Immune complexes of B2glycoprotein I in patients with IgA antiphospholipid antibodies indentify patients with elevated risk of early mortality after heart transplantation

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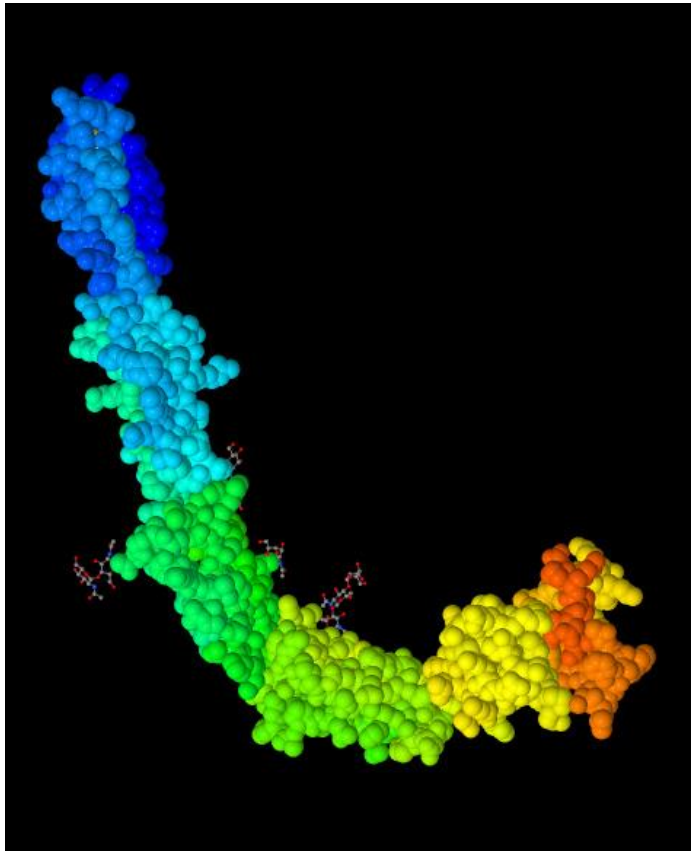
Beta-2 glycoprotein I



A protein of 321 amino acids, distributed in 5 sushi domains

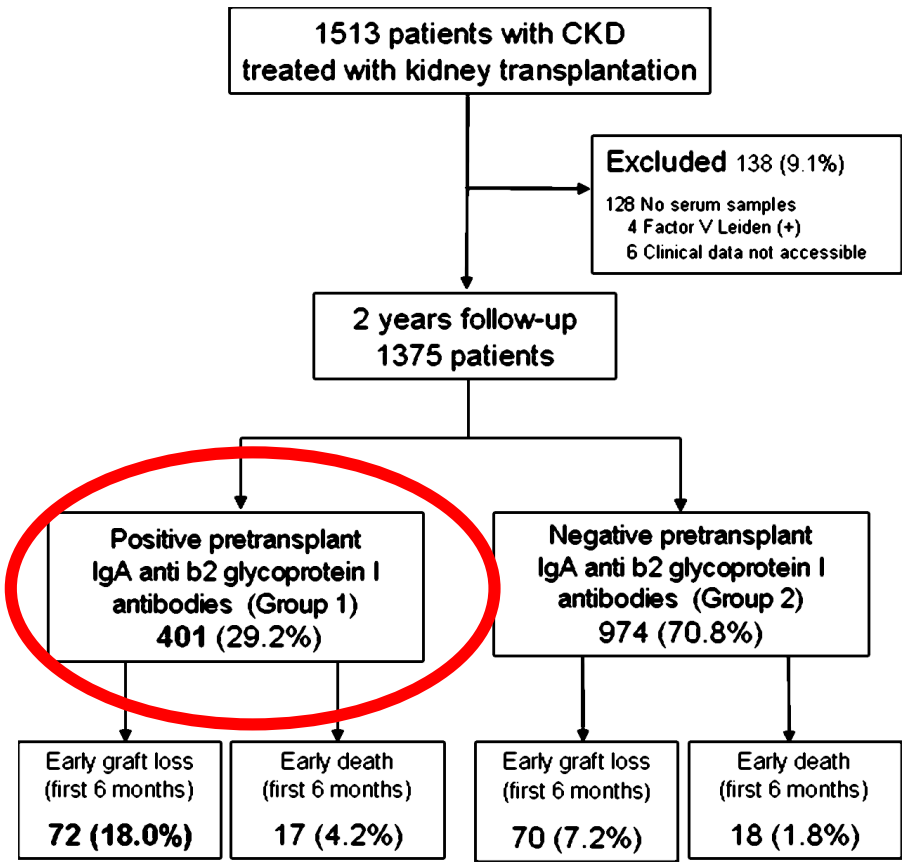
elaborated by **liver, heart and kidney**

Its function is not well known.

