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Male vs Female Lupus

A comparison of ethnicity, clinical features, serology and outcome over a 30 year period.

*A. I. Renau ¹, D. A. Isenberg ²

¹Internal Medicine Unit. Hospital Universitario La Fe. Valencia. Spain

²Rheumatology Unit. Department of Medicine. University College of London Hospital (UCLH). England

Abstract

Objective

To review the differences between male and female lupus patients with respect to clinical features, serology and outcome over a thirty year period.

Material and methods

An observational study of all SLE patients seen at the University College of London Hospital between 1976 and 2005 was performed. Demographic, clinical and serological data and outcome were retrospectively collected from hospital records or questionnaires and reviewed.

Comparisons between continuous variables were made using Kruskal Wallis test. Chi-square test or Fisher's exact test were used for categorical variables when it was appropriate.

Results

484 patients (439 females and 45 males) were identified between 1976 and 2005. Their mean age at diagnosis was 29.3 years (12.6) with no significant differences between men and women. There were no significant differences between the number of men and women diagnosed at the different decades or in the mean age at diagnosis. Female gender was significantly associated with the presence of oral ulcers (29.2% vs 13.3%, $p<0.05$) and Ig M ACA (9.9% vs 0%, $p<0.05$). There were no significant differences in the comparison of other variables.

With respect to outcome, although renal failure and death were higher in females (7.7% vs 5.4% and 15.1% vs 8.1% respectively), no statistically significant differences were found. Cardiovascular disease was the commonest cause of death in men.

Conclusion

Over this thirty year follow up period, relatively few differences have emerged comparing the frequencies of clinical and serological features or outcome in male and female lupus patients.

Keywords: Systemic lupus erythematosus; Clinical features; Serology; Death; Renal Failure.

Introduction

Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease characterized by the presence of autoantibodies directed against nuclear antigens. It is, by definition, a multi-system disease, and patients present in many different ways, in terms of clinical and immunological manifestations [1]. The pathogenesis and etiology remain unclear, but multiple genetic and environmental factors are likely to play a role in its pathogenesis [2-3].

SLE is up to 10 times more common in women than men during the child bearing years [4]. An increase in frequency of SLE among females is believed to be related to the effect of endogenous sex hormones which has been discussed in several reviews [5-11]. Sex hormones have been shown to interact with the immune system, including the B cell and T cell compartment, dendritic cells and cytokine networks. It is thought that female sex hormones cause the enhanced autoimmune reactivity and contribute to the immunological perturbation that results in SLE. The female hormonal influences include supporting the survival of autoreactive B cells and modifying their maturation toward a marginal zone phenotype, while male hormones produce the opposite effects. Further evidence comes from the fact that the ratio of female to male cases is much lower in prepuberal children and after menopause, although a female predominance remains [12-14].

Since 1975 a number of articles have been published analyzing the differences between male and female SLE. In general, the results of these studies revealed that male patients develop similar typical clinical

manifestations of lupus as in females, although male SLE may have some distinguishing frequencies of organ involvement notably haematological [15, 16], neurological involvement [17, 16] or nephritis [15, 18]. Variable reports of the prognosis of lupus in males (worse or the same) compared to females have also been published [15, 19].

We were interested to review our male and female lupus patients with respect to clinical features, serology and outcome over a thirty year period. We wondered whether there might be a discernable difference over time. Thus we have divided the patients who entered the cohort into three decades, from 1976 to 1985, from 1986 to 1995 and from 1996 to 2005, and now report on our observations over this long period of time.

Material and methods

Patients

484 patients with SLE were followed up in the Centre for Rheumatology at University College of London Hospital (UCLH) and were stratified by year of lupus diagnosis in three groups (from 1976 to 1985, from 1986 to 1995, from 1996 to 2005). All patients diagnosed outside these periods, were excluded.

SLE was diagnosed when a fourth ACR diagnostic criterion (1982, revised in 1997) developed [20, 21].

Collection of clinical and serological data

Demographic, clinical and serological data were retrospectively reviewed from hospital records or questionnaires and reviewed.

We recorded clinical features and serological data as present or absent and considered them as cumulative clinical features and serological data at diagnosis respectively.

Clinically we recorded rash, photosensitivity, alopecia, oral ulcers, arthritis, serositis, nephritis, central nervous system (CNS) involvement, haemolytic anaemia, leucopenia, lymphopenia, thrombopenia, Sjögren's, antiphospholipid syndrome (APS) and myositis.

