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ORIGINAL ARTICLE

Miscellaneous

Antiphospholipid antibodies in end-stage renal disease: A systematic review and meta-analysis

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Introduction: The relationship between autoimmune hemolytic anemia and antiphospholipid antibodies (aPL) and/or antiphospholipid syndrome has never been systematically addressed.

Methods: Systematic review of EMBASE and PubMed databases performed according to PRISMA guidelines from inception to March 2020; meta-analysis performed by Peto's odds ratio for rare events.

Findings: Forty-five studies with different outcomes met the inclusion/exclusion criteria. The pooled prevalence (PP) of IgG anticardiolipin antibodies (aCL) positivity was greater in end-stage renal disease (ESRD) than controls (20.2% vs. 2.6%, $P = 0.001$, I^2 >80%; I^2 = heterogeneity), particularly in hemodialysis patients (18.3% vs. 8%, I^2 = 0%). The PP of lupus anticoagulant was greater in ESRD than controls (8.7% vs. 0.2%, $P < 0.0001$, I^2 = 0%). The standardized mean difference of IgG aCL favored ESRD rather than controls ($P < 0.0001$, I^2 =97%). The PP of fistula occlusion was greater in IgG aCL-positive patients than negative patients (39% vs. 27%, I^2 =97%); the PP of IgG aCL positivity was greater in patients with fistula occlusion than without fistula occlusion (26.9% vs. 23.2%, P = 0.01, I^2 =72%); the same applied to the PP of lupus anticoagulant positivity (23% vs. 0.3%, $P < 0.0001$, I^2 = 0%). The standardized mean difference of IgG aCL favored fistula occlusion ($P = 0.004$, $I^2 = 91\%$).

Discussion: Lupus anticoagulant relates to ESRD regardless of management whereas IgG aCL relates specifically to ESRD on hemodialysis, but only lupus anticoagulant associates with fistula occlusion. The expression of aPL as patients positive for aPL rather than as titers precludes further assumptions on the relationship.

Keywords: Antiphospholipid antibodies, end-stage renal disease, Fistula occlusion

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INTRODUCTION

The presence and persistence of antiphospholipid antibodies (aPL) detected via immune or clotting assays in association with vascular occlusions in either arterial or venous districts characterize the antiphospholipid syndrome (APS). APS may occur in autoimmune disease, the so-called "secondary APS," or in systemic lupus erythematosus ("lupus-related APS") but may present in isolation as "primary APS."[1] While renal artery stenosis and thrombosis, renal infarction, renal vein thrombosis, and chronic nephropathy are recognized features of kidney involvement in the APS,[2] the role of aPL in chronic kidney disease, especially in end-stage renal disease (ESRD) patients, whether on hemodialysis or not, is less clear given the varying types of studies performed, the different aPL measured and the different endpoints employed. We performed this systematic review and meta-analysis to evaluate the frequency of aPL in patients with chronic renal disease and their potential association with fistula occlusion outside the setting of systemic lupus erythematosus.

SEARCH STRATEGY AND SELECTION CRITERIA

We carried out a systematic review according to the PRISMA guidelines[3] by searching the electronic databases MEDLINE and EMBASE from inception to June 2019; we used the terms "hemodialysis" OR "end-stage renal disease" OR "uremia" OR "chronic renal disease" and "anticardiolipin" OR "anti-beta 2-glycoprotein-I" OR "antiphospholipid" OR "lupus anticoagulant" (LA) OR "lupus inhibitor" for the search strategy. We also used the same search terms to screen Open Gray. The search yielded 995 records from MEDLINE and EMBASE but none from Open Gray: they were processed according to the flow diagram in Figure S1. In a preliminary screening process, we noted that adding the term arterovenous fistula occlusion restricted the search yield by around 25% and led to the omission of a few articles containing relevant data, so we performed the searches without this term.

Criteria for selecting articles

Three investigators (P. R. J. A., T. B., and F. G.) screened all the retrieved papers for relevancy. Inclusion criteria were: (1) observational studies (retrospective, prospective, case–control, cross-sectional, and/or cohort) investigating: (a) the difference in the prevalence or titers of aPL between patients with ESRD and control groups; (b) the difference in the prevalence or titers of aPL between patients with and without fistula occlusion; (c) the difference in the prevalence of fistula occlusion in patients positive or negative for aPL; (2) aPL measured by immune or clotting assays; (3) articles written in English, French, and Spanish. If more than two studies investigated the same population, the latest or highest-quality study was chosen. Exclusion criteria were: (1) prevalence studies only; (2) studies investigating systemic lupus erythematosus; (3) nonoriginal research (review articles, case studies); (4) studies not reporting the relationship between aPL and ESRD; (5) articles not written in the languages indicated in the inclusion criteria.