Actually 3 conformations have been described

Figure 6 The spread of antiphospholipid syndrome (APS).

G.Hughes. Lupus (2014) 23, 400–406



Original Clinical Science—General

The Presence of Pretransplant Antiphospholipid Antibodies IgA Anti-β-2-Glycoprotein I as a Predictor of Graft Thrombosis After Renal Transplantation

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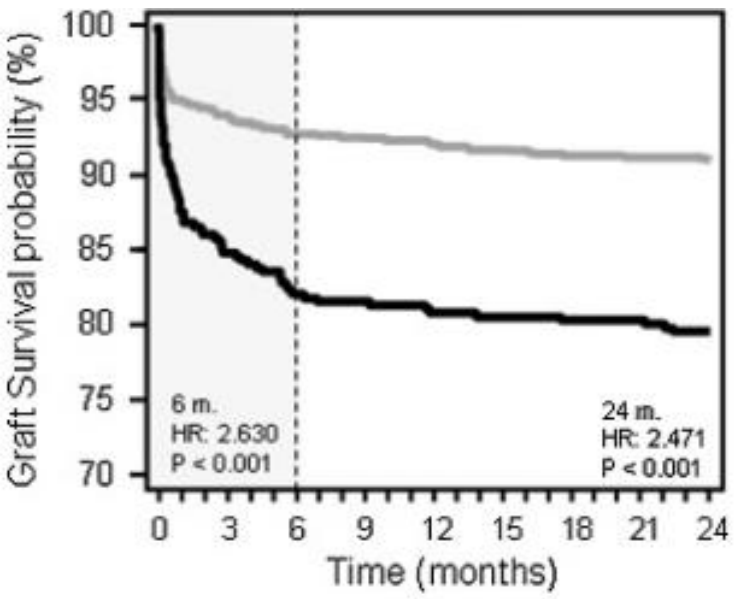

IgA aB2GP1 -

IgA aB2GP1 +

Morales et al. Transplantation. 2016

β_2-Glycoprotein I/IgA Immune Complexes

A Marker to Predict Thrombosis After Renal Transplantation in Patients With Antiphospholipid Antibodies

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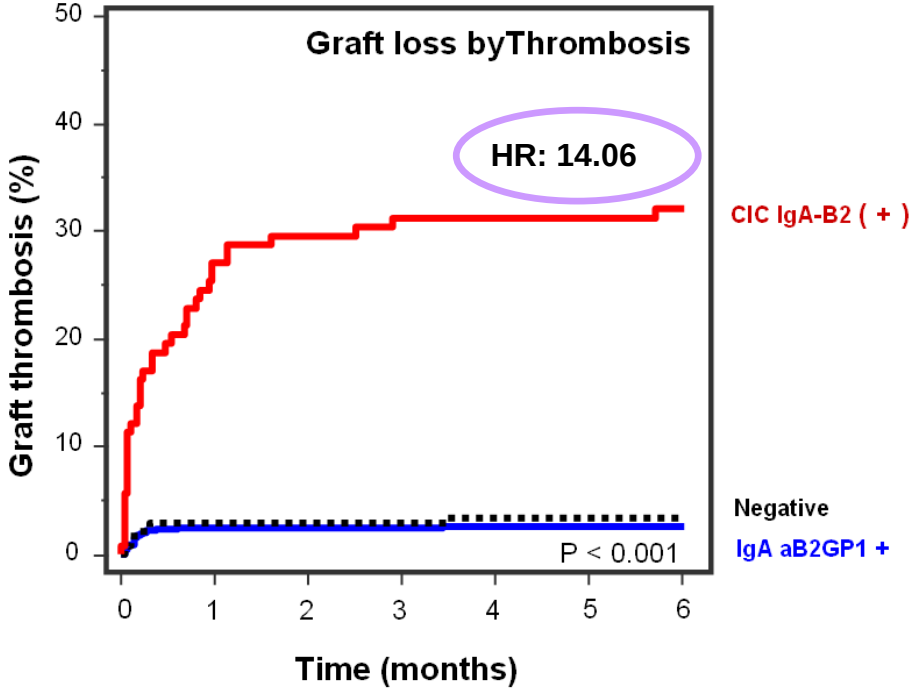

