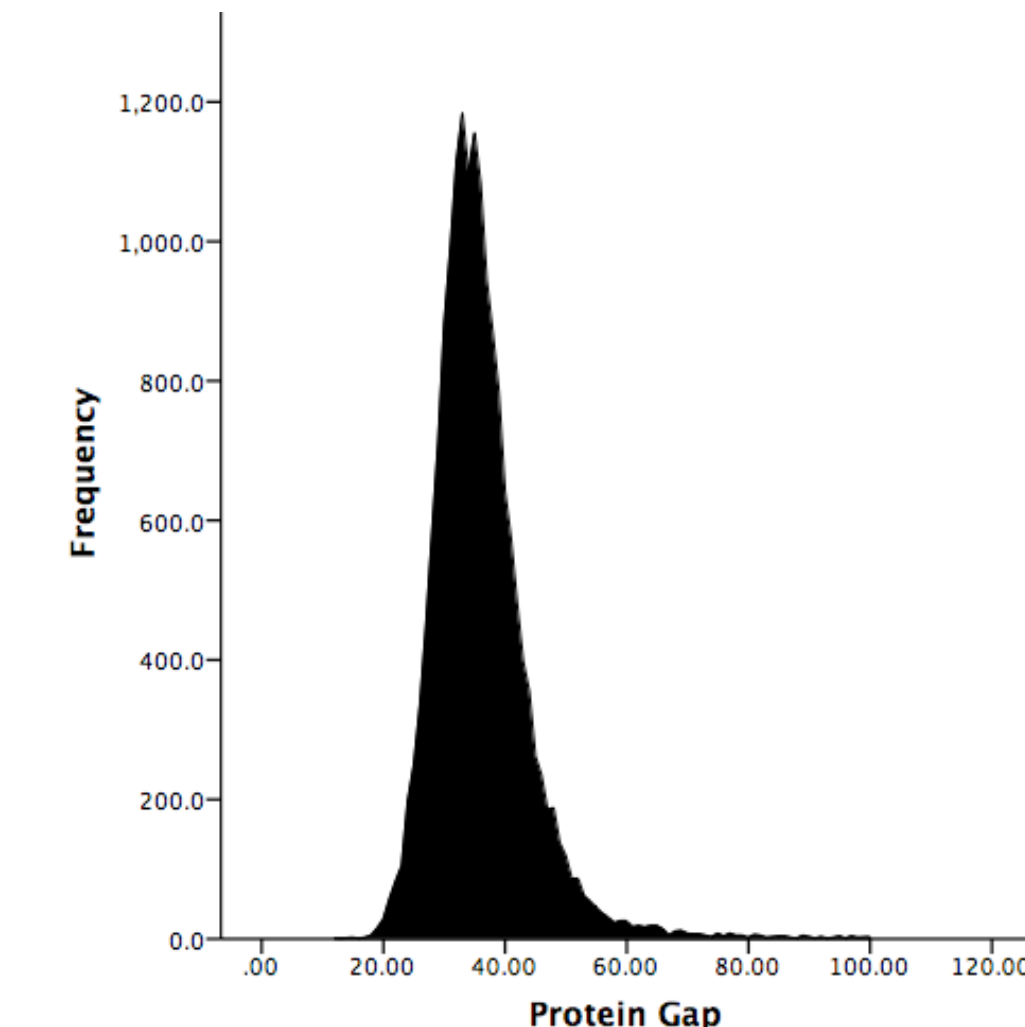


Figure 4. Histogram of protein gap distribution of 19 575 patients. Mean gap is 36 and standard deviation is 8.