EVALUATION OF THE QUALITY OF THE STUDIES

The quality of the studies identified was assessed by the Newcastle Ottawa Quality Assessment Scale for case–control and cohort studies specifically developed to assess the quality of observational studies; the studies included in the meta-analysis are simply comparing two different groups because they had no real exposure to qualify as true case–control, and the same applies to the ESRD cohorts, with or without aPL.[4] The scale covers three major domains (selection of cases and controls, comparability of groups, and ascertainment of either the exposure or the outcome of interest) and the resulting score may range between 0 and 8, a higher score representing a better methodological quality. Data were independently extracted into a standard electronic form, averaged, and any discrepancies were resolved by consensus.

Outcome measures

The primary outcomes were: (1) the comparative pooled prevalence (PP) of aPL in ESRD participants and controls; (2) the comparative PP of aPL in ESRD participants with and without fistula occlusion; (3) the standardized mean difference of aPL titers between the groups indicated in number one and two; (4) the comparative PP of fistula occlusion on ESRD patients with and without aPL. The secondary outcomes were: (1) the comparative PP of aPL of ESRD patients on different types of hemodialysis; (2) the comparative PP of aPL of ESRD patients using different types of dialysis membranes.

Statistical analysis

We employed random effects meta-analyses for categorical and continuous outcomes because the estimates derived from observational studies and not from planned experiments. Peto's odds ratio explored the effect size between groups as it is the appropriate statistical method for rare events.[5] Subgroup analyses were based on clinical judgment. Statistical heterogeneity was estimated by I^2 statistics: an I^2 value of 0% indicated no heterogeneity; values less than 25% indicate low, between 25% and 50% moderate and over 50% high heterogeneity. Examination of the funnel plot generated by 15 studies (Figure S2) having similar outcomes revealed a minor degree of publication bias due to imprecise study effect,[6] but we did not rely on this result, as funnel plots may yield fallacious results when performed on a small number of studies.[7,8] The statistical analysis was carried out using Comprehensive Meta-Analysis, Biostat (Englewood, NJ); Cohen's kappa assessed the inter-rater agreement of two investigators.

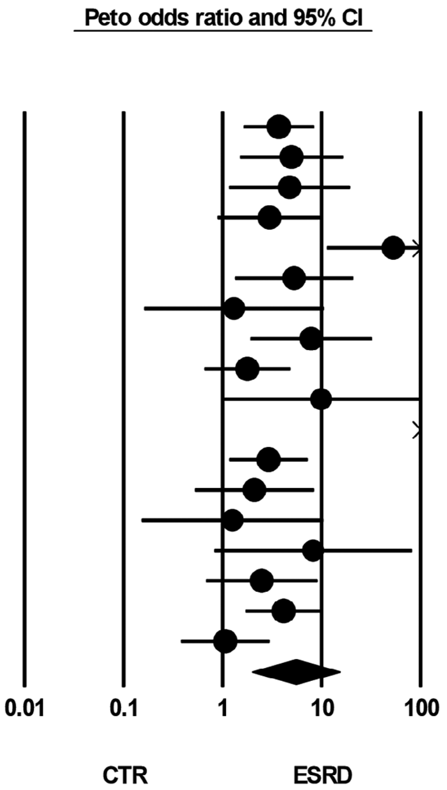
RESULTS

Number and quality of the studies

After completion of the screening and exclusion process (Figure 1), we identified 45 articles exploring the relationship between aPL and ESRD[9-53] (Table 1). A Newcastle–Ottawa quality assessment score (NOQAS) ≥7 defined a good study and only two studies had low score at 4; reasons for achieving lower scores were failure to show the ages and sex of the patients and controls, poor documentation of inclusion/exclusion criteria, limited comparability, and failure to describe average titers of aPL. The inter-rater reliability agreement (Cohen's kappa) of the two investigators (T. B. and P. R. J. A.) for NOQAS was 0.76 (95% confidence interval = 0.643–0.884).

IgG anticardiolipin antibodies in end stage renal disease and controls

Study name	Statistics for each study				
	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Gronhagen-Riska	3.707	1.642	8.371	3.153	0.002
Garcia-Martin 1991	4.981	1.504	16.495	2.628	0.009
Matsuda 1993	4.753	1.167	19.352	2.176	0.030
Sitter 1993	2.982	0.891	9.977	1.773	0.076
Sallam 1994	53.108	11.357	248.336	5.048	0.000
Oymack 1995	5.280	1.340	20.810	2.378	0.017
Ferlazzo 1998	1.304	0.162	10.497	0.250	0.803
Fabrizi 1999	7.864	1.918	32.237	2.865	0.004
Palomo 2002	1.782	0.657	4.836	1.134	0.257
Nampoory 2003	9.905	1.001	97.971	1.961	0.050
Molino 2004	1710.335	734.290	3983.773	17.256	0.000
Gengiz 2004	2.914	1.177	7.213	2.312	0.021
Antoniadi 2005	2.098	0.527	8.361	1.051	0.293
El Yazeed 2006	1.261	0.153	10.412	0.215	0.829
Skouri 2006	8.227	0.830	81.554	1.801	0.072
Ukar 2008	2.486	0.684	9.031	1.384	0.166
Sfar 2009	4.145	1.713	10.026	3.155	0.002
Ghisdal 2011	1.065	0.381	2.979	0.121	0.904
	5.497	1.994	15.152	3.294	0.001



Overall: I squared 91% p<0.0001

Figure 1 Forest plot showing effect size of IgG anticardiolipin antibodies from end stage renal disease (ESRD) patients relative to controls (CTR).

