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Comparison of prognostic models for predicting severe noninfectious complications in common variable immunodeficiency

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Abstract
A significant clinical heterogeneity of common variable immunodeficiency (CVID) complicates the prediction of severe noninfectious complications (NICs), thereby hindering personalized treatment strategies. This study aimed to compare retrospectively the performance of three distinct prognostic models—low switched memory B-cell (SMB) count, the composite Variable Immunodeficiency Score by Upfront Analytic Link (VISUAL), and the monogenic common variable immunodeficiency (Mo-CVID) score—for predicting NIC development in a single-center Turkish patient cohort. Clinical and immunologic data from 71 CVID patients were analyzed. Univariate analyses were used to compare patient groups, while multivariate logistic regression was employed to identify independent risk factors. During follow-up, 62.0% of patients developed at least one NIC. At diagnosis, patients with NICs exhibited significant immunologic differences, including lower platelet counts, a reduced CD4-CD8 ratio, and significantly lower SMB proportions. The multivariate analysis revealed that only the VISUAL score was a significant and independent predictor of NICs (odds ratio: 1.481; P = 0.005). Furthermore, receiver operating characteristic analysis confirmed its good discriminatory ability (area under the curve: 0.764), with an optimal cut-off value of >8.5. In contrast, neither a low SMB count as a categoric variable nor the Mo-CVID score remained as independent predictors in the final model. The VISUAL score, which integrates multiple B- and T-cell abnormalities, is a superior and more reliable tool for risk stratification in CVID. Its successful validation supports its use as a universal clinical instrument to identify high-risk individuals who may benefit from closer surveillance and earlier therapeutic interventions.

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Introduction

Common variable immunodeficiency (CVID) is the most prevalent symptomatic primary immunodeficiency characterized by an increased susceptibility to infections.[1] However, the clinical significance of the disease extends beyond infections. Approximately half of patients with CVID develop severe noninfectious complications (NICs), which are the primary determinants of morbidity and mortality.[2] These complications encompass a wide spectrum, including autoimmune cytopenia, granulomatous-lymphocytic interstitial lung disease (GLILD), enteropathy, and malignancies. This leads to significant heterogeneity in the clinical course of the disease.[3]

This heterogeneity presents a major challenge for clinicians. It is often impossible at the time of diagnosis to predict which patients will have a disease course limited to infections and which will develop severe NICs. This lack of predictive ability hinders risk-stratified patient monitoring and the implementation of personalized treatment strategies.[4]

To overcome this challenge, various immunologic markers and scoring systems are developed in recent years to predict the prognosis of CVID. One such approach relies on a single advanced immunophenotyping marker, such as a low percentage (<2%) of CD19+CD27+IgD-IgM- switched memory B cells (SMBs), whose prognostic value was established by the European classification (EUROclass) study.[5] More recent and comprehensive approaches include composite scoring systems such as the Variable Immunodeficiency Score by Upfront Analytic Link (VISUAL), which combines multiple immunologic parameters involving B cells, T cells, and immunoglobulin abnormalities.[4] Recently, new tools, such as the monogenic common variable immunodeficiency (Mo-CVID) score, have been described to predict the monogenic causes underlying severe clinical phenotypes.[6] However, the validity and comparative superiority of these different prognostic models are not sufficiently investigated in populations with diverse geographic and genetic backgrounds.

This study aims to compare retrospectively the performance of these three different approaches (low SMB count, the VISUAL score, and the Mo-CVID score as a tool for defining severe phenotypes) in predicting the development of NICs within a single-center Turkish CVID cohort. The ultimate objective is to identify the most reliable, practical, and clinically applicable risk assessment tool for our patient population. This establishes an evidence-based foundation for a more proactive and personalized management approach in patients with CVID.

Methods

Study design and patient population

This study was designed as a single-center, descriptive, analytic, and retrospective cohort study. Initially, 130 patients who were screened with a diagnosis of CVID in the hospital record system were evaluated for inclusion. Following a detailed review of medical records, 17 patients were excluded because they did not completely conform to the diagnostic criteria of the European Society for Immunodeficiencies (ESID).[7] An additional 13 patients were excluded due to the presence of secondary causes of hypogammaglobulinemia.

