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Prediction Model for Hypogammaglobulinemia Using Serum Globulin and Illness Status

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Abstract

Rationale: Hypogammaglobulinemia is a condition that required prompt diagnosis and treatment. Serum immunoglobulin (Ig) G measurement is not widely accessible in many countries. Serum globulin is potentially the best candidate for screening hypogammaglobulinemia due to its high availability, low cost and rapid turnover time. However, many factors can influence the probability of prediction. Our study aimed to establish a simple prediction model using serum globulin to predict the likelihood of having hypogammaglobulinemia.

Methods: Data of subjects who suspected of having hypogammaglobulinemia and measured both serum IgG and globulin at the same time were collected. Potential factors that might interfere with serum globulin and IgG levels were selected and investigated using bivariate binary logistic mixed regression. A multivariate binary logistic mixed-effect regression was used for generating the formula and score to predict hypogammaglobulinemia.

Results: Nine hundred and fifty-three samples from 143 subjects were obtained. The mean age±SD of subjects was 7±5.23 years old. A strong positive correlation between serum globulin and IgG levels were demonstrated, r = 0.83, p < 0.001. Formula for predicting hypogammaglobulinemia was generated as follows; Predicted score = (2 x globulin(g/dl)) – illness condition score (well = 0, illness = 1). When score is < 4, the subject has the probability to have hypogammaglobulinemia with sensitivity 0.78 (0.71, 0.84), specificity 0.71 (0.68, 0.74), PPV 0.34 (0.29, 0.40) and NPV 0.94 (0.92, 0.96).

Conclusions: Early detection of hypogammaglobulinemia is crucial. A screening test model using serum globulin and illness status can be constructed to predict hypogammaglobulinemia. This will be useful as a rapid and inexpensive screening tool for early detection of hypogammaglobulinemia, especially in places where serum IgG measurement is not accessible.

Introduction

- Measurement of serum IgG is an important test to assess hypogammaglobulinemia and primary immunodeficiency.
- Diagnostic delay is associated with increased morbidity and mortality.
- In developing countries, test for IgG is not available in most hospitals.
- Since immunoglobulins contribute a major component of gamma-globulins, serum globulin level is potentially the best candidate for screening hypogammaglobinemia due to its high availability, low cost and rapid turnover time.

Objective

Our study aimed to establish a simple formula and score calculated from serum globulin to predict the probability of hypogammaglobulinemia in clinical setting.

Methods

Medical records of subjects under 18 years old with suspected hypogammaglobulinemia and presented at Department of Pediatrics, King Chulalongkorn Memorial Hospital, Bangkok, Thailand during 2011-2016 were reviewed. The subjects were enrolled when serum IgG and globulin level were measured at the same time point.

A multivariate binary logistic mixed effect regression was used for generating the formula and score to predict hypogammaglobulinemia.

Hypogammaglobulinemia

Defined as serum IgG level below 500 mg/dl regardless of age.

Illness condition

"Sickness" if he (she) had fever, admitted to the hospital or received intravenous antibiotics due to infections. Otherwise, the subject was defined as in a **"well"** condition.

Serum Globulin levels (g/dl)

measured by using the colorimetric bromocresol green (BCG) method for albumin and the architect biuret method for total protein.

Calculated globulin fraction = Total protein - Albumin

Serum Immunoglobulin G levels (mg/dl)

measured by Nephelometry.

Result

Table I: Demographic characteristics

Characteristic	Primary Immunodeficiency N = 725 (76.1%)	Secondary Immunodeficiency N = 228 (23.9%)	Total N = 953
Age of subjects; mean years (SD)	7.8 (5.1)	4.8 (5.0)	7.0 (5.2)
Male gender; n (%)	25 (73.5)	74 (67.9)	99 (69.2)
Subgroup; n (%)	B cell defect; 411 (56.7) T cell defect; 251 (34.6) Phagocyte defect; 63 (8.7)	Sepsis/Severe infection; 92 (40.3) Recurrent pneumonia; 63 (27.7) Lymphoproliferative malignancies; 73 (32)	
Serum globulin levels (g/dl); mean (SD)	2.40 (0.68)	2.52 (0.84)	2.43 (0.72)
Serum IgG levels (mg/dl); mean (SD)	819.16 (419.98)	861.43 (520.07)	829.27 (446.05)

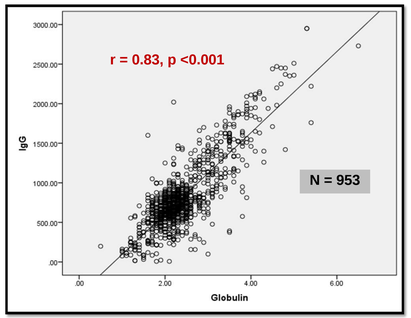

Figure 1: A scatter plot showing a strong positive correlation between serum globulin levels and serum IgG levels in all 953 serum samples; r = 0.83, p <0.001.

Table 2: Performance characteristics of different models for diagnosis of hypogammaglobinemia

Model for calculated predictive score (x)	Cutoff score	Sensitivity (95%CI)	Specificity (95%CI)	PPV	NPV
X = age + (60 x globulin) – (25 x I)	127.6	0.77 (0.69, 0.83)	0.79 (0.76, 0.81)	0.41	0.95
X = -2.85 x globulin (g/dl) + (1.62 x I)	5.6	0.77 (0.69,0.83)	0.79(0.76,0.82)	0.42	0.95
X = (2 x globulin) – I	3.9	0.75 (0.68, 0.82)	0.80 (0.77, 0.83)	0.42	0.94
X = (2 x globulin) – I	4.0	0.78 (0.71, 0.84)	0.71 (0.68, 0.74)	0.34	0.94

X: Predictive score I: Illness condition score (well = 0, sick = 1)
age was described in years, unit of globulin level was g/dl

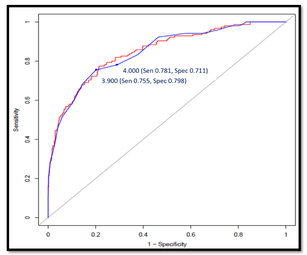

Figure 2: ROC curves illustrate the diagnostic ability of an original model (red line) and a simplified model with 2 different cutoffs predictive score (blue line)

Original model: Predictive score = -2.85 x globulin (g/dl) + (1.62 x illness condition score)

Simplified model: Predictive score = 2 x globulin (g/dl) - illness condition score

Conclusion

Early diagnosis of hypogammaglobulinemia is crucial. Serum globulin is a rapid and simple tool to predict hypogammaglobulinemia. A screening test model was constructed as follows;

Predicted score = (2 x globulin (g/dl)) – illness condition score

(well = 0, sick = 1) with the cut off predicted score of ≤ 4 for predicting hypogammaglobulinemia. This would be valuable in reducing diagnostic delay and optimizing the use of health resources for diagnosis hypogammaglobulinemia in developing countries where measurement of serum IgG not generally available.