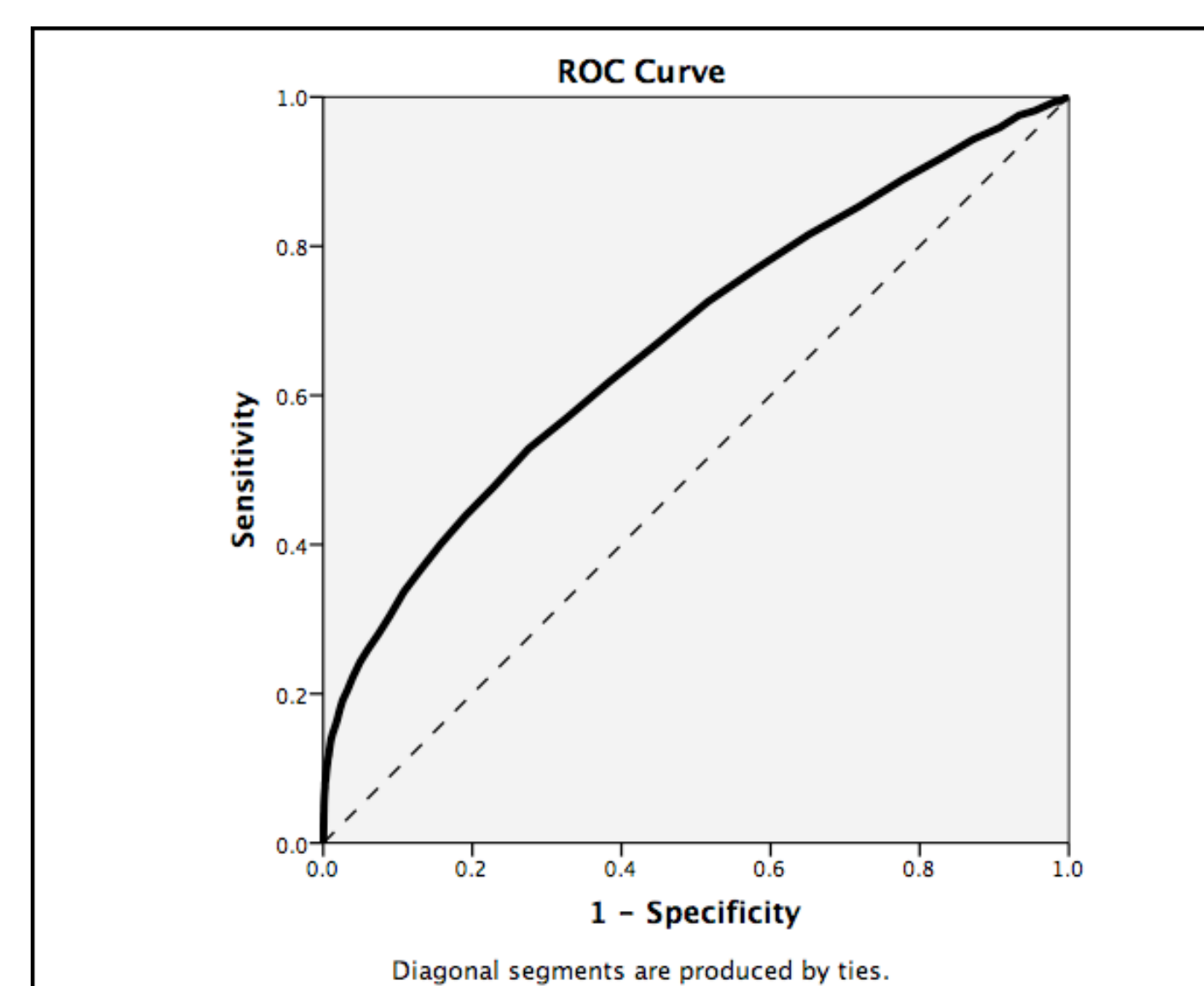


Figure 5. ROC Curve using the protein gap to predict a positive SPE result. A total of 19 575 patients are included in the analysis. The area under the curve is 0.672 (95% CI 0.659-0.686).

Gap Value	Sensitivity	Specificity	LR+	LR-
>45	28.0%	92.6%	3.8	0.8
>31	85.3%	28.2%	1.2	0.5

Variables included in the multiple logistic model to predict a **positive result on serum protein electrophoresis** included:

- Age
- Total Protein (Serum)
- Serum Albumin
- Calcium
- Creatinine
- CRP
- Hemoglobin
- Calcium (corrected for albumin)
- Protein Gap