Of the remaining patients, another 29 were not included in the analyses because of missing critical data from the time of diagnosis, required for calculating prognostic scores. At the end of this selection process, 71 patients who met all inclusion criteria constituted the final study cohort (Figure 1).

The study was approved by the Necmettin Erbakan University Clinical Research Ethics Committee (Approval No.: 2025/5997).

Data collection and definitions

Demographic, clinical, and laboratory data of patients were recorded retrospectively onto a standardized data collection form from the Hospital Information Management System (HIMS) as well as from physical or electronic medical records. The primary endpoint of the study was defined as the development of at least one severe NIC during the follow-up period. The NIC category included autoimmune cytopenias, granulomatous-lymphocytic interstitial lung disease (GLILD), autoimmune enteropathy, liver involvement, and malignancies. Lymphadenopathy (short axis >1 cm) and splenomegaly (long axis >12 cm) were considered severe NICs only when they were persistent (>6 months), unexplained by acute infection, or biopsy-proven.

Assessment of prognostic models

The three prognostic models tested for their performance in predicting the development of NICs were defined and calculated for each patient as follows:

- Low SMB count derived from the EUROclass classification: Patients were divided into two groups based on the percentage of switched memory B cells (SMBs; CD19+CD27+IgD-IgM-), the primary prognostic marker of the EUROclass classification. Patients with an SMB percentage less than or equal to 2% of the total B-cell population were defined as the “Low SMB” group.[5]
- VISUAL score : A numerical score ranging from 5 to 20 was calculated for each patient using the following five immunologic parameters at the time of diagnosis: SMB percentage, serum immunoglobulin A (IgA) and immunoglobulin M (IgM) levels, specific antibody responses, and cluster of differentiation 4 (CD4) T-cell count.[4]
- Mo-CVID score: Although this score was described in the literature to predict the likelihood of an underlying monogenic cause, it was evaluated in the present study as a potential tool for identifying a severe clinical phenotype.[6] The score was based on a 0–13-point system derived from the following eight different clinical and immunologic features: family history, early onset, severe/sequelae-forming infections, panhypogammaglobulinemia, severe autoimmunity–lymphoproliferation, and an SMB percentage <0.30.

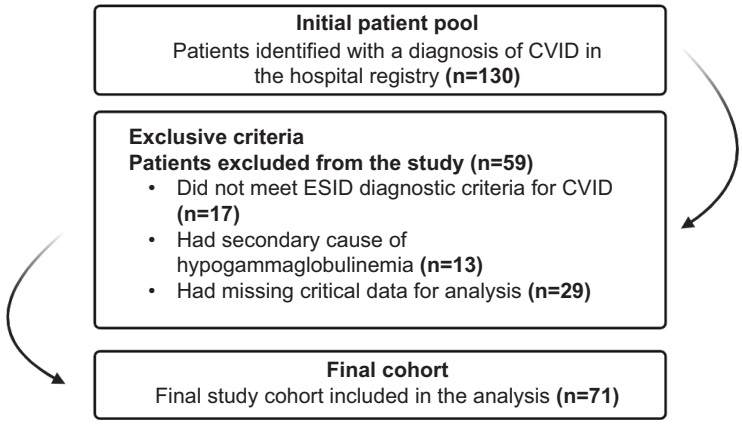

Figure 1 Patient selection flowchart.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. After testing for the normal distribution of data, continuous variables were presented as mean ± standard deviation (SD) or median [interquartile range/IQR]. Categoric variables were presented as numbers (n) and percentages (%). For comparisons between the groups with and without NICs, the Mann-Whitney U test was used for continuous variables, while the Chi-squared or Fisher's Exact test was used for categoric variables.

To evaluate the performance of prognostic models, the Chi-squared test and receiver operating characteristic (ROC) curve analysis were performed. Performance of the VISUAL score in predicting NICs was measured by ROC analysis as area under the curve (AUC), and the optimal cut-off value was determined. Finally, a multivariate logistic regression analysis was used to identify independent risk factors for the development of NICs. $P > 0.05$ was considered statistically significant for all analyses.

Table 1 Demographic and clinical characteristics of the study cohort (n = 71).