Table 1 demographics of the studies included in the meta-analysis

		End-stage renal disease														Controls							
						Hemodialysis −ve				Hemodialysis +VE													
								aCL					aCL							aCL			
		SLE		Age	M/F		LA	IgG	IgM		Duration	LA	IgG	IgM	FO	Nr	Age	M/F	LA	IgG	IgM	FO	NOS
Articles	Study type	No	No	Months	No	No	No	No	No		Months	No	No	No			Months		No	No	No		
Quereda et al.[9]	CC/CHT	0	100	46 (18/71)	60/40	44	5			56	42 ± 31	17				50			0				5
Grönhagen-Riska et al.[10]	CC/CHT	6	146	48 (13–76)						146	37 (0–252)		34			53				2			4
García-Martín et al.[11]	CC/CHT	0	73	54 ± 15	35/42	22	3	4		51	51 ± 34	11	16		6	20	44 ± 8	12/8	0	0			4
Chew et al.[12]	CHT/ABS	0	60	61 (29/84)	39/21					60	44 (−286)	4	6										4
Matsuda et al.[13]	CC	0	59	30–53	30/29	20	3	0		39	12–120	13	12			20	30–50	10/10	0	0			5
Philips et al.[14]	CC	2	42	49 (25/17)	25/17					42	60 ± 48		2	7		30	45(23–62)			0	0		5
Sitter et al.[15]	CC	0	73	25–86	26/47	19		1		54			9			50				2			6
Sallam et al.[16]	CC/RTS	0	48	12 ± 3.3	27/21					48	20 ± 17		42	30		10	12 ± 3.3			1	0		5
Brunet et al.[17]	CHT	0	97	58 ± 15	58/39					97	84 ± 75	16	15										6
Oymack et al.[18]	CC	0	45	40	27/18					45	46		8		1	43	39	25/18		1			4
Prakash et al.[19]	CHT/RTS	2	74	51 (22–80)	36/38					74	69 (8–215)				28								5
Petersen et al.[20]	CHT/RTS	5	86	56 (24–79)	32/54					86				3									6
Ferlazzo et al.[21]	CC/CHT PSP	2	61	60 (19–80)	36/25					61	44 (3–240)		4			20	46			1			5
George et al.[22]	CC	0	81	61 ± 16	53/28					81	66 ± 56					100							5
Ozdemir et al.[23]	CHT/RTS	0	104	44 ± 16	49/55					104	36 ± 28		21	4	19								4
Le Sar et al.[24]	CHT/ABS	0	34	61	12/22					34	28	6	7										6
Valeri et al.[25]	CHT/ABS	6	230	55 (9–88)	104/126					230	55 (9–88)		67	10									6
Fabrizi et al.[26]	CC/CHT/RTS	0	180	57 ± 14	76/104					101	32 ± 10	4				100	50 ± 13	56/44	0				4
Haviv et al.[27]	CC/CHT	0	73	56 ± 8.6	38/35	19		2	3	54	77		21	8									7
Palomo et al.[28]	CC	0	208	53 ± 18	112/96					208	35 ± 29		14			110				4			6
Jamshid et al.[29]	CHT/PSP	0	218	52 ± 16	145/73					218/171	29 ± 22		97										7
Nampoory et al.[30]	CC/PSP	0	82	44 ± 17	31/51					82	39 ± 27	4	3			104		42/64	0	0			6
Molino et al.[31]	CC		40	52 ± 9	22/18					40	24–36					400							4
Gengiz et al.[32]	CC/RTS	0	48	42 ± 4	24/19	29										30	41 ± 4	17/13					6