Patients IgA aB2GP1 and Iga-B2 CIC –
Have same risk of thrombosis as patients aPL negative

- B2GP1 misfolded is presented in complete form by HLA II (Takamura et al.)
- Recently we described elevated prevalence of IgA aB2GP1 in chronic kidney disease, associated to early graft loss by thrombosis after transplantation

Hipothesis

Chronic Failure of kidney could produce an misfolded protein, so organs B2GP1-producers could sintetize an misfolded protein too, showing epitopes with homology to proteins of microorganism, that are criptic in physioligical form

Early mortality after heart transplantation related to IgA anti–β2-glycoprotein I antibodies

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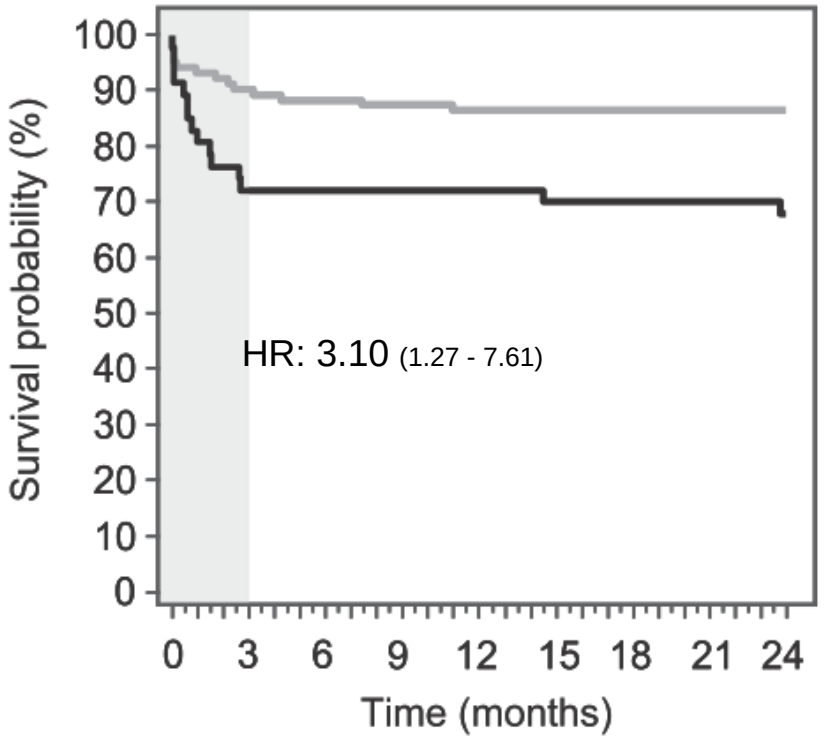