Characteristics	n (%)
Gender, Female	41 (57.7)
Consanguinity	42 (59.2)
Presence of NICs	44 (62.0)
Complications	
Autoimmune cytopenia	19 (26.8)
Bronchiectasis	7 (9.9)
Malignancy	7 (9.9)
Rheumatologic disease	7 (9.9)
Enteropathy	6 (8.5)
Liver involvement	5 (7.0)
Endocrinogic disease	5 (7.0)
Dermatologic disease	4 (5.6)
GLILD	2 (2.8)
Mortality	10 (14.1)

Notes: NICs: noninfectious complications; GLILD: granulomatous-lymphocytic interstitial lung disease.

Results

Demographic and clinical characteristics of the study cohort

A total of 71 patients with CVID were included in the study. The baseline demographic and clinical characteristics of the cohort are presented in Table 1. The median follow-up duration of the cohort was 7.0 years (range: 0.5–27 years). A key finding was that the majority of patients (62.0%) developed at least one NIC during follow-up, with autoimmune cytopenia being the most frequent complication. The overall mortality during the follow-up period was 14.1% (Table 1).

Comparison of characteristics between patients with and without NICs

The characteristics of patients with and without NICs were compared (Table 2). While no significant differences were observed in demographic data, patients who developed NICs had significantly higher median VISUAL and Mo-CVID scores.

The NIC group also presented with a lower median platelet count and notable T-cell abnormalities, including a reduced CD4–CD8 ratio. Furthermore, the median percentage of switched memory B cells was significantly lower in these patients. Other laboratory parameters did not differ significantly between the groups.

Identification of independent risk factors for the development of NICs

A multivariate logistic regression analysis was performed to identify independent risk factors for NICs. The platelet count was excluded to prevent circular reasoning.

Of the variables analyzed, only the VISUAL score emerged as a significant and independent predictor of NICs ($P = 0.005$).

Table 2 Comparison of demographic, clinical, and laboratory characteristics of patients according to NIC status.

Characteristics	No NICs (n = 27)	NICs (n = 44)	P value
Demographic data			
Age (years), median [IQR]	43.0 [28.0-53.0]	38.0 [31.7-47.2]	0.619
Gender (female), n (%)	15 (55.6)	26 (59.1)	0.770
Consanguinity (present), n (%)	14 (51.9)	28 (63.6)	0.327
Prognostic score			
VISUAL score (points), median [IQR]	8.0 [6.0-9.0]	10.0 [9.0-11.0]	**<0.001**
Mo-CVID score (points), median [IQR]	1.0 [1.0-2.0]	2.0 [1.0-4.0]	**0.047**
Hematology			
WBC (×10³/μL), median [IQR]	7.90 [5.8-10.4]	6.95 [4.8-10.9]	0.168
Neutrophil (×10³/μL), median [IQR]	5.11 [3.5-8.0]	3.46 [2.7-7.1]	0.091
Lymphocyte (×10³/μL), median [IQR]	1.90 [1.3-2.4]	1.50 [1.0-2.5]	0.135
Eosinophil (×10³/μL), median [IQR]	0.10 [0.0-0.2]	0.10 [0.0-0.2]	0.948
Hemoglobin (g/dL), median [IQR]	13.6 [11.8-14.9]	12.5 [10.6-14.3]	0.173
Platelet (×10³/μL), median [IQR]	275.0 [198-333]	203.5 [149-270]	**0.011**
Immunology			
IgG (mg/dL), median [IQR]	494 [230-670]	411 [230-600]	0.538
IgA (mg/dL), median [IQR]	35 [0-90]	27 [0-70]	0.618
IgM (mg/dL), median [IQR]	47 [10-90]	26 [0-80]	0.413
CD3+ T-cell (%), median [IQR]	77.0 [73.0-84.0]	77.5 [70.0-86.7]	0.981
CD3+CD4+ T-cell (%), median [IQR]	37.0 [33.0-48.0]	32.0 [23.2-42.0]	**0.029**
CD3+CD8+ T-cell (%), median [IQR]	34.0 [30.0-39.0]	40.0 [33.0-49.7]	**0.027**
CD4-CD8 ratio, median [IQR]	1.10 [0.6-1.2]	0.84 [0.7-1.5]	**0.026**
CD19+ B-cell (%), median [IQR]	7.80 [4.0-11.8]	7.00 [5.2-13.9]	0.413
CD16+56+ NK cell, median [IQR]	10.20 [6.8-17.0]	8.80 [5.0-13.8]	0.280
CD19+CD27+IgD-IgM-SMB (%), median [IQR]	7.90 [1.8-9.6]	2.31 [1.0-6.7]	**<0.001**
Low CD19+CD27+IgD-IgM-SMB (<2%), n (%)	13 (48.1)	21 (47.7)	0.345
Biochemistry and inflammation			
Urea (mg/dL), median [IQR]	25.0 [19.0-29.0]	25.0 [22.0-33.0]	0.799
Creatinine (mg/dL), median [IQR]	0.70 [0.6-0.7]	0.65 [0.5-0.8]	0.547
AST (U/L), median [IQR]	18.0 [15.0-20.0]	21.1 [15.0-24.6]	0.182
ALT (U/L), median [IQR]	17.0 [12.0-21.5]	18.5 [13.0-22.5]	0.163
CRP (mg/L), median [IQR]	5.00 [2.0-13.2]	8.00 [2.7-12.7]	0.640
ESR (mm/h), median [IQR]	6.00 [3.0-14.0]	7.00 [4.0-15.0]	0.230

