A NEW IMMUNOSCORE BASED ON IMMUNOGLOBULINS LEVELS INFLUENCING MORTALITY RISK IN SEPSIS

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Introduction

Sepsis ranks in the top 10 causes of death. New diagnosis and prognostic biomarkers are needed to improve the understanding of sepsis physiopathology in addition to reduce its incidence. Persistence of low levels of immunoglobulins in serum is a frequent finding in severe sepsis and septic shock.

Objective

To evaluate the influence of simultaneous low levels of endogenous immunoglobulins in sepsis prognosis by creating **Immuno-scores (IS).**

Material and Methods

- A prospective **multicentric study** involving nine general ICUs was performed including 172 patients with severe sepsis or septic shock at ICU admission.
- Different **immunoglobulin** isotypes and subclasses **levels** were measured in plasma at sepsis diagnosis.
- First, we calculated decils for immunoglobulins levels. Then,we built **IS** for each decil identifying those patients who showed simultaneous presence of low levels of two or more immunoglobulins (Table 1). The immunoglobulins included in the IS were IgG1 (because it counts up to the 70% of total IgG), IgM and IgA. Kaplan Meier analysis identified the cut-offs for immunoglobulin levels associated with outcome.
- Finally, the association between IS and **mortality risk** was assessed using logistic regression analysis.

Results

The only significant decil using log Rank test was p30. Cut-offs identified for p30 were 306 mg/dl for IgG1, 27 mg/dl for IgM and 196 mg/dl for IgA. IgG1 and IgM levels were compatible with hipogammaglobulinemia according to our laboratory reference values (IgG1=344-966mg/dl; IgM=60-220mg/dl). The Kaplan-Meier analysis showed that patients with low immunoglobulins levels died before (Figure 1). Univariate analysis evidenced a direct association between all the IS and the ICU mortality risk, being more accentuated in the IS containing the three immunoglobulins. Multivariate analysis was adjusted with the following variables: age, sex, APACHE-II score, and those personal antecedents with a $p<0.1$ in the univariate analysis. Multivariate analysis showed a synergic effect of simultaneous low levels in patients with IgG1, IgM and IgA under the established cut-offs (Table 1).

Inmunoscore	Assigned value	
	0	1
IS IgG1 IgM IgA	Patients with: **IgG1 ≤ 306 mg/dl + IgM ≤ 27 mg/dl + IgA ≤ 196 mg/dl**	Rest of combinations
IS IgG1 IgM	Patients with: **IgG1 ≤ 306 mg/dl + IgM ≤ 27 mg/dl**	
IS IgG1 IgA	Patients with: **IgG1 ≤ 306 mg/dl + IgA ≤ 196 mg/dl**	
IS IgM IgA	Patients with: **IgM ≤ 27 mg/dl + IgA ≤ 196 mg/dl**	

Table 1: IS definitions. Patients with concomitant presence of immunoglobulin levels below the cut-offs forming part of each respective score were given a 0, while the remaining patients were given a 1.

Inmunoscore	Univariate		Multivariate	
	OR [95% CI]	*p*	OR [95% CI]	*p*
IS IgG1_IgM_IgA	4.04[1.51-10.76]	***0.005***	4.62[1.33-15.99]	***0.016***
IS IgG1_IgM	2.82[1.17-6.82]	*0.021*	2.75[0.95-7.96]	*0.063*
IS IgG1_IgA	2.67[1.18-6.06]	*0.019*	3.83[1.35-10.91]	*0.012*
IS IgM_IgA	2.82[1.17-6.82]	*0.021*	2.36[0.80-6.90]	*0.118*

Table 2: Univariate and multivariate logistic regression analysis for ICU mortality risk. OR:Odds Ratio.

Conclusions

I. Our results support a **synergic detrimental effect of low levels of IgG1,IgM and IgA in severe sepsis and septic shock**.

II. We have designed **a new and innovative score**, useful in clinical practice for evaluating mortality risk in patients suffering from severe sepsis and septic shock.

III. **Monitoring immunoglobulin levels** could improve clinical trials designs that evaluate intravenous immunoglobulin treatment in sepsis by a better stratifying way of the study population.

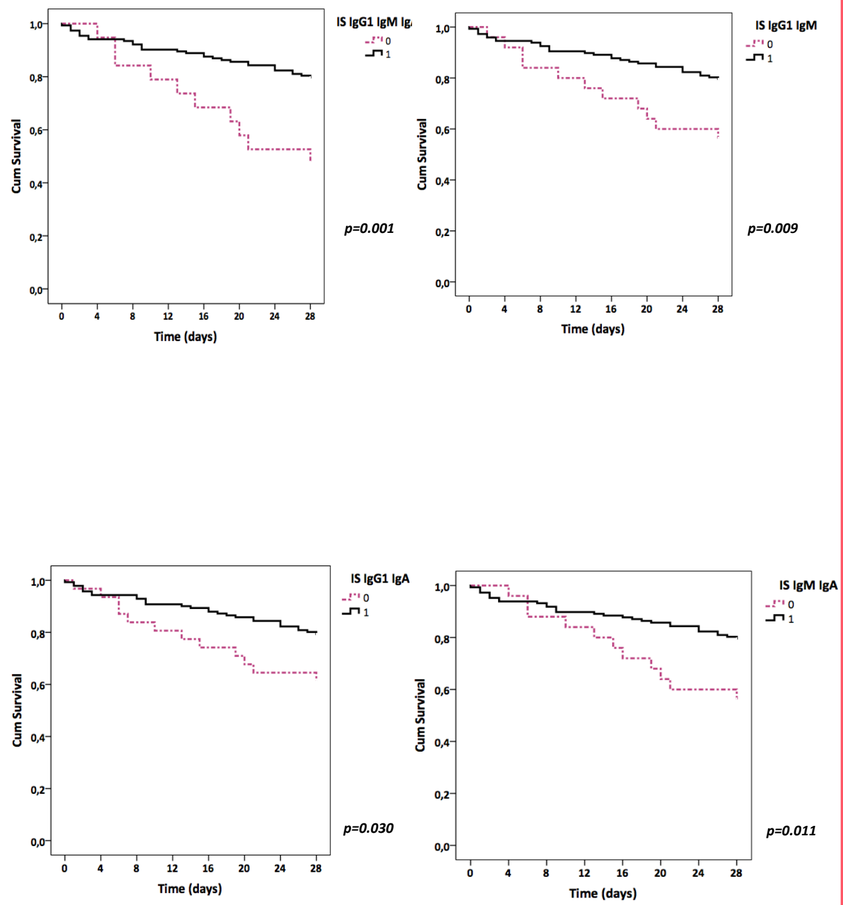

Figure 1: Kaplan-Meier Survival curves based upon combined immunoglobulin-scores (IS). 0 and 1 represent patients with lower and higher immunoglobulin values respectively.