We reviewed serological data notably antinuclear antibodies (ANA) measured by indirect immunofluorescence using Hep-2 as the substrate (positive ANA at $\geq 1:80$), rheumatoid factor (RF) measured by the latex test and RAPA (agglutination assay) technique (positive RF at $\geq 1:80$), antibodies to extractable nuclear antigens (ENA), including Sm, RNP, Ro, La, measured by enzyme-linked immunosorbent assay (ELISA), anti-ds DNA measured by ELISA and indirect immunofluorescence with Crithidia Lucidae as the substrate, lupus anticoagulant (LAC) measured by Dilute Russell Viper Venom Screen (DRVVT), anticardiolipin (IgM and IgG ACA) antibodies measured by ELISA and C3 measured by laser nephelometry.

With respect to outcome, we took into account death (early death defined as <50 y and late death as ≥ 50 y) and renal failure, taking the latter to be the need for dialysis or renal transplant.

Statistical analysis

All data were analyzed using SPSS 15.0 software. Continuous variables were described as mean with standard deviation (SD) and categorical variables were described as percentages. Clinical and serological manifestations of SLE were compared between male and female lupus patients in the three periods, of diagnosis, groups. Comparisons between continuous variables were made using Kruskal Wallis test. Chi-square test or Fisher's exact test were used for categorical variables when it was appropriate. A probability level less than 0.05 in two-tailed test was used as the criterion of significance.

Results

The total cohort consisted of 484 patients diagnosed from 1976 to 2005, 45 (9.3%) males and 439 females (90.7%); the ratio of female to male was 9.7:1. The mean age at diagnosis was 29.3 years (12.6) with no significant differences between the male and female means which were 30.9 years (15.6) and 29.1 years (12.2) respectively (Fig 1a and Fig 1b).

The majority of patients (58.7%-284 patients) were Caucasian, 21.7% (105 patients) Afro-Caribbean, 11.6% (56 patients) South Asian (India, Pakistan, Bangladesh), 5.4% (26 patients) Chinese and 2.7% mixed ethnicities.

Stratifying patients by gender and race, it is noteworthy that, among the male patients, 13.3% (6 patients) were Afro-Caribbean, 17.8% (8 patients) Asian, 66.7% (30 patients) Caucasian and 2.2% (1 patient) Chinese; whereas

among the female population, 22.6% (99 patients) were Afro-Caribbean, 10.9% (48 patients) Asian, 57.9% (254 patients) Caucasian, 5.7% (25 patients) Chinese and 3% mixed ethnicities.

The ratio of female to male was different in these four groups, in Afro-Caribbeans 16.5:1, in Asians 6:1, in Caucasians 8.4:1 and in Chinese 25.3:1. However, due to the limited sample in some of the subgroups, although a trend could be observed, the differences are not statistically significant.

Analyzing the mean age at diagnosis of men and women in different races, we found significant differences between these groups with a p value of 0.004, although again, some populations were so small, that it could distort the results (Table 1).

The vast majority of patients in our lupus cohort (83.3%-403 patients) were diagnosed between ages of 15 and 49. However, 7.9% (38 patients) out of these patients developed lupus over the age of 50 and 8.9% (43 patients) under the age of 14.

Considering the male patients, 13.3% (6 patients) were diagnosed before 14 years of age, 75.6% (34 patients) between 15 and 49 years old and 11.1% (5 patients) between 50 and 79. In the female population, 8.4% (37 patients) were diagnosed before 14 years of age, 84.1% (369 patients) between 15 and 49 years old and 7.5% (33 patients) between 50 and 79.

The ratio of female to male in these three groups was different, in the young onset group (under 14 years) it was 6.14:1, in the adult onset group (15-49 years) 10.9:1 and in older onset group (over 50 years) 6.6:1. Again, no statistically significant difference between these groups was evident.

Regarding the distribution of our population in three decades, 23% (115 patients) were diagnosed between 1976 and 1985, 33.9% (164 patients) between 1986 and 1995 and 42.4% (205 patients) between 1996 and 2005.

There were no significant differences between the number of men and women diagnosed during the different decades. There were also no significant differences in the mean age at diagnosis between male and female in these three groups as seen in Table 2.

In Table 3 and 4 the cumulative clinical features and serology of the male and female patients, divided into the three decades, are shown.

