Renal and extra renal outcomes in ANCA negative and ANCA positive small vessel vasculitis

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Introduction

Background and Objective

Presence of circulating ANCA is not essential for diagnosis of pauci-immune small vessel vasculitis (SVV) and approximately 10-30% of these patients are ANCA negative.[1] A limited number of studies have looked specifically at ANCA negative patients.[2,3] In a large study of EGPA, 31% of patients were ANCA positive and 69% ANCA negative and they found that there were significantly fewer relapses in the ANCA negative patients.[4] This data would suggest that ANCA negative vasculitis are likely to have different outcomes.

Similar data from UK patients is not available therefore the aim of this study is to carry out a retrospective study on a British cohort of patients. We compared ANCA negative patients with ANCA positive patients presenting at a single tertiary renal centre in a sequential manner over a period of 13 years.

Methods

In this retrospective study, we collected data regarding demographics, ANCA status, organ involvement, cumulative cyclophosphamide doses, plasma exchange, renal and patient survival for 221 consecutively diagnosed patients with pauci-immune SVV at a single centre over a period of 13 years between 1998 to 2011.

Statistics

Between-group comparisons of quantitative outcomes were made using the Independent Samples T-Test or Mann-Whitney U Tests depending on the skewness of the distribution of the data. Categorical outcomes were compared between groups using the Fisher's Exact test.
Cox regression analysis was performed on the data comparing ANCA negative and ANCA positive and adjusting for age in terms of renal survival and also patient survival. Kaplan Meier curves were used to present renal and patient survival for ANCA positive and ANCA negative patients.
Logistic regression was used to look at survival at 3 and 12 months.

Results

Extra Renal Manifestations

There were 221 patients in total of which 165 were ANCA positive (74.7%) and 56 were ANCA negative (25.3%). A complete data set was used to make comparisons between ANCA negative and positive patients with regards to organ involvement of which there were a total of 201 patients.

Table 1: Comparison of ANCA negative and positive patients in regards to organ involvement