IgA aB2GP1 -

IgA aB2GP1 +

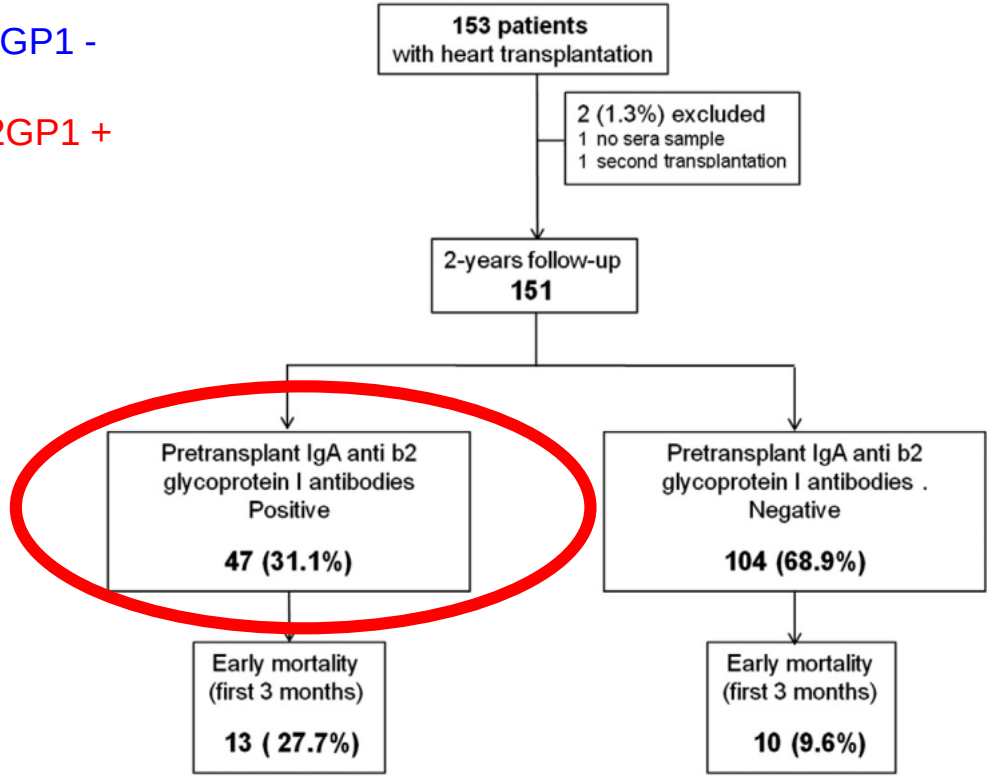
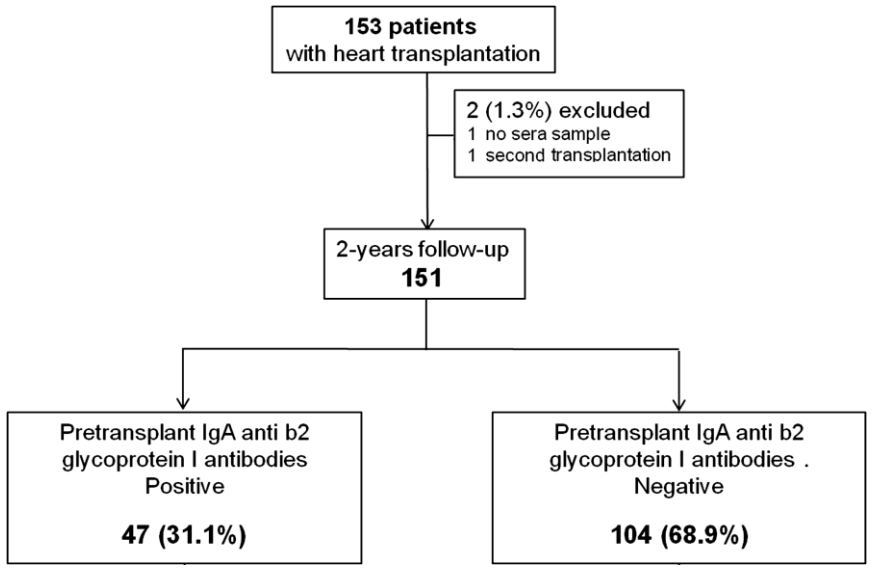


Figure 1 Algorithm of disposition and outcomes.



IgA aB2GP1 + vs -
-More risk of early death
-More thrombotic events

Mortaliy and post-transplant thrombotic events in the first trimester

Patients on Group-1 vs Group-2.

* Death causes percentage is in reference to total of deaths. ** Several patients have more than one event. OR: Odds ratio. CI: Confidence interval. NS: Non significant.