Table 1 Continued

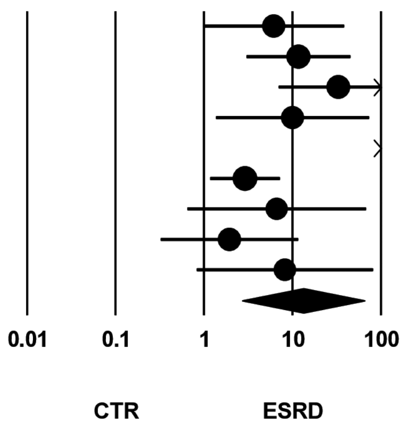
			End-stage renal disease														Controls						
						Hemodialysis −ve				Hemodialysis +VE													
								aCL					aCL							aCL			
		SLE		Age	M/F		LA	IgG	IgM		Duration	LA	IgG	IgM	FO	Nr	Age	M/F	LA	IgG	IgM	FO	NOS
Articles	Study type	No	No	Months	No	No	No	No	No		Months	No	No	No			Months		No	No	No		
Gultekin et al.[33]	CC	0	100			20		0	0	80			2	1									4
Chuang et al.[34]	CHT/RTS	13	483	64 ± 15	102/46					483	62 ± 71			84	32	0					399	152	5
Chuang et al.[35]	CHT /RTS	13	483	57	194/ 289			105		483	68 ± 1.5		105										5
Antoniadi et al.[36]	CHT/PSP	0	27	58 ± 13	14/13					27	>6		7	3		22				3	0		4
Yazeed et al.[37]	CC/CHT/RTS	0	40	50 ± 12	19/21					40	41 ± 21	8	5	8		10	55 ± 10	5/5	1	1	0		4
Roozdeh et al.[38]	CHT/PSP	0	171	53 ± 15	116/55					171	25 ± 21		97		31								5
Lee et al.[39]	CC/CHT/PSP	1	98	58 ± 12	29/69					98	>6		28										5
Skouri et al.[40]	CC	0	38	10 ± 3	20/18					38		2	3	3		40			0	0	0		5
Fernandez et al.[41]	CHT/RTS	0	63	48 ± 15	43/20	31	0			32		4											5
Serati et al.[42]	CHT/PSP	0	118	54 ± 14	80/38					118	26 ± 23		68										6
Danis et al.[43]	CHT	0	116	45 ± 16	51/65					116			8	8									5
Ucar et al.[44]	CHT		158							158			15			38				1			4
Sfar et al.[45]	CC HCV + ve		200	49 (13–80)	90/120					200			23			100				1			4
Ozmen et al.[46]	CHT HCV + ve	0	103	53.1 ± 15.5	53/50					103	68.5 ± 35		15										4
Ghisdal et al.[47]	CHT/RTS	0	310			21	3	5		248		96	61										6
Serrrano et al.[48]	CHT/PSP	0	124	64 ± 15	82/42					124	37				10							6	7
Hadhri et al.[49]	CC/PSP	0	101	51.1 ± 13.4	63/38					101													6
Salmela et al.[50]	CHT/PSP	0	219	57 (16–83)	146/73																		7
Bataille et al.[51]	CHT/RTS	1	192	70	107/85					192	48 (19–99)		29	32									5
Broder et al.[52]	CHT/RTS	0	64	55 (38, 65)	29/35																	16	6
Fadel et al.[53]	CHT/PSP	0	55	9 ± 6	25/30					55						20	10 ± 8.8	12/8					5

ABS = ambispective; aCL = anticardiolipin antobodies; CC = case–control; CHT = cohort; HCV = hepatitis C virus; FO = fistula occlusion; LA = lupus anticoagulant; No = number; NOS = Newcastle–Ottawa Scoring; PSP = prospective; RTS = retrospective; SLE = systemic lupus erythematosus; +ve = positive; −ve = negative.

IgM anticardiolipin antibodies in end stage renal disease and controls

Study name	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Philips 1993	6.151	0.987	38.354	1.945	0.052
Sallam 1994	11.703	3.029	45.215	3.567	0.000
Fabrizi 1999	33.050	7.016	155.686	4.424	0.000
Nampoory 2003	10.031	1.371	73.384	2.271	0.023
Molino 2004	1183.705	382.252	3665.535	12.270	0.000
Gengiz 2004	2.914	1.177	7.213	2.312	0.021
Antoniadi 2005	6.644	0.650	67.877	1.597	0.110
El Yazeed 2006	1.942	0.326	11.583	0.729	0.466
Skouri 2006	8.227	0.830	81.554	1.801	0.072
	13.260	2.700	65.126	3.183	0.001

Peto odds ratio and 95% CI



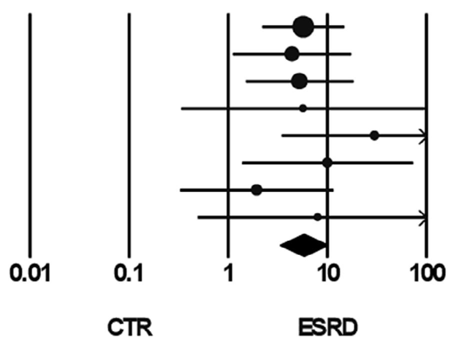
Overall: I squared 89% p<0.0001

Figure 2 Forest plots showing the effect size of IgM anticardiolipin from end-stage renal disease (ESRD) patients relative to controls (CTR).