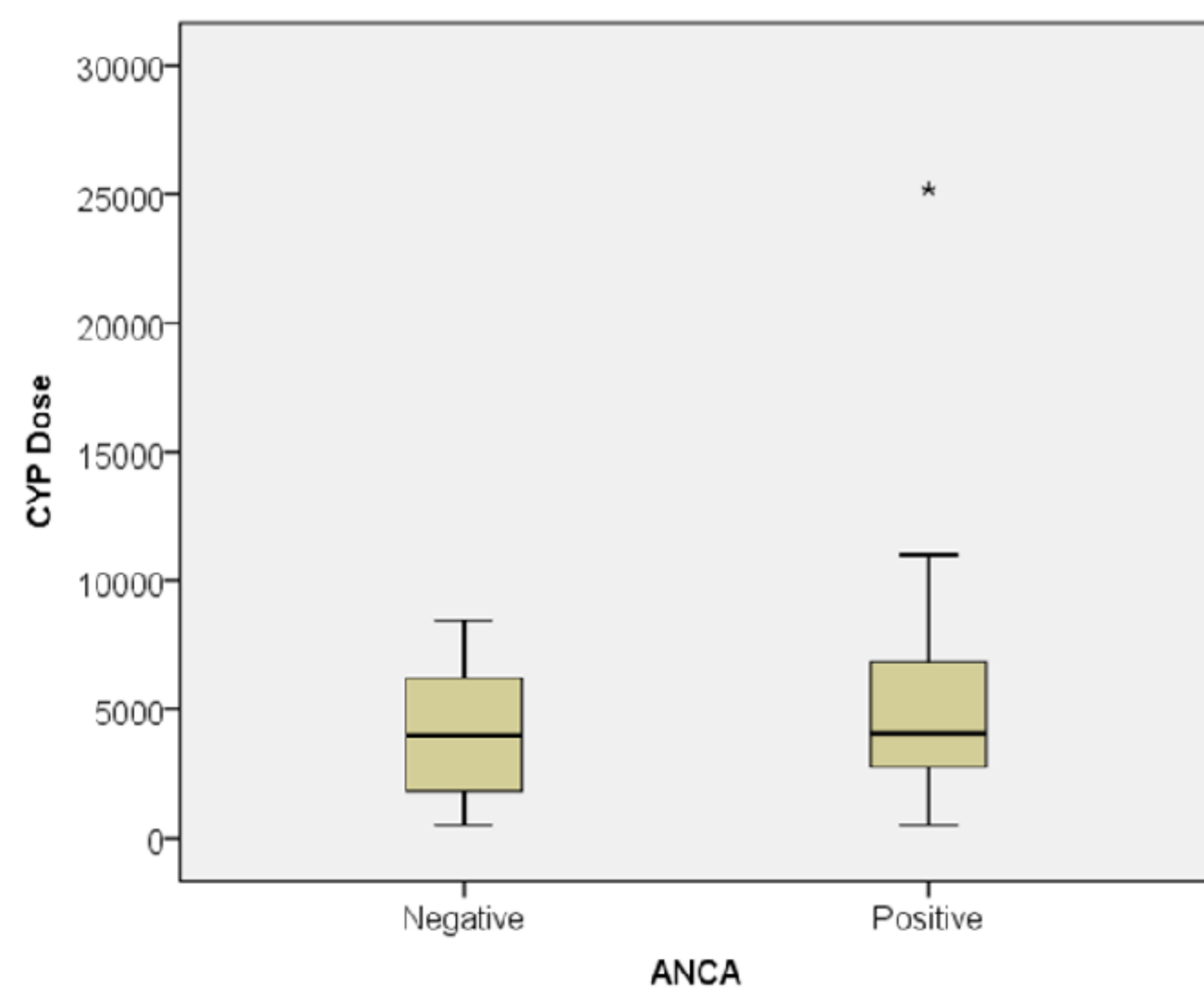| Feature	ANCA (–ve) (n=49)	ANCA (+ve) (n=152)	p
Male/female	32/17	76/76	0.071
Age of disease onset Mean (range)	51.9 (18.03, 17-85)	62.4 (14.64, 21-87)	<0.001
Renal involvement n (%)	48 (98.0%)	144 (94.7%)	0.691
Extra Renal involvement total n (%)	24 (49.0%)	89 (58.6%)	0.251
Extra renal organ threatening n (%)	12 (24.5%)	73 (48.0%)	0.004
Pulmonary involvement n (%)	6 (12.2%)	44 (28.9%)	0.022
EENT involvement n (%)	3(6.1%)	43 (28.3%)	0.001
CNS/PNS involvement n (%)	4 (8.2%)	14 (9.2%)	>0.9999
Joint involvement n (%)	7 (14.3%)	32 (21.1%)	0.406
Skin involvement n (%)	15 (30.6%)	26 (17.1%)	0.065
Constitutional symptoms n (%)	16 (32.7%)	58 (38.2%)	0.610

Extra renal organ threatening includes Pulmonary, EENT and CNS/PNS; EENT= eyes, ear nose and throat; CNS=central nervous system; PNS=peripheral nervous system; Constitutional symptoms include fatigue, malaise, aches, night sweats, weight loss, anorexia, fever.

Treatment and Relapse

Table 2: Comparison of ANCA negative and positive patients with regards to relapse, plasma exchange and cyclophosphamide dose

Feature	ANCA (-ve) (n=44)	ANCA (+ve) (n=142)	p
Relapse n (%)	5 (11.4%)	36 (25.4%)	0.061
	(n=40)	(n=125)	
Plasma exchange n (%)	10 (25.0%)	37 (29.6%)	0.689
	(n=15)	(n=64)	
CYP dose (outlier included) Median (IQR)	4000 (1750 to 6600)	4075 (2727 to 6925)	0.394
	(n=15)	(n=63)	
CYP dose (outlier excluded) Median (IQR)	4000 (1750 to 6600)	3950 (2700 to 6700)	0.441

Figure 1: Boxplots for CYP dose for ANCA positive and ANCA negative patients

Renal Survival

Data was not available regarding renal survival for two patients. Hence, renal survival was analysed on 219 patients in total, of which 56 were ANCA negative patients (25.6%) and 163 were ANCA positive patients (74.4%).
Renal survival was significantly worse in the ANCA negative patients compared with ANCA positive patients (p=0.003, Hazard ratio=2.00, 95% confidence interval = 1.28 to 3.14). Thus the estimated hazard with ANCA negative is 200% of that with ANCA positive.