CONDITION	Total N=151		Group-1 N=47		Group-2 N=104		p	OR	95% CI OR
	N	%	N	%	N	%			
Early outcomes (first 3months)									
Patients dead	**23**	**(15.2%)**	**13**	**(27.7%)**	**10**	**(9.6%)**	**0.004**	**3.59**	**1.44 to 8.96**
Graft failure	9	[39%]*	4	(8.5%)	5	(4.8%)	N.S.	-	-
Hyperacute rejection.	1	[4%]*	0		1	(1%)	N.S.	-	-
Sneddon's syndrome like	1	[4%]*	1	(2.1%)	0		N.S.	-	-
Infection	5	[22%]*	3	(6.4%)	2	(1.9%)	N.S.	-	-
Cardiac arrest	4	[17%]*	3	(6.4%)	1	(1%)	N.S.	-	-
Cerebrovascular hemorrhage	1	[4%]*	1	(2.1%)	0		N.S.	-	-
Multiple organ failure	2	(9%)*	1	(2.1%)	1	(1%)	N.S.	-	-
Patients with thrombotic events	**17**	**(11.3%)**	**11**	**(23.4%)**	**6**	**(5.8%)**	**0.002**	**4.99**	**1.72 to 14.48**
Total thrombotic events **	20		13		7		<0.001	5.30	1.95 to 14.38
Deep venous thrombosis	2	(1.3%)	0	(0%)	2	(1.9%)	N.S.	-	-
Pulmonary embolism	2	(1.3%)	1	(2.1%)	1	(1%)	N.S.	-	-
Intracavitary thrombus	6	(4%)	6	(12.8%)	0	(0%)	<0.001	32.7	1.8 to 594
Arterial thrombus	3	(2%)	2	(4.3%)	1	(1%)	N.S.	-	-
Stroke	7	(4.6%)	4	(8.5%)	3	(2.9%)	N.S.	-	-
Mortality in 24 months	**29**	**(19.2%)**	**15**	**(31.9%)**	**14**	**(13.5%)**	**0.015**	**3.01**	**1.31 to 6.93**
Mortality from months 4 to 24	6	(4%)	2	(4.3%)	4	(3.8%)	N.S.	-	-