Lupus anticoagulant in end stage renal disease and in controls

Study name	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Quereda 1988	5.732	2.203	14.917	3.578	0.000
Garcia-Martin 1991	4.409	1.114	17.452	2.113	0.035
Matsuda 1993	5.248	1.498	18.387	2.591	0.010
Philips 1993	5.690	0.335	96.535	1.204	0.229
Fabrizi 1999	29.885	3.446	259.141	3.083	0.002
Nampoory 2003	10.031	1.371	73.384	2.271	0.023
El Yazeed 2006	1.942	0.326	11.583	0.729	0.466
Skouri 2006	8.002	0.491	130.391	1.460	0.144
	5.737	3.306	9.956	6.212	0.000

Peto odds ratio and 95%CI

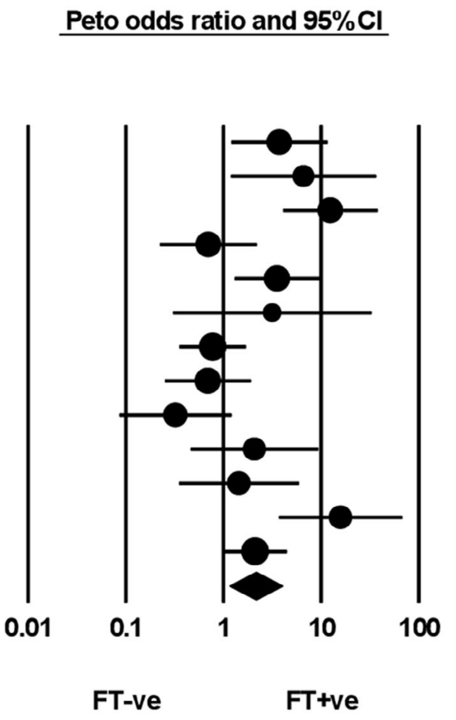


Overall: I squared 0%, p=0.7

Figure 3 Forest plots showing the effect size of lupus anticoagulant from end-stage renal disease (ESRD) patients relative to controls (CTR).

IgG anticardiolipin antibody in haemodialysis patients with and without fistula thrombosis

Study name	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study				
Prakash 1995	3.742	1.205	11.625	2.282	0.022
LeSat	6.612	1.191	36.695	2.160	0.031
Haviv 2000	12.439	4.092	37.814	4.444	0.000
Palomo 2002	0.701	0.223	2.205	-0.607	0.544
Molin0 2004	3.546	1.304	9.646	2.480	0.013
Guktekin 2005	3.163	0.304	32.866	0.964	0.335
Roozbeh 2006	0.777	0.355	1.699	-0.633	0.527
Serati 2007	0.694	0.252	1.907	-0.708	0.479
Ozmen 2008	0.323	0.087	1.209	-1.678	0.093
Danis 2008	2.078	0.462	9.354	0.953	0.341
Hadhri 2013	1.442	0.351	5.927	0.507	0.612
Salmela 2013	15.789	3.684	67.673	3.716	0.000
Bataille 2015	2.114	1.000	4.467	1.961	0.050
	2.143	1.155	3.977	2.417	0.016



Overall I squared 72% $p<0.0001$

Figure 4 Forest plot showing the effect size of IgG anticardiolipin antibodies in end-stage renal disease (ESRD) patients with and without fistula thrombosis (FT).

Clinical definitions

Fistula occlusion

The diagnosis of fistula occlusion varied across studies: (1) inability to use the fistula for more than one dialysis session[9,43,46]; (2) palpation and auscultation[28,29,34,35,38,42,46,49,53]; (3) duplex scanning[38,50,53]; (4) fistulography[12,28,34,35,50]; the remaining studies did not include a diagnostic method for fistula occlusion.

Type of dialysis membranes employed

Twenty-six articles reported the type of dialysis membrane employed. Eleven groups used bioincompatible membranes only (cuprophane)[12,14,15,18,19,20,23,25,28,29,36] though three used undisclosed membranes alongside cuprophane[12,15,29]; six groups used biocompatible membranes[40,43,44,46,49,53] and nine groups used a mix of bioincompatible and biocompatible membranes.[17,21,26,27,34,35,38,39,42]

Expression of aPL positivity

Positivity for anticardiolipin antibodies (aCL) was reported as the frequency of positive participants in 24 studies,[9,12,17,20,21,24,25,28,29,33–35,39–43,45–52] in numerical format in 7 studies[22,23,32,36,37,44,53] and 4 studies[10,11,13–16,18,19,26,27,30,31,36,38] employed both formats. Three studies expressed aCL in optical densities[13,22,32]: the average IgG aCL of patients from the above studies ranged from 5.67 ± 1.4 to 25.7 ± 10 GPL. The demographics of each study are shown in Table 1. Only few studies measured IgG/IgM anti beta-2-glycoprotein-I and anti-prothrombin antibodies[31,48,49,51] and the data were not evaluable in the meta-analysis.

