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ORIGINAL ARTICLE

Antiphospholipid syndrome in rural, remote, and First Nations peoples in the Top End of the Northern Territory, Australia

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Abstract

Background: The Northern Territory of Australia has a high proportion of First Nations peoples living in remote communities and a high burden of chronic autoimmune diseases. The epidemiology and clinical outcomes of antiphospholipid syndrome (APS) in First Nations Australians are poorly characterized.

Objectives: To determine the epidemiology, presenting features, and outcomes of patients with APS using an 18-year retrospective cohort of newly diagnosed patients presenting to Royal Darwin Hospital (2002-2020).

Methods: Patients admitted to Royal Darwin Hospital with a new incident diagnosis of APS between January 2002 and December 2020 were identified and followed until December 2022, with data on baseline demographics, clinical and laboratory features, and overall survival extracted from electronic and paper medical records.

Results: Fifty-three patients with APS were included, of whom 40 (75%) were First Nations and 46 (87%) were female. Thirty (75%) of First Nations patients with APS resided in very remote Australia vs 0 (0%) non–First Nations patients. Eighteen cases (34%) had primary APS, and 35 cases (66%) had secondary APS, most in association with lupus. Eight (15%) cases developed catastrophic APS (CAPS), all in First Nations patients. There were 13 deaths (of which 11 were among First Nations patients). Patients with CAPS had significantly shorter median overall survival (8.3 years from diagnosis), with median survival in non-CAPS patients not reached (P = .003).

Conclusion: There is a high prevalence of APS in First Nations patients living in very remote Australia admitted for tertiary care in the tropical north of the Northern Territory, Australia. The rate of CAPS in First Nations patients was high, and CAPS was associated with significantly shorter survival. Larger prospective studies are required to inform improved models of care for First Nations and remote Australians living with APS.

KEYWORDS
Aboriginal Australians, Aboriginal health, antiphospholipid antibodies, antiphospholipid syndrome, catastrophic antiphospholipid syndrome

Essentials

- Antiphospholipid syndrome (APS) increases the risk of blood clots and, in women, harm to pregnancy.
- We report APS features and outcomes in admitted hospital patients of remote northern Australia.
- APS in the Northern Territory is most common in First Nations peoples in very remote Australia.
- There is a need for improved models of care for remote First Nations peoples living with APS.

1 | INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune thrombophilic clinicopathological condition associated with significant morbidity and mortality. APS is defined by the presence of antiphospholipid (aPL) antibodies and clinical thrombotic or obstetric events. aPL antibodies are tested by immunoassays for anticardiolipin (aCL) antibody and anti–β2 glycoprotein-I (β2GPI) antibodies and by functional assay for the presence of a lupus anticoagulant (LAC). Defining clinical events for the diagnosis of APS include either venous and/or arterial thromboses or obstetric complications, including recurrent fetal loss in pregnant women [1–4]. The exact pathogenic mechanism of APS is not well understood. APS can be a primary disorder or occur secondary to, or in association with, other autoimmune conditions, most notably systemic lupus erythematosus (SLE) [1,3,5]. APS confers a high risk of recurrent thromboses and obstetric morbidity. The treatment of APS vascular thromboses generally entails long-term anticoagulation with warfarin for treatment and secondary prevention, which is superior to other anticoagulants such as direct oral anticoagulants [6]. For pregnancy complications in obstetric APS, low-dose aspirin and low-molecular-weight heparin are used. Immunosuppression has a therapeutic role for APS in association with autoimmune disease such as SLE, or in certain settings for refractory forms of APS [1,7]. In a small proportion of cases (<1% of all APS cases), catastrophic APS (CAPS) develops [5,8]. CAPS is a severe life-threatening variant of APS marked by widespread small vessel multiorgan thromboses leading to acute multiorgan dysfunction or failure. CAPS has a high mortality rate of approximately 50% despite treatment [1,5,8].

The epidemiology, presenting features, and outcomes of APS in Aboriginal and Torres Strait Islander peoples of Australia (herein respectfully referred to as First Nations peoples) are not well understood. The Northern Territory (NT) of Australia spans a land mass of more than 1.4 million km^2, with a population of more than 250,000. More than 30% of the NT's population identify as First Nations peoples, many of whom reside in some of the remotest parts of Australia. First Nations peoples are culturally and linguistically diverse and, in the context of Australia's history of colonization, are disproportionately affected by poorer health outcomes. This manifests as higher rates of infections; autoimmune diseases, including SLE; nutritional deficiencies; and cardiovascular disease (including some of the highest reported rates of rheumatic heart disease [RHD] in the world) [9–14]. Age-standardized death rates are higher for First Nations than for non–First Nations Australians and for Australians living in more remote areas than for those living in metropolitan areas [15].