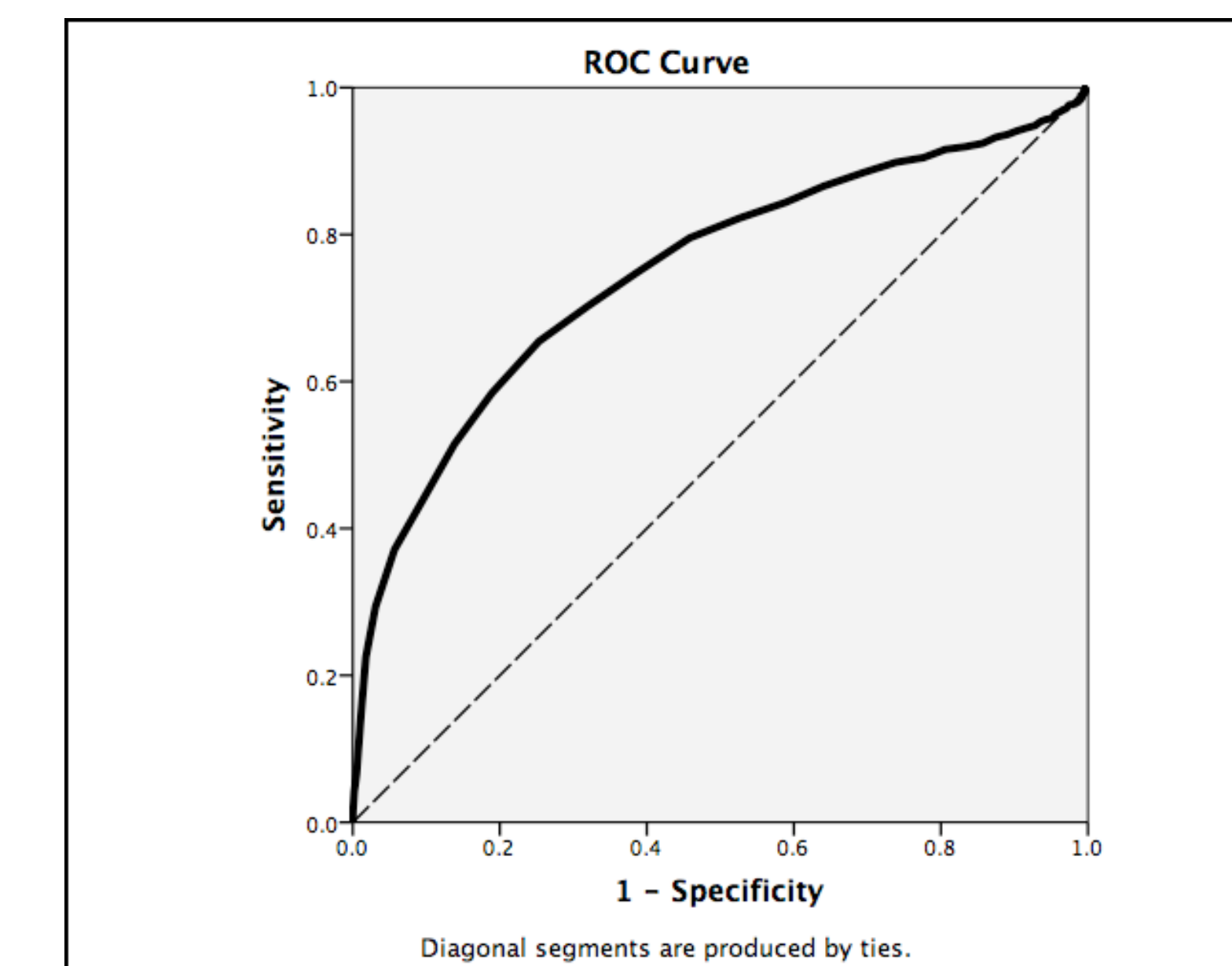
A total of 1728 cases were included in the complete-case analysis. The model had a Cox and Snell R Square of 0.052.

The variables included in the equation were:

- Age - **Odds Ratio 1.055** (95% CI 1.037-1.074)
- C-Reactive Protein - **Odds Ratio 0.995** (95% CI 0.989-1.000)
- Protein Gap - **Odds Ratio 1.084** (95% CI 1.060-1.109)

Results (cont'd)

Figure 6. ROC Curve using the protein gap to predict a serum IgG <7. A total of 5419 patients are included in the analysis. The area under the curve is 0.749 (95% CI 0.731-0.767).



Gap Value	Sensitivity	Specificity	LR+	LR-
<30	43.4%	90.7%	4.7	0.6
<28	29.4%	96.9%	9.5	0.7

Discussion

To our knowledge, this is the first study of its kind of directly examine the correlation between the protein gap and both hyper- and hypogammaglobulinemia.

Our results suggest that a high protein gap, i.e. higher than 45g/L, has a high specificity to rule in the presence of a positive SPE. However, the low sensitivity of using the protein gap as a predictor suggests that with high clinical suspicion, a SPE should still be ordered if there is high clinical suspicion of hypergammaglobulinemia.

Our results suggest that a low protein gap, i.e. lower than 28g/L, has a high specificity to rule in the presence of hypogammaglobulinemia. However, the low sensitivity once again suggests that if there is a high clinical suspicion of hypogammaglobulinemia, a total gamma globulin should be ordered.

Therefore, the protein gap is not a useful screening tool.

References

- 1) Thakkinstian A, Tran H, Reeves G, Murch S, Attia J. A Clinical Decision Rule to Aid Ordering of Serum and Urine Protein Electrophoresis for Case-Finding of Paraproteins in Hospitalized Inpatients. *J Gen Intern Med.* 2008 Oct;23(10):1688–92.
- 2) Juraschek SP, Moliterno AR, Checkley W, Miller ER. The Gamma Gap and All-Cause Mortality. *PLoS ONE* [Internet]. 2015 Dec 2;10(12). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4668045/>