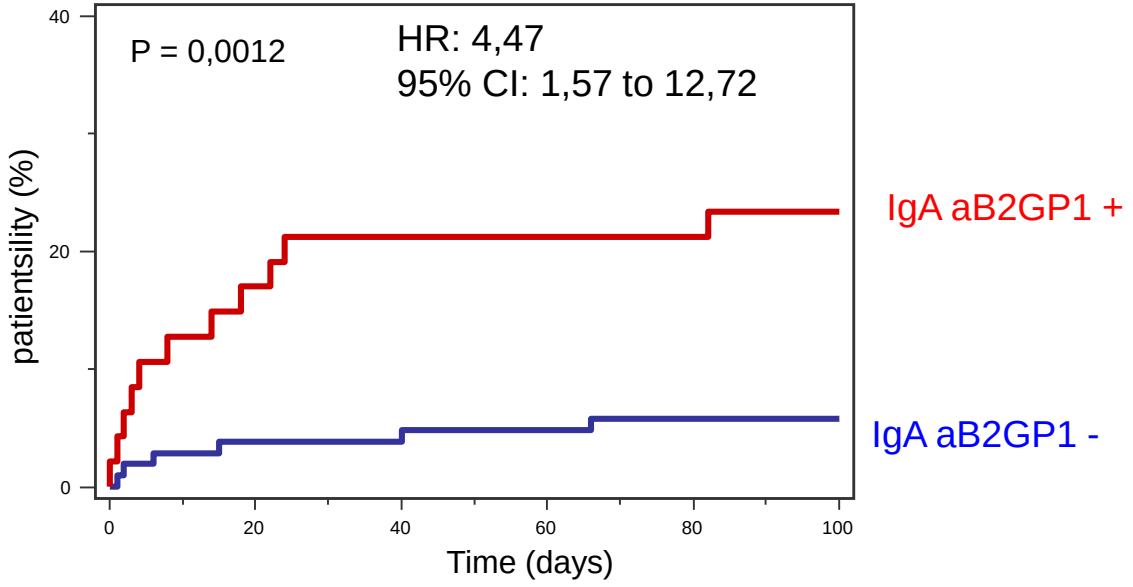
Univariate analysis for death

CONDITION	Dead N=23 (15%) N / mean	% / SE	Alive N=128 N / mean	% /SE	p
Sex (female)	**8**	**(34.8%)**	**20**	**(15.6%)**	**0.030**
Age (years)	50.4	2.6	47.8	1.6	N.S.
IgA aB2GP1ab positive	**13**	**(56.5%)**	**34**	**(26.6%)**	**0.009**
Smoking					
No smoking	11	(47.8%)	64	(50%)	N.S.
Ex smoker	5	(21.7%)	36	(28.1%)	N.S.
Active smoker	7	(30.4%)	28	(21.9%)	N.S.
Diabetes	5	(21%)	31	(24.2%)	N.S.
Renal dysfunction	5	(21.7%)	23	(18%)	N.S.
Dislipidemia	8	(34.8%)	41	(32.3%)	N.S.
Hyperuricemia	1	(4.3%)	17	(13.3%)	N.S.
Hyperbilirubinemia	9	(39.1%)	25	(19.5%)	N.S.
ALT / AST High levels	3	(13%)	34	(26.6%)	N.S.
HTA antecedents	5	(21.7%)	38	(29.7%)	N.S.
Mechanical ventilation	6	(26.1%)	16	(12.5%)	N.S.
Previous Infection	5	(22.7%)	18	(14.1%)	N.S.
Thrombotic antecedents*	1	(4.3%)	6	(4.7%)	N.S
Pulmonary embolism	1	(4.3%)	4	(3.1%)	N.S.
Deep venous thrombosis	1	(4.3%)	3	(2.3%)	N.S.
Previously anticoagulated	15	(65.2%)	69	(53.9%)	N.S.
Other vascular diseases					
Peripheral vascular disease	3	(13%)	6	(4.7%)	N.S.
Paroxysmal atrial flutter	7	(30.4%)	27	(21.1%)	N.S.
Permanent atrial flutter	7	(30.4%)	34	(26.6%)	N.S.
Trhombosis a/V	1	(4.3%)	8	(6.3%)	N.S.
Trhomboflebitis	0	(0%)	2	(1.6%)	N.S.
Etnicity Caucasian	22	(95,7%)	123	(96,1%)	N.S.
Etnicity: others	1	(4,3%)	5	(3,9%)	N.S.
Blood type					
Group 0	7	(30.4%)	61	(47.7%)	N.S.
Group A	**15**	**(65.2%)**	**48**	**(37.5%)**	**0.024**
Group B	1	(4.3%)	14	(10.9%)	N.S.
Group AB	0	(0%)	5	(3.9%)	N.S.
Rh positive	21	(91.3%)	107	(85.6%)	N.S.

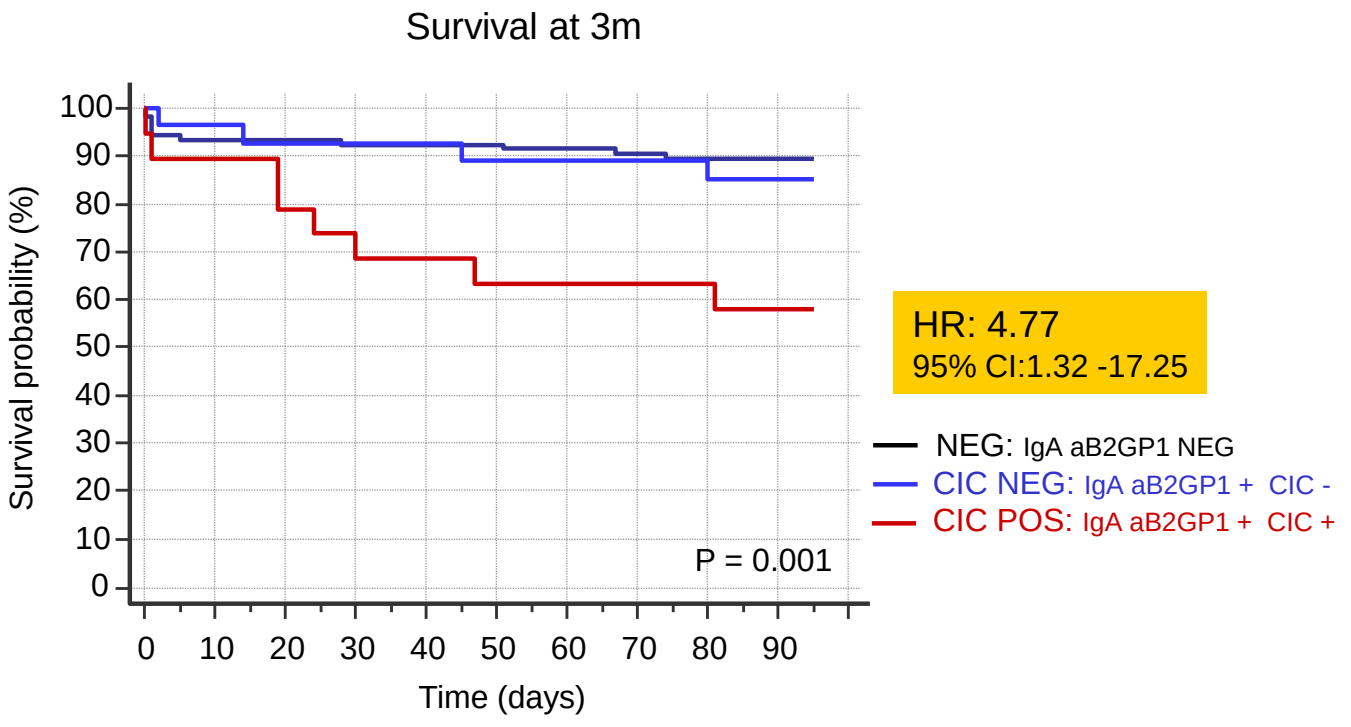
Multivariate analysis (p<0.001) of first-trimester mortality-associated factors.
Area under the ROC curve: 0.760; 95% CI: 0.684 to 0.826. CI: Confidence interval.