Figure 2: Kaplan Meier curves of Renal Survival by ANCA status

p=0.003
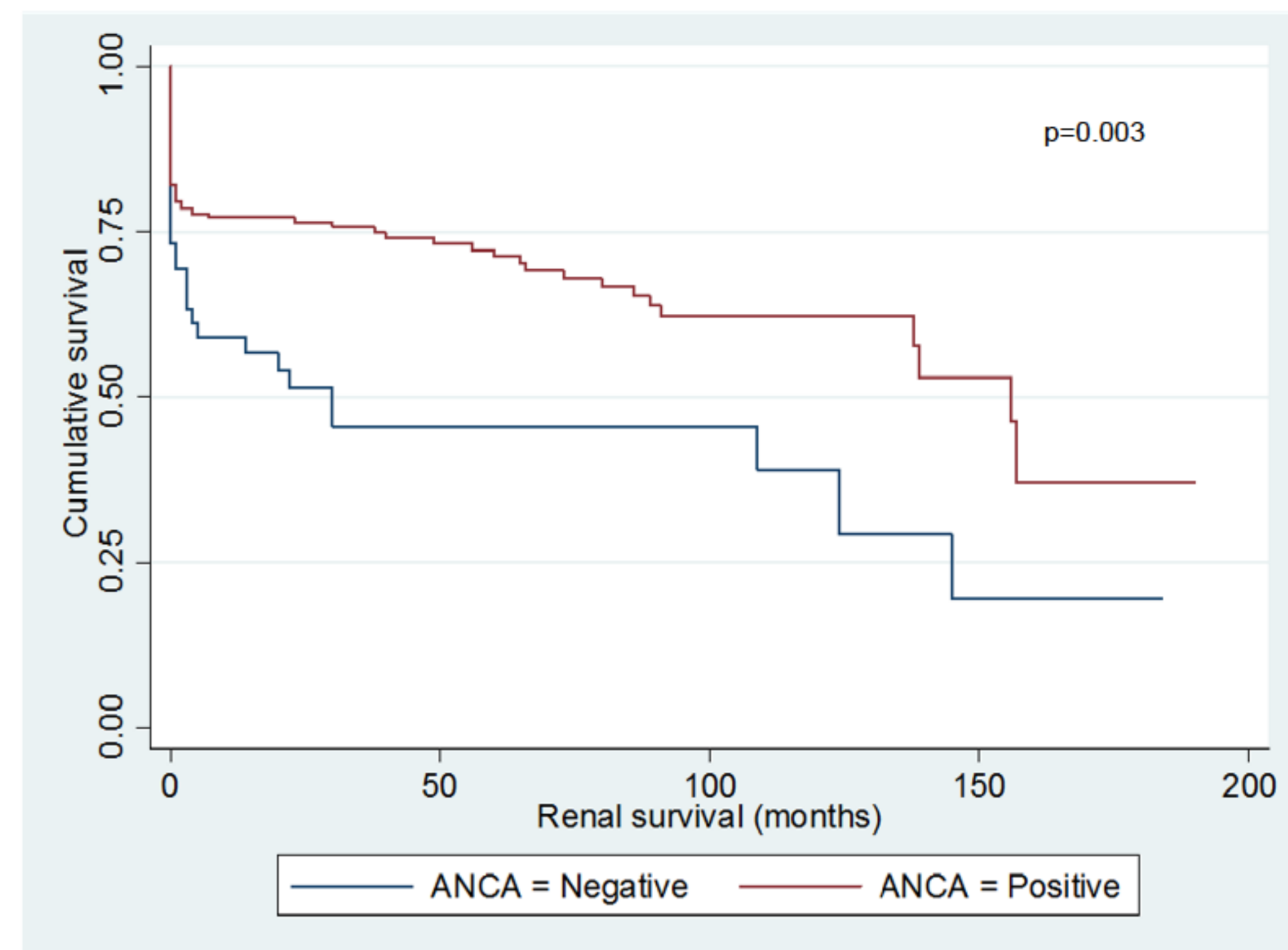
Patient Survival

Patient survival was worse in the ANCA negative patients compared with ANCA positive patients (p=0.062, Hazard ratio=1.54, 95% confidence interval = 0.98 to 2.42). Thus the estimated hazard with ANCA negative is 154% of that with ANCA positive. However, this did not reach statistical significance at the 5% level.
Patient survival was significantly worse in the ANCA negative patients compared with ANCA positive patients when adjusted for age (p=0.004, Hazard ratio=1.97, 95% confidence interval=1.24 to 3.12). Thus the estimated hazard with ANCA negative is 197% of that with ANCA positive.