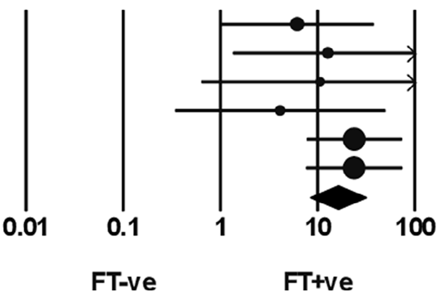
Comparative PP of aCL positivity in ESRD and in controls

We first compared the pooled frequency of positivity for different aCL between ESRD and controls. Eighteen

Lupus anticoagulant in haemodialysis patients with and without fistula thrombosis

Study name	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
LeSat	6.181	1.004	38.059	1.964	0.050
Nampoori 2003	12.784	1.342	121.765	2.216	0.027
Molino 2004	10.672	0.635	179.235	1.645	0.100
Fernandez 2007	4.125	0.341	49.972	1.114	0.265
Hadhri 2013	23.905	7.702	74.197	5.493	0.000
Bataille 2015	23.797	7.560	74.906	5.418	0.000
	16.098	8.356	31.011	8.306	0.000

Peto odds ratio and 95%CI



Overall: I squared 0%, p=0.6

Figure 5 Forest plot showing the effect size of lupus anticoagulant in end-stage renal disease (ESRD) patients with and without fistula thrombosis (FT).

articles (14 dealing with hemodialysis alone and 4 with hemodialysis plus conservatively managed ESRD), comprising 1709 patients and 1221 controls compared the frequency of IgG aCL: the PP of IgG aCL positivity was greater in ESRD than in (25.6% vs. 2.6%), with high heterogeneity (I^2 = 91%, $P < 0.0001$) (Figure 1). Nine articles (all dealing with hemodialysis), comprising 438 patients and 746 controls compared the frequency of IgM aCL; the PP of IgM aCL was greater in ESRD than in controls (26% vs. 1.4%), with high heterogeneity (I^2 = 89.7%, $P < 0.0001$) (Figure 2). Eight articles (5 on hemodialysis and 3 on hemodialysis plus conservatively managed ESRD) comprising 822 patients and 484 controls, compared the frequency of LA; the PP of LA was greater in ESRD than in controls (8.7% vs. 0.2%), with no heterogeneity (Figure 3).

Comparative pooled aCL averages in ESRD and in controls

We then compared the pooled averages of aCL between ESRD and controls. Average IgG aCL titers from 10 studies (8 dealing with hemodialysis alone, 2 pediatric studies, and 1 dealing with hemodialysis plus conservatively managed ESRD), comprising 714 ESRD patients and 750 controls, were pooled for the effect size of this outcome: random effect meta-analysis revealed wide heterogeneity (I^2 = 97%, $P < 0.0001$), invalidating the pooled estimate (Figure S3). Subgroup analysis, excluding the two pediatric studies, changed neither heterogeneity nor the pooled estimate (graph not shown). Average IgM aCL titers from eight studies (all dealing with hemodialysis alone, two pediatric studies), comprising 570 ESRD patients and 704 controls, were pooled for the effect size of this outcome: random effect meta-analysis revealed wide heterogeneity (I^2 = 99%, $P < 0.0001$), invalidating the pool estimate (Figure S4). Subgroup analysis excluding the two pediatric studies and by type of dialysis membrane changed neither heterogeneity nor the pooled estimate (graphs not shown).

Comparative PP of aPL positivity in conservatively and hemodialyis-managed ESRD

Seven studies compared the prevalence of IgG aCL from 742 patients managed with hemodialysis and from 149 managed conservatively for the effect size of this outcome: the PP of IgG aCL was greater in the former than in the latter patients (18.3% vs. 8%), with no heterogeneity (Figure S5). Six studies compared the prevalence of LA from 426 hemodialysis managed with and from 138 conservatively managed patients for the effect size of this outcome: the PP of LA was greater in the former than in the latter patients (33% vs. 10.1%), with low heterogeneity (I^2 = 19%, P = 0.28; Figure S6).

Comparative PP of aCL positivity by dialysis type and membrane

Three studies compared aCL (2 on IgG and 1 on IgM) in 59 patients on continuous ambulatory peritoneal dialysis and 259 on hemodialysis: the PP of aCL was similar in the two groups (8.4% vs. 8.9%), with moderate heterogeneity (I^2 = 55%, P = 0.1; Figure S7). Three studies compared aCL (2 on IgG and 1 on IgM in 69 patients dialyzed with cuprophane and 102 with other membranes: the PP of aCL was similar in the 2 groups (21.7% vs. 16.6%), with low heterogeneity (I^2 = 0%, P = 0.7; Figure S8).