Notes: Data are presented as median [IQR] or n (%).
Statistically significant P values are indicated in bold.
NICs: noninfectious complications; IQR: interquartile range; WBC: white blood cells; Ig: immunoglobulin; SMB: switched memory B-cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Each one-point increase in the score was associated with a 1.48-fold increase in the odds of developing NICs (Table 3). ROC analysis confirmed the score's good discriminatory ability (AUC = 0.764; Figure 2) and identified an optimal cut-off value of >8.5, with a sensitivity of 86.4% and a specificity of 63.0%. In the final model, neither the Mo-CVID score nor the CD4-CD8 ratio was significant predictors (Table 3).

To test whether the VISUAL score's predictive power was driven solely by its B-cell component, a second model was run with the SMB percentage replacing the composite score. In this alternative model, no variable, including the SMB percentage, was a significant predictor of NICs.

Discussion

Common variable immunodeficiency is a heterogeneous disorder that complicates patient risk stratification. This study compared three prognostic models for predicting severe NICs in a Turkish CVID cohort. Our primary finding is that the VISUAL score, a composite of five immunologic parameters, is a powerful and independent predictor of NICs, outperforming standalone markers. This was supported by the identification of significant immunologic differences in patients with NICs, including T-cell dysregulation and lower platelet counts, underscoring the value of a multivariate assessment approach.