Female gender was significantly associated with the presence of oral ulcers (29.2% vs 13.3%, $p < 0.05$) and Ig M anticardiolipin antibodies (ACA) (9.9% vs 0%, $p < 0.05$). There were no significant differences in the comparison of the other variables, although, interestingly, dermatological manifestations were more frequent in females, in the whole cohort and in each decade; and no man suffered from concomitant myositis. Sjögren's and APS were also more frequent in females, although no significant differences were found.

Analysing the serological data, the presence of anti-Sm antibodies was more frequent in the female group (15.3% vs 8.9%). Anti-ds DNA antibodies were observed in 71.1% of males compared to 66.7% of females, however, complement (C3) was reduced in a 37.8% and 48.7% respectively. These differences were not significant.

In the whole cohort, renal failure was higher in females (7.7% vs. 5.4%) as was death, 15.1% (10.4% early death) in females and 8.1% (2.7% early death) in males. No statistically significant difference was found (Table 5).

The causes of death were variable in the female group (cardiovascular 19%, renal 8.6%, infectious disease 27.6%, cancer 22.4% and others 22.4%) but in the male group cardiovascular disease (66.7%) and cancer (33.3%) occurred more often but were not significant different.

Renal disease as a cause of death decreased during the three decades, being responsible for 7.7% of deaths in female population between 1976 and 1985, 5% between 1986 and 1995 and 0% between 1996 and 2005.

Discussion

In the present study, we analyzed whether gender has an influence on the manifestations and outcome of SLE over 30 years (from 1976 to 2005).

There was no significant difference in the mean age at diagnosis between male and female patients, which was similar to previous studies [15, 22] although it was slightly higher in men as reported in a previous study [17]. There was no statistically significant difference in the mean age at diagnosis between male and female patients over the three separate decades. However significant differences were found in the mean age at diagnosis between male and female patients in different ethnic groups, with Afro-Caribbean and Asian patients presenting earlier compared to Caucasian patients.

In our study, the general ratio of female to male was 9.7:1; this ratio in adult onset group was 10.9:1, and decreased in younger and older onset groups (6.1:1 and 6.6:1 respectively), which is in agreement with previous studies [13, 14, 22].

Although a difference in the ratio of female to male in the different ethnic groups was observed, due to the small sample size of some of the groups, we can not draw any meaningful conclusions, as the differences were not statistically significant.

Most studies have reported a significantly higher prevalence of skin involvement in males as opposed to females [18, 23, 24]. Some studies found that discoid and/or subacute lesions were more common in male patients but malar rash was less common [16, 25, 26]. In our analysis, we did not distinguish between different types of rash and, although there was no significant difference, a trend to the presence of rash being more frequent in females was noted. Our findings are in accordance with data from other studies [15, 27, 28].

We also noted a female preponderance for photosensitivity [15, 22, 26] and alopecia [15, 22, 28, 29] as described previously, but this was not statistically significant.

The presence of oral ulcers in the present study was significantly higher in females compared to males. This result is similar to other series [22, 26, 30].

In our cohort, we did not find differences between male and female SLE patients with respect to other clinical manifestations of SLE. However, some authors have detected higher frequency of the following features in male

patients: haematological involvement [15, 16, 27, 31, 32], serositis [16, 25, 26, 33-35], neurological involvement [16, 17, 31, 36] and nephritis [15, 16, 18, 19, 23, 26, 29, 31, 32, 37-39].

In the current study, Sjogren's, APS and myositis were more prevalent among female patients although the sample is too small to establish a statistically significant difference, but, interestingly no man developed myositis compared to 3.9% of the female patients.

With respect to serological findings, some studies have reported a decreased prevalence for anti-Ro [26, 30, 40] and anti-La [26, 29] antibodies in men. In the present series we have observed this trend, but it was not statistically significant. Anti-ds DNA antibodies were found to be more prevalent among males in our cohort, consistent with other studies [16, 24, 37], but, again, there was no statistically significant difference. The remaining autoantibodies in our patients were more frequent among females, including a low C3. IgM ACA was significantly higher among female population, and this result is in agreement with the report Garcia et al [15].

In relation to outcome, we investigated the differences in mortality and renal failure (dialysis and/or renal transplant) between male and female SLE patients. Although we did not calculate comparative 5-, 10-, 15-year survival rates for males and females [41], death was observed in 15,1% of females compared to 8,1% of males (3 patients died), with no significant differences as noted in previous studies [15, 38]. Interestingly just 1 male patient (2.7%) died under than 50 years old, as compared to 10.4% in the female group although

this early death percentage has decreased over the time in agreement with other studies [42]. No men died as a result of renal disease, the causes identified in this group were cardiovascular disease (2 patients) and cancer (1 patient).