Comparative PP of fistula occlusion in hemodialysis patients positive and negative for aPL

Eleven articles comprising 384 IgG aCL-positive and 994 IgG aCL-negative hemodialysis patents evaluated the retrospective relationship between IgG aCL and fistula occlusion but one article reported no fistula occlusion in either group[14]; the PP of fistula occlusion was greater in IgG aCL-positive patients than negative patients (39% vs. 27%), with high heterogeneity (I^2 = 97%, $P < 0.0001$) that invalidated the pooled estimate (Figure S9). Exclusion of a pediatric study[16] improved the effect size (P = 0.001), with a modest decrease in heterogeneity (I^2 = 65%, P = 0.003) (graph not shown). Three articles, comprising 168 IgG aCL-positive and 294 IgG aCL-negative hemodialysis patients, evaluated the prospective relationship between IgG aCL and fistula occlusion; the PP of fistula occlusion was similar between aPL-positive and aPL-negative patients (36.3% vs. 31.9%), with moderate heterogeneity (I^2 = 55%, P = 0.1; Figure S10). Four articles, comprising 32 LA-positive and 290 LA-negative hemodialysis patients, evaluated the retrospective relationship between LA and fistula occlusion; the PP of fistula occlusion was similar between LA-positive and LA-negative patients (46.8% vs. 34.4%), with moderate heterogeneity (I^2 = 35%, p = 0.2) (Figure S11).

Comparative PP of aPL positivity in hemodialysis patients with and without fistula occlusion

Thirteen articles, comprising 474 patients with and 1080 patients without fistula occlusion, compared the frequency of IgG aCL that was slightly greater in patients with than patients without fistula occlusion (26.9% vs. 23.2%), but with a high heterogeneity (I^2 = 72%, $P < 0.0001$), (Figure 4). Six articles, comprising 201 patients with and 310 patients without fistula occlusion, compared the PP of LA; this was markedly higher in patients with than without fistula occlusion (23% vs. 0.3%), with no heterogeneity (Figure 5). Data from 6 cohort studies, comprising 123 hemodialysis patients with 2 or more fistula occlusions and 237 hemodialysis patients with none or only 1 fistula occlusion, were pooled to determine the standardized mean difference of IgG aCL between the two groups: random effect meta-analysis revealed wide heterogeneity (I^2 = 91%, $P < 0.0001$), which invalidated the effect size (Figure S12).

DISCUSSION

Our meta-analysis indicates that aCL positivity of either IgG/IgM isotype was more common in patients with ESRD in comparison to controls, and despite the elevated heterogeneity, almost all studies favored the relationship. On the other hand, the greater prevalence of LA in ESRD was devoid of heterogeneity, probably indicating a greater reproducibility of the coagulation assays for LA compared to the evolution of the aCL immunoassays over the decades. When splitting ESRD patients according to management (hemodialysis vs. conservative), IgG aCL and LA were more common among patients on hemodialysis, an issue addressed by seven studies. At variance, dialysis modality did not affect the prevalence of aPL positivity, though only three studies investigated this aspect. These accruing figures indicate that aPL might play some clinical role in ESRD: data from the pooled average IgG aCL titers lend support to this possibility, but the significant effect size was offset by elevated heterogeneity, though most of the studies presented higher mean IgG aCL levels in the ESRD groups. However, the average IgG aCL titers were below the thrombogenic threshold of 40 GPL determined in a study on APS patients from the mid-1990s.[54] Conversely, the effect size for the pooled average of IgM aCL was not significant and was accompanied by high heterogeneity.

With regard to a possible relation between aPL and fistula occlusion, our systematic review evidenced two complementary scenarios: in the first one, the PP of fistula occlusion was compared between aPL-positive and aPL-negative hemodialysis groups, in the second one, the prevalence of aPL positivity was compared between hemodialysis groups with and without fistula occlusion.

In the first scenario, we separately evaluated the retrospective and prospective studies assessing the PP of fistula occlusion in IgG aCL-positive patients; the retrospective studies showed slightly more common fistula occlusion in IgG aCL-positive hemodialysis patients, with a significant effect size, but offset by high heterogeneity, whereas the fewer prospective studies did not show a difference in fistula occlusion frequency between IgG aCL-positive and IgG aCL-negative hemodialysis patients; likewise, patients on hemodialysis positive and negative for LA did not show a different fistula occlusion frequency.