Variable	Univariate			Multivariate		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
IgA aB2GP1 antibodies	3.59	1.44 to 8.96	0.006	3.16	1.22 to 8.21	0.018
Blood group A	3.13	1.23 to 7.92	0.016	3.83	1.38 to 10.62	0.010
Sex (female)	2.88	1.08 to 7.69	0.035	3.52	1.17 to 10.58	0.025

Thrombotic events in the first trimester Post-transplant



Thrombotic events are concentrated in first 3 months



- Immunecomplexes IgA/B2GP1 Increases HR
- Patients negative for CIC have same mortality risk than patients negative for aPL

Statistical analysis for mortality in first 3 month

	Univariate analysis			Multivariate analysis		
	OR	95% CI OR	P	OR	95% CI OR	P
CIC IgA-B2GP1	**5.15**	1.81-14.64	0.0021	**5.81**	1.84-18.26	0.0026
blood type A	3.13	1.23-7.92	0.0163	4.16	1.47-11.71	0.0071
Sex (female)	2.88	1.08-7.69	0.0347	2.24	1.37-13.15	0.0121

CIC IgA-B2GP1 are a independent risk factor of mortality

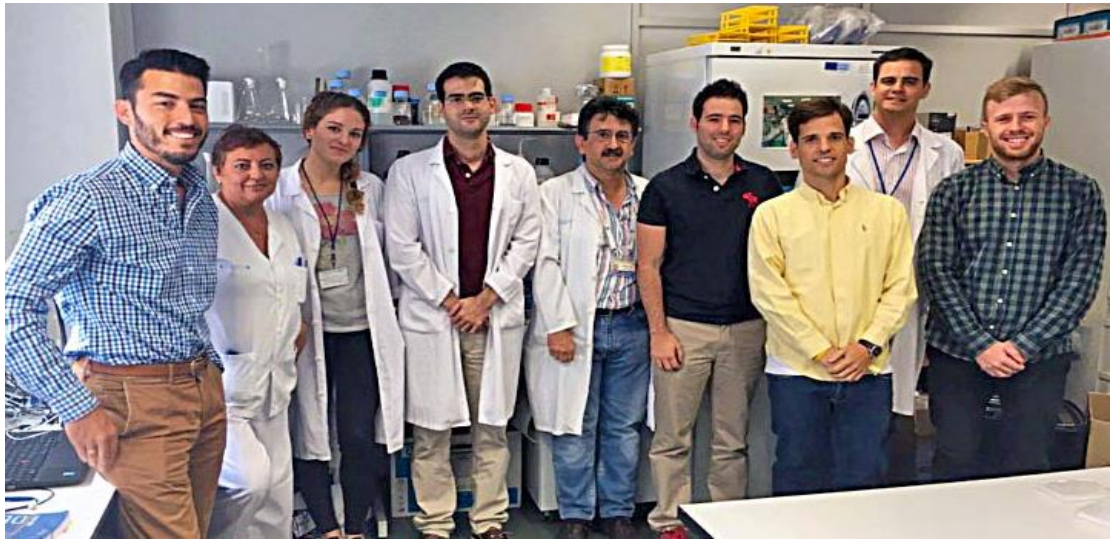
Conclusions

•Failure of organs B2GP1 producers could induce a misfolding protein that shows criptic epitopes, as origin of antibodies and immunecomplexes

•Immune complexes of B2GP1-IgA is a biomarker of acute disease, that could select better to population at real risk of thrombotic events.

•Heart transplantation implies death in most of cases, we cannot study graft thrombosis as renal transplantation.

•Limitations of study, Unicenter study, statistic associations were not too strong because of small sample, It is mandatory to develop further studies to confirm this hipothesis



Thanks for you attention

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