Results produced from logistic regression analyses showed that ANCA negative patients appeared to have a worse survival at 3 months compared with ANCA positive patients; however this did not reach statistical significance at the 5% level (p=0.091, Odds ratio=2.303 and 95% confidence interval=0.876 to 6.056). ANCA negative patients had a significantly worse survival at 12 months compared with ANCA positive patients (p=0.003, Odds ratio=2.798, 95% confidence interval=1.411 to 5.552).

Figure 3: Kaplan Meier curves of Patient Survival by ANCA status
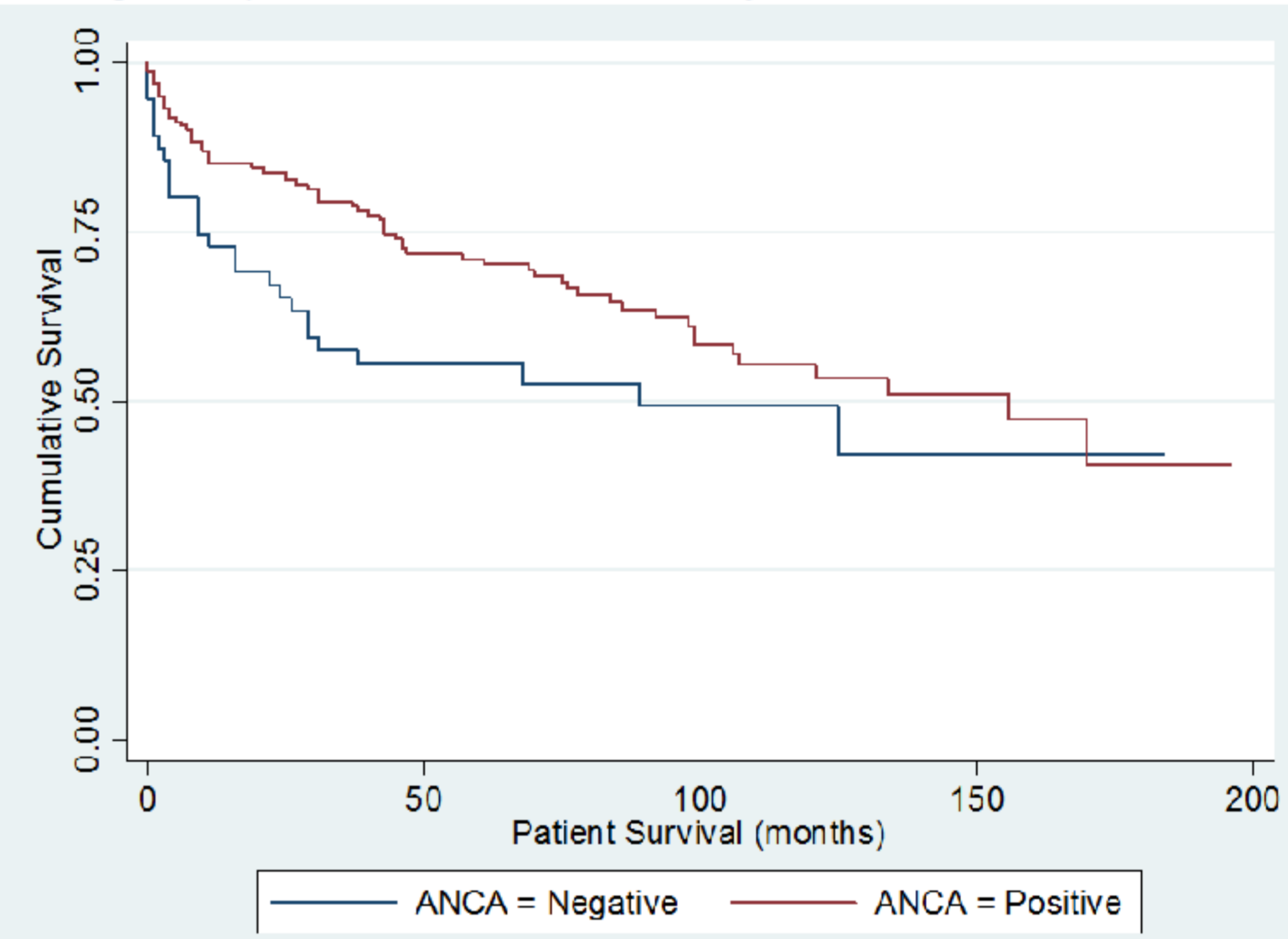
Discussion