In women, the causes of death were variable. Most deaths were due to infectious disease, cancer and cardiovascular disease in that order. In contrast cardiovascular causes were the most common in men. We should highlight that renal disease as a cause of death has decreased in the female population during the time studied; from 7.7% in the first period (1976-1985) to 5% in the second period (1986-1995) and 0% in the third period (1996-2005) as previously reported [43]. The reason is likely to be the improvement in diagnosis and treatment during this time.

Despite the decrease in renal disease as a cause of death, the incidence of infections as a cause of mortality has not changed over the last 30 years as was reported in a recent review [44].

Renal failure was slightly higher in females compared to males (7.7% vs. 5.4% respectively) contrary to other studies [23, 39, 45, 46]. The percentage of renal failure in female population was lower in the third decade compared to the first (6% vs. 9.7%). In the male group just 2 patients presented with renal failure so it is not possible to compare the frequencies between the three decades.

This study has some limitations, for example we did not assess the influence of the variable duration of follow-up in the outcome because some patients moved away and the follow-up was difficult. However, the number of

lost-to-follow up is small (<20 patients) and thus unlikely to influence our results very significantly.

Conclusions

Over fifteen years ago, one of us (DAI) wrote that attempting to identify the special characteristics of the male lupus patient was rather like “trying to spot the “Loch Ness” monster [47]. Many attempts have been made but none have truly convinced all of the observers”. Based on observations over a 30 year period, in the current study this observation continues to be true. We analyzed the association of sex with clinical features and serological data. Except for oral ulcers and IgM ACA (more common in women), there were no significant difference in other common clinical and laboratory features between male and female lupus patients in each of the decades studied.

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Fig 1a. Age distribution of SLE male patients at onset.

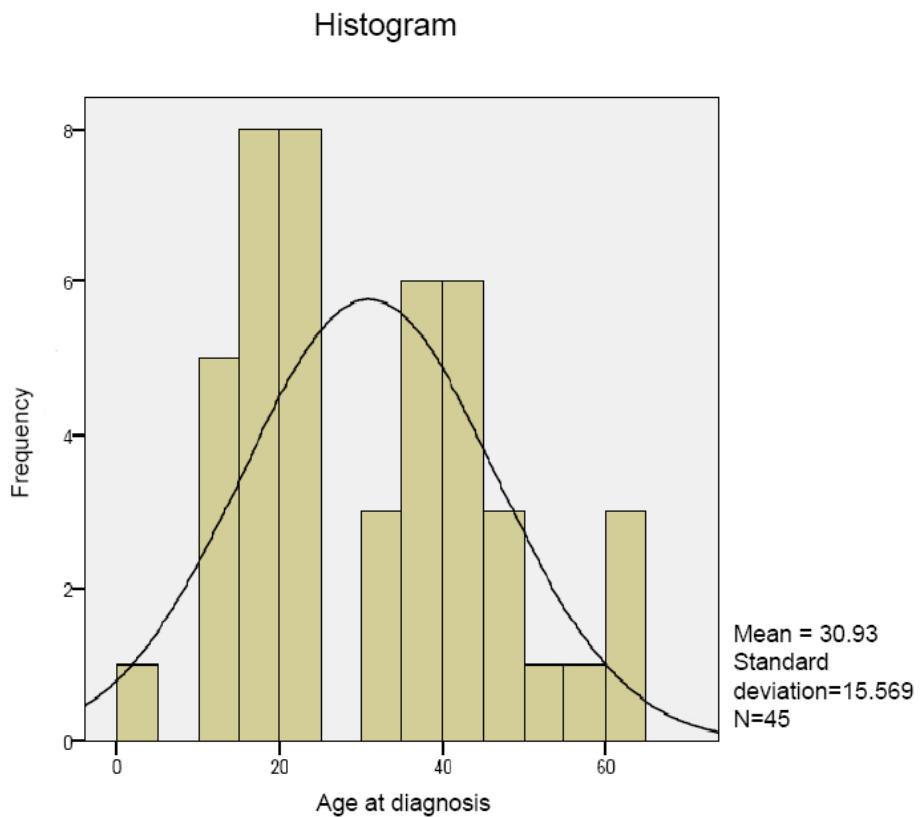


Fig 1b. Age distribution of SLE female patients at onset.