In the second scenario, the PP of IgG aCL positivity was slightly greater in hemodialysis patients with fistula occlusion, but the effect size was offset by high heterogeneity; conversely, the PP of LA was much greater in patients with fistula occlusion, with a strong effect size devoid of heterogeneity. The standardized mean difference of average IgG aCL titer favored fistula occlusion on hemodialysis patients, in support of a pathogenic role for aPL in fistula occlusion though also in this scenario the average titers of hemodialysis patients with fistula occlusion from individual studies were below the thrombogenic threshold of 40 GPL established for IgG aCL.[54]

At first glance, our findings challenge a thrombogenic role of aPL in ESRD, but they cannot exclude it, as even low aPL titers could be relevant in ESRD: in fact APS and ESRD share common pathogenic mechanisms such as oxidative stress and coagulation activation,[31,55–57] and pre-existing or de novo aPL developing in patients with ESRD may add to the oxidative and thrombogenic potential of the background status to favor fistula occlusion. Indeed, in a previous meta-analysis on aPL and systemic sclerosis patients with low aPL titer had worse renal function than systemic sclerosis patients without aPL.[58]

On the other hand, some of the aPL measured in ESRD may be cross-reactive against epitopes of oxidized lipids[59] and in this respect they may behave as natural auto-antibodies (not always of the IgM isotype),[60–62] devoid of thrombogenic potential and simply reflecting a response to oxidation that worsens as ESRD progresses.[57] This phenomenon could also explain the presence and strong relation of LA with fistula occlusion in our meta-analysis, because IgG directed against oxidized phospholipids strongly associate with LA positivity.[63] Accordingly, the low heterogeneity displayed in the relation between LA and fistula occlusion might imply that the fluid phase coagulation assays detect a wider repertoire of aPL against native and oxidized lipid epitopes than aPL detected by solid-phase immunoassays. The cessation of oxidative stress postrenal transplant may decrease or prevent the generation of these oxidized lipid epitopes,[64] which in turn may account for the disappearance of LA after the allograft, as previously shown.[65]

Alternatively, an atherogenic hypothesis may explain the link between aPL and fistula occlusion: the arterovenous junction undergoes changes in hemodynamic flow, vessel wall remodeling and thickening, whereas the venous endothelium and adventitia adapt to the new hemodynamic forces, maintaining the patency of the vessel.[66] The latter is supported by the vasodilator effect of nitric oxide generated by endothelial nitric oxide synthase, in addition to its anti-inflammatory and antiplatelet properties.[67] APL can impair the re-endothelialization of a denuded endothelium,[68] as well as the biologic activity of nitric oxide[69]; moreover, persistent systemic inflammation, including elevated plasma levels of clotting factors,[31] endothelial dysfunction,[70] and dyslipidemia occur in ESRD,[57] as well as in APS[71,72]: therefore, aPL might either contribute to the early failure of a non-mature fistula or to the late failure of a mature but rapidly aging fistula.

In keeping with this atherogenic hypothesis, one study reported that 34% of fistulas were stenosed rather than thrombosed[23] and three studies reported a temporal relationship between longer hemodialysis duration and increased rates of fistula occlusion.[27,30,49] This atherogenic theory receives support by an unrelated study exploring the role of aPL in lower limb bypass graft on 147 patients who underwent elective suprainguinal or infrainguinal bypass graft surgery. The progression of atherosclerotic occlusive disease, particularly in the distal limb segments, was greater in aPL positive than negative patients (73% vs. 37%, $P < 0.001$) and aPL independently predicted progression postrevascularizations ($P < 0.001$).[73]

The limitations of the meta-analysis are: (1) variability in sample size of the studies; (2) a degree of publication bias evidenced by our preliminary funnel plot, the performance of which, however, can be misleading when run on a limited number of studies ([7,8]); (3) expression of data as frequency of aPL-positive participants, rather than average antibody titers in many papers; (4) lack of enough studies measuring additional aPL, such as anti-beta-2-glycoprotein-I and antiprothrombin; (5) lack of aPL measurement over time; (6) inability for older studies to conform to the current laboratory criteria for aPL; (7) inability to evaluate the number of patients with fistula occlusion from some studies that instead reported the average number of occlusions per patient; (8) inability to account for some background disorders, themselves associated with an increased atherothrombotic risk, such as diabetes, though systemic lupus erythematosus was excluded.

To conclude, the meta-analysis does not prove causality between aPL and fistula occlusion, rather it shows that: (1) aPL differentially relate to ESRD: IgG aCL associates with ESRD on hemodialysis whereas LA associates with ESRD regardless of hemodialysis; (2) fistula occlusion relates to LA whereas the relation with IgG aCL is less certain; nevertheless an atherogenic effect of aPL leading to progressive stenosis of the fistula wall cannot be excluded, a possibility that should be assessed in a dedicated prospective study.

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CONFLICT OF INTERESTS

None of the authors has (1) any financial or not financial relationship with pharmaceutical firms, device firms or other entities; and (2) ownership of intellectual property in any way related to the work under consideration or with any entity in the biomedical world.

AUTHOR CONTRIBUTIONS

Paul R. J. Ames is the guarantor and analyzed the data. Paul RJ Ames, MIra Merashli and Vincenzo Bellizzi developed the search strategy; Tommaso Bucci, Daniele Pastori and Paul RJ Ames screened the articles; Paul RJ Ames, Tommaso Bucci and Pasquale Pignatelli drafted the manuscript; Fabrizio Gentile and Alessia Arcaro provided input for the immunology issues; all authors approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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