In this study over a quarter of patients were ANCA negative which makes this set of patients a significant patient group to consider when treating pauci immune small vessel vasculitis. A strength of this study is that, to our knowledge, it is the largest study to date comparing ANCA negative and positive patients.

Comparison between ANCA positive and ANCA negative patients shows that there was no difference in cyclophosphamide dose and particularly plasma exchange therefore allowing more accurate comparison of outcomes between the two groups.

In this study we found that ANCA negative patients have significantly less extra renal involvement than ANCA positive patients, confirming the findings of Chen et al.[2]

This study found that ANCA positive patients are more likely to relapse compared to ANCA negative patients which supports what the French Vasculitis study group found.[4]

Renal survival was significantly worse for ANCA negative patients which supports what Chen et al. found.[2] This could be because they are diagnosed later due to their lack of extra renal involvement and lack of biomarker.

Although ANCA negative patients were younger, their age adjusted survival was worse compared to ANCA positive patients both at 12 months and long term. This probably reflects their poor renal function at presentation and long term. This is unlike what Chen et al. found in their Chinese study where survival was the same between the 2 groups.[2]

These findings are important because they show that ANCA negative patients have a worse survival and this needs to be discussed with the patient when the disease is being explained and the prognosis explored. More research is required for us to understand the pathogenesis of ANCA negative pauci immune small vessel vasculitis.

Limitations

1] Retrospective study.
2] Incomplete data set for patients diagnosed in the early part of the study.
3] Lack of incorporation of histology data regarding chronicity indices.
4] Data regarding treatment related adverse events was not collected.

Conclusion

ANCA negative small vessel vasculitis is common, occurring in 25% of the patients in this study.
In this retrospective study we found that ANCA negative patients compared to ANCA positive patients:

1] Are significantly younger. (p=0.001)
2] Have significantly less frequent extra renal organ involvement of major organ systems (p=0.004)
3] Have significantly worse renal survival (p=0.003)
4] Have significantly worse age adjusted patient survival (p=0.004)
5] Are less likely to have relapse (p=0.06)

These differences in the presentations and outcomes could help in managing these patients.

These significant differences between ANCA positive and ANCA negative subgroups would seem to suggest that the pathogenesis and/or disease course is different between the two subgroups.

References

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