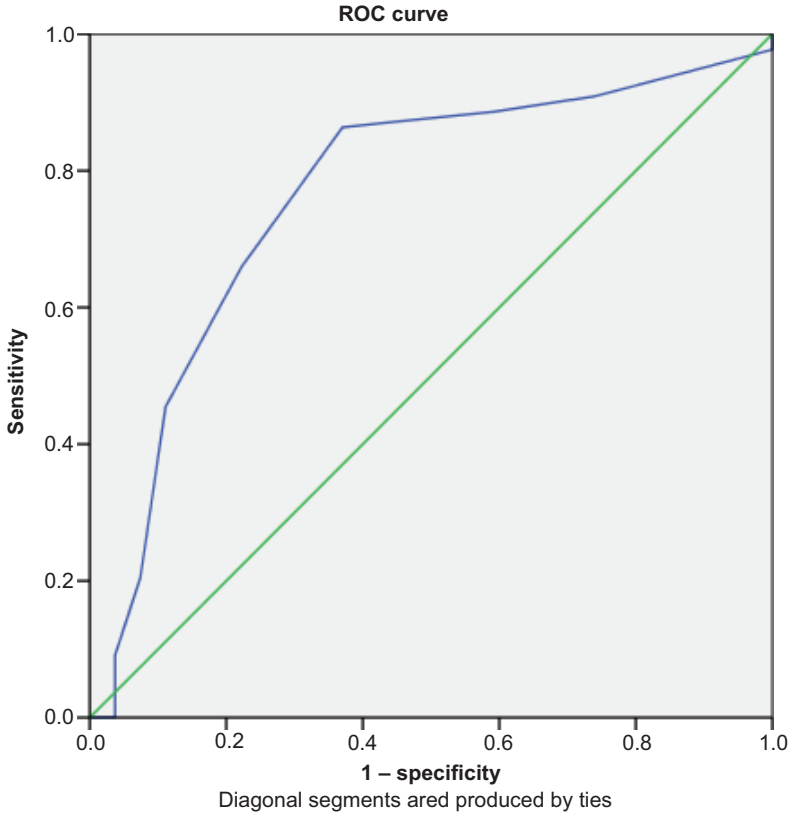

Figure 2 ROC curve for the VISUAL score in predicting the development of NICs (AUC = 0.764, P < 0.001).

Table 3 Results of multivariate logistic regression analysis for the development of NICs.

Variable	B	S.E.	Wald	P value	Odds ratio (OR)	95% Confidence interval for OR
VISUAL score	0.392	0.141	7.763	**0.005**	1.481	1.123–1.951
Mo-CVID score	0.231	0.193	1.435	0.231	1.260	0.863–1.837
CD4-CD8 ratio	−0.580	0.426	1.849	0.174	0.560	0.243–1.292

Notes: B: regression coefficient; SE: standard error; OR: Odds Ratio.
Statistically significant P values are indicated in bold.

The VISUAL score demonstrated superior performance and robustness. Its predictive power, reflected by an AUC of 0.764, was consistent with the original validation study and showed good discriminatory ability in our population. A cut-off of >8.5 identified at-risk patients with high sensitivity (86.4%). Crucially, in the multivariate regression analysis, the VISUAL score remained the sole independent risk factor for NIC development (OR: 1.481), a testament to its comprehensive design. The successful validation of this score in our population reinforces its potential as a universal clinical tool, reflecting the multi-layered immune dysregulation of CVID that extends beyond mere antibody deficiency.[8-10]

Interestingly, the widely used EUROclass marker of a low SMB count (<2%) was not a significant standalone predictor of NICs in our cohort. This divergence from the original EUROclass study may stem from population differences or our broader NIC definition, as the prognostic value of this classification is variable.[11-13] Although the ESID diagnostic criteria define low SMBs as <70% of age-related normal values, we utilized the EUROclass cutoff of <2% (or absolute counts).[7] This choice was made because the <2% threshold is specifically established in the literature as a prognostic marker for noninfectious complications in CVID, rather than for diagnostic purposes.[5] However, the role of SMB cells remains important; when analyzed as a continuous variable, its percentage was significantly lower in the NIC group (P < 0.001). This suggests that while a fixed cut-off may be suboptimal, a general reduction in SMBs reflects underlying immune dysregulation. This finding indirectly supports our main conclusion that the VISUAL score is more reliable because it integrates the SMB value holistically with other immunologic abnormalities.

We also evaluated the Mo-CVID score as a tool for identifying severe phenotypes.[6] While it was associated with NIC development, its utility was limited by very low sensitivity (9.1%) and its failure to remain an independent predictor in the multivariate analysis. This is likely because the VISUAL score captures the same immunologic disturbances more precisely. Importantly, the original Mo-CVID description did

not validate the score against clinical outcomes, such as autoimmunity, GLILD, or lymphoproliferation; its primary purpose was to estimate the likelihood of monogenic disease. Therefore, direct prognostic comparisons with previous cohorts are not applicable. Nevertheless, clinical phenotyping remains a powerful prognostic tool, independent of genetic diagnosis.[1,3,14] Therefore, Mo-CVID score retains potential as a simple preliminary risk assessment tool, especially in centers with limited resources.