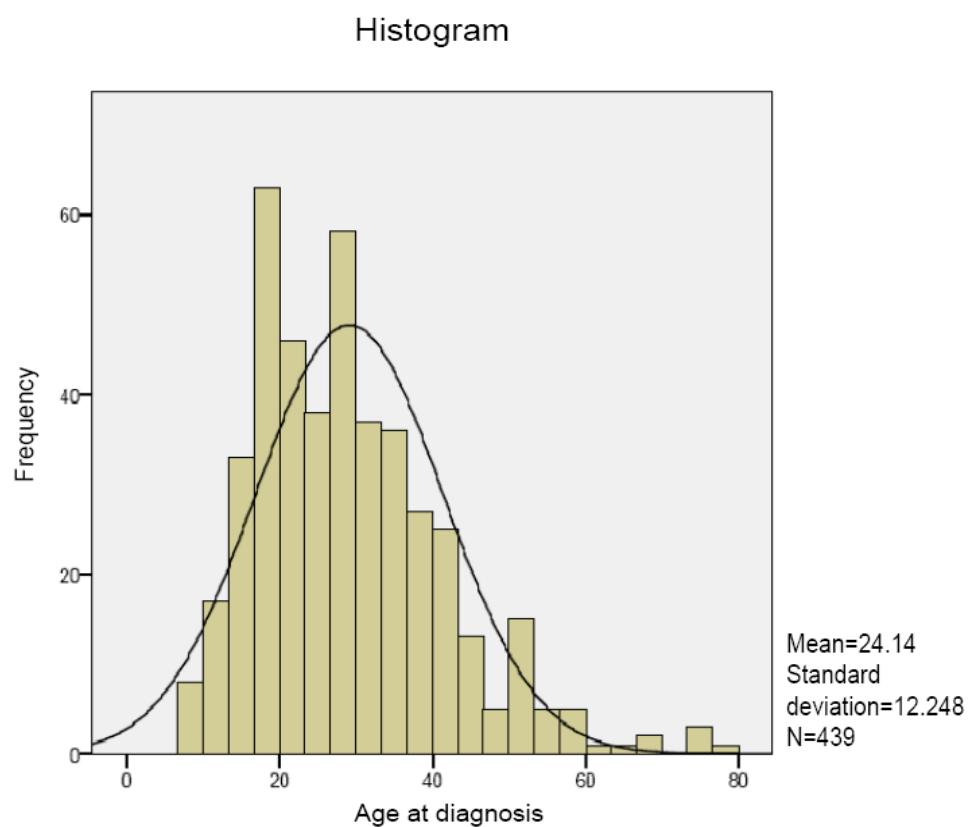


Table 1. Male and Female mean age at diagnosis in different ethnic groups.

Mean (SD)	Afro-Caribbean	Asian	Caucasian	Chinese
Male	24 (7.874)	23 (14.948)	34.13 (16.199)	40 (1 patient)
Female	28.78 (10.675)	23.94 (9.648)	30.85 (13.156)	25.8 (11.365)

Table 2. Population distribution and mean age at diagnosis depending on the decade of diagnosis.

	1976-1985			1986-1995			1996-2005		
	N	%	Mean (SD)	N	%	Mean (SD)	N	%	Mean (SD)
Male	9	7.8%	36.3(13.51)	13	7.9%	26.38(15.18)	23	11.2%	31.39(16.38)
Female	106	92.2%	30.51(10.92)	151	92.1%	28.15(11.63)	182	88.8%	29.16(13.41)
Total	115	100%	30.97(11.19)	164	100%	28.01(11.90)	205	100%	29.41(13.74)

Table 3. Cumulative clinical manifestations in different period of diagnosis: comparison between male and female patients.