Our findings also underscore the central role of T-cell dysregulation in CVID pathogenesis. Patients with NICs exhibited a significantly reduced CD4–CD8 ratio, a finding consistent with the recent literature linking T-cell imbalances to complications such as autoimmune cytopenia and interstitial lung disease.[15,16] Furthermore, chronic CD8 activation triggered by viral agents, such as cytomegalovirus (CMV), has also been reported to lead to inflammatory CVID phenotypes.[17] This observation helps to explain the VISUAL score's success; unlike models focused solely on B-cells, it incorporates the CD4 T-cell count, thereby capturing a critical dimension of the disease's pathology and providing a superior risk assessment.

Finally, a lower median platelet count in the NIC group probably reflects the high prevalence of autoimmune thrombocytopenia (ITP) within this cohort.[18] We interpreted this not as a predictor of a future event but as a direct manifestation of the underlying disease. Consequently, to avoid circular reasoning, the platelet count was excluded from our multivariate model, a methodologic choice that allowed for a clearer demonstration of the VISUAL score's independent prognostic value.

Certain limitations should be considered when interpreting our findings. The retrospective, single-center design is a primary limitation, which may have led to selection bias because of the exclusion of 29 patients with missing data. Additionally, a relatively small cohort size (n = 71) limits the generalizability of our results and necessitates their validation in larger, multicenter studies. Conclusions regarding the Mo-CVID score, in particular, must be interpreted with caution because of the small number of patients in the "high probability" group (n = 4) and the absence of genetic analysis.

Despite these limitations, our study has significant strengths. To our knowledge, it is the first study in the Turkish population to compare directly three different modern prognostic models: an immunophenotypic marker, a composite score, and a severe phenotype score. The single-center follow-up according to standard protocols increased data consistency, while the use of advanced statistical methods, such as multivariate logistic regression analysis, strengthened the robustness of our findings. The demonstration that the VISUAL score is an independent predictor for the development of NICs provides valuable evidence that can be directly integrated into clinical practice for risk stratification in CVID.

Conclusion

This study demonstrates that the composite VISUAL score is a superior and more reliable prognostic tool for predicting the development of NICs in CVID patients compared to single markers. Its successful validation in our Turkish cohort supports its potential as a universal clinical instrument for risk stratification at the time of diagnosis. These findings suggest that patients with a high score may warrant closer monitoring and earlier consideration of immunomodulatory therapies. Confirmation of these results in larger, prospective studies is essential for advancing a personalized and proactive approach to CVID management.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

The authors declared no potential conflict of interest with respect to research, authorship, and/or publication of this article.

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Supplementary

Table S1 Components of the VISUAL score.

Parameter	Definition/range	Points
Switched memory B cells (% of total B cells)	Normal (>6%)	1
	Moderate reduction (2–6%)	2
	Severe reduction (1–2%)	3
	Very severe reduction (<1%)	4
Serum IgA llevels	Normal	1
	Low (<2 SD for age)	2
	Undetectable (<0.07 g/L)	4
Serum IgM levels	Normal	1
	Low (<2 SD for age)	2
	Undetectable (<0.05 g/L)	4
Specific antibody responses	Normal response to both protein and polysaccharide vaccines	1
	Impaired response to one type (protein or polysaccharide)	2
	Impaired response to both types	4
CD4+ T-cell count	Normal (>700/μL)	1
	Mild reduction (500–700/μL)	2
	Moderate reduction (200–500/μL)	3
	Severe reduction (<200/μL)	4

Notes: Total score range: 5–20.[4]

Table S2 Components of Mo-CVID score.

Clinical/ımmunologic feature	Points
Family history of PID	2
Early onset (<5 years)	2
Severe infections or sequelae	1
Failure to thrive	1
Panhypogammaglobulinemia (IgG, IgA, IgM: all low)	2
Severe autoimmunity or lymphoproliferation	2
B-cell phenotype (low SMB < 0.30%)	2
T-cell phenotype (CD4 < 300/μL or low naïve CD4)	1

Note: Total score range: 0–13.[6]

Definition of switched memory B-cells (SMB)

Switched memory B-cells were identified by flow cytometry as CD19+CD27+IgD−IgM− cells, consistent with the established immunophenotypic definitions used in the studies of primary immunodeficiency disorders. For prognostic stratification in this study, low SMB was defined as ≤2% of total B-cells, in accordance with the EUROclass classification.[5]

- Warnatz K, et al. *J Allergy Clin Immunol*. 2002.