	Total		1976-1985		1986-1995		1996-2005	
	Male (n=45)	Female (n=439)	Male (n=9)	Female (n=106)	Male (n=13)	Female (n=151)	Male (n=23)	Female (n=182)
Rash	29 64.4%	298 67.9%	6 66.7%	89 84%	7 53.8%	103 68.2%	16 69.6%	106 58.2%
Photosensitivity	16 35.6%	185 42.1%	5 55.6%	53 50%	5 38.5%	66 43.7%	6 26.1%	66 36.3%
Alopecia	7 15.6%	102 23.2%	0 0%	24 22.6%	2 15.4%	29 19.2%	5 21.7%	49 26.9%
Oral Ulcers	*6 13.3%	*128 29.2%	3 33.3%	38 35.8%	1 7.7%	42 27.8%	2 8.7%	48 26.4%
Artritis	42 93.3%	419 95.4%	9 100%	105 99.1%	13 100%	145 96%	20 87%	169 92.9%
Serositis	19 42.2%	180 41%	5 55.6%	60 56.6%	7 53.8%	65 43%	7 30.4%	55 30.2%
Nephritis	14 31.1%	157 35.8%	2 22.2%	33 31.1%	5 38.5%	59 39.1%	7 30.4%	65 35.7%
CNS	12 26.7%	109 24.8%	3 33.3%	36 34%	4 30.8%	29 19.2%	5 21.7%	44 24.2%
H. Anaemia	2 4.4%	20 4.6%	0 0%	5 4.7%	0 0%	6 4%	2 8.7%	9 4.9%
Leucopoenia	12 26.7%	140 31.9%	5 55.6%	51 48.1%	5 38.5%	54 35.8%	2 8.7%	35 19.2%
Lymphopenia	38 84.4%	329 74.9%	9 100%	83 78.3%	10 76.9%	113 74.8%	19 82.6%	133 73.1%
Thrombopenia	5 11.1%	72 16.4%	0 0%	26 24.5%	2 15.4%	22 14.6%	3 13%	24 13.2%
S. Jögren	3 6.7%	43 9.9%	3 33.3%	23 21.9%	0 0%	11 7.4%	0 0%	9 5%
APS	1 2.2%	29 6.6%	0 0%	16 15.1%	0 0%	9 6%	1 4.3%	4 2.2%
Myositis	0 0%	17 3.9%	0 0%	6 5.7%	0 0%	6 4%	0 0%	5 2.7%

* p<0.05

Table 4. Serological data in different period of diagnosis: comparison between male and female patients.

	Total		1976-1985		1986-1995		1996-2005	
	Male (n=45)	Female (n=439)	Male (n=9)	Female (n=106)	Male (n=13)	Female (n=151)	Male (n=23)	Female (n=182)
ANA	42 93.3%	402 93.2%	8 88.9%	96 90.6%	13 100%	144 95.4%	21 91.3%	168 92.8%
RF	10 22.7%	109 25.8%	2 22.2%	23 22.1%	4 30.8%	34 23.3%	4 18.2%	52 30.1%
Sm	4 8.9%	67 15.3%	1 11.1%	6 5.7%	0 0%	24 15.9%	3 13%	37 20.3%
RNP	9 20%	127 29%	2 22.2%	25 23.6%	3 23.1%	38 25.2%	4 17.4%	64 35.4%
Ro	14 31.1%	171 39%	2 22.2%	34 32.1%	5 38.5%	55 36.4%	7 30.4%	82 45.3%
La	5 11.1%	66 15.1%	1 11.1%	16 15.1%	2 15.4%	21 13.9%	2 8.7%	29 16%
ds DNA	32 71.1%	291 66.7%	5 55.6%	63 59.4%	10 76.9%	96 64%	17 73.9%	132 73.3%
Low C3	17 37.8%	213 48.7%	2 22.2%	38 35.8%	5 38.5%	77 51.3%	10 43.5%	98 54.1%
LAC	5 11.4%	74 17.1%	0 0%	24 22.9%	3 23.1%	21 14.1%	2 9.1%	29 16.2%
ACA IgG	9 20.5%	98 22.6%	2 22.2%	32 30.2%	2 15.4%	28 19%	5 22.7%	38 21%
ACA IgM	*0 0%	*43 9.9%	0 0%	18 17%	0 0%	15 10.2%	0 0%	10 5.5%

*p<0.05

Table 5. Outcomes in the general population and in each decade.

	Total		1976-1985		1986-1995		1996-2005	
	Male	Female	Male	Female	Male	Female	Male	Female
Renal Failure	5.4% (2p)	7.7% (30p)	0%	9.7% (9p)	10% (1p)	8.5% (11p)	5.3% (1p)	6% (10p)
Early Death (<50y)	2.7% (1p)	10.4% (40p)	12.5% (1p)	14.1% (13p)	0%	11.8% (15p)	0%	7.2% (12p)
Late Death (≥50y)	5.4% (2p)	4.7% (18p)	12.5% (1p)	14.1% (13p)	0%	3.9% (5p)	5.3% (1p)	0%