This study aimed to better understand APS epidemiology, presenting features, and outcomes including overall survival in First Nations peoples and rural and remote residents of the tropical north of Australia.

2 | METHODS

We report an 18-year retrospective cohort of patients with a new incident diagnosis of APS admitted to the Royal Darwin Hospital from 2002 to 2020. The Royal Darwin Hospital is a 360-bed tertiary referral hospital serving the tropical northern "Top End" of the NT of Australia, with a catchment population of 200,450. Of these, 26% identify as First Nations peoples and 25% live outside of the urban area of Darwin, its capital city [11]. In addition to being the tertiary referral hospital for the whole Top End of the NT, Royal Darwin Hospital also provides NT-wide tertiary specialist services in hematology, rheumatology, and immunology.

Potentially eligible new cases of APS presenting to Royal Darwin Hospital between January 1, 2002, and December 31, 2019, were initially screened for via search of electronic medical records of patients presenting with either a primary or other coded diagnosis of "other thrombophilia," as defined by the 2019 International Classification of Diseases, 10th Revision, code D68.6. The electronic and paper-based medical records of these potentially eligible patients were then all manually reviewed to confirm a primary or other diagnosis of APS. Included patients with APS were followed until January 1, 2022, death, or loss to follow-up. Data on Patient demographics, clinical and laboratory variables, and date of last contact or death were retrieved from existing NT-wide electronic and paper-based Royal Darwin Hospital medical chart and laboratory records review. This study has ethics clearance from the Human Research Ethics Committee of NT Health and Menzies School of Health Research (approval no. 2018-3246). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [16].

New incident cases of APS eligible for inclusion in the study were either those meeting the 2006 Sydney criteria, where both Royal Darwin Hospital medical and laboratory records were available to the study authors for independent review, or, if these records were incomplete, patients having a documented history of APS by a treating specialist hematologist, immunologist, or rheumatologist. In brief, the 2006 Sydney criteria require one or more clinical criteria (vascular thrombosis and/or obstetric event) and the confirmed presence of a

persistent aPL antibody or LAC. Clinical criteria include vascular thromboses (venous or arterial) and/or pregnancy morbidity (including recurrent fetal loss, unexplained fetal death, and/or premature birth due to eclampsia/severe preeclampsia or placental insufficiency) [4,17]. Laboratory criteria include at least 1 LAC or aPL antibody (aCL and β2GPI) positive on 2 or more occasions measured at least 12 weeks apart [17]. Royal Darwin Hospital does not perform in-house laboratory testing for LAC or aPL, and all testing was performed by referral to laboratories accredited by Australia's National Association of Testing Authorities and participating in the Royal Australasian College of Pathologists' Quality Assurance Program. In brief, LAC testing was performed using both dilute Russell viper venom time–and activated partial thromboplastin time–based assays, and aCL and β2GPI (both for immunoglobulin G of medium to high titer) were accessed by standardized enzyme immunoassay.

Date of diagnosis was defined as either the first date the patient met Sydney criteria for diagnosis or when these data were not available to the study authors, the first date in the medical record where a specialist documented the diagnosis. Patients with a date of diagnosis prior to January 1, 2002 (prevalent cases), were excluded. Included patients with APS were classified as either having primary APS or having secondary APS where an underlying autoimmune or connective tissue disorder was present (eg, SLE). Female patients meeting the obstetric clinical criterion only for the diagnosis of APS were classified as obstetric APS. CAPS was defined as per the 2003 international consensus statement's definitions of probable or definite CAPS by Asherson et al. [8]: in brief, the development of thrombosis simultaneously or in less than a week involving ≥3 organ systems or tissues with positive laboratory criteria of APS [8].

For calculating expected proportions of First Nations vs non–First Nations patients, the 2019 NT Department of Health estimates of the 2019 catchment population of the Top End Health Service were used (estimated 26% First Nations identification in catchment population) [11]. Remoteness area of residence was classified as per the 2016 Australian Bureau of Statistics Australian Statistical Geography Standard Remoteness Structure—RA2, Inner Regional Australia; RA3, Outer Regional Australia (which includes the NT's capital city, Darwin); RA4, Remote Australia; and RA5, Very Remote Australia [18].

The primary outcome of interest was overall survival. Descriptive statistics were used to analyze baseline demographics, clinical features, outcomes, and interventions. Kaplan-Meier analysis and log-rank tests were used for survival analysis. Statistical significance was defined as a P value of <.05. Statistical analyses were performed using GraphPad Prism for Windows version 9.5.0.

3 | RESULTS

Fifty-eight patients were identified with a recorded diagnosis of APS presenting to Royal Darwin Hospital between 2002 and 2020 inclusively. Of these, 5 were prevalent cases with a date of first diagnosis before January 1, 2002, and were excluded, leaving 53 new incident cases included in the analysis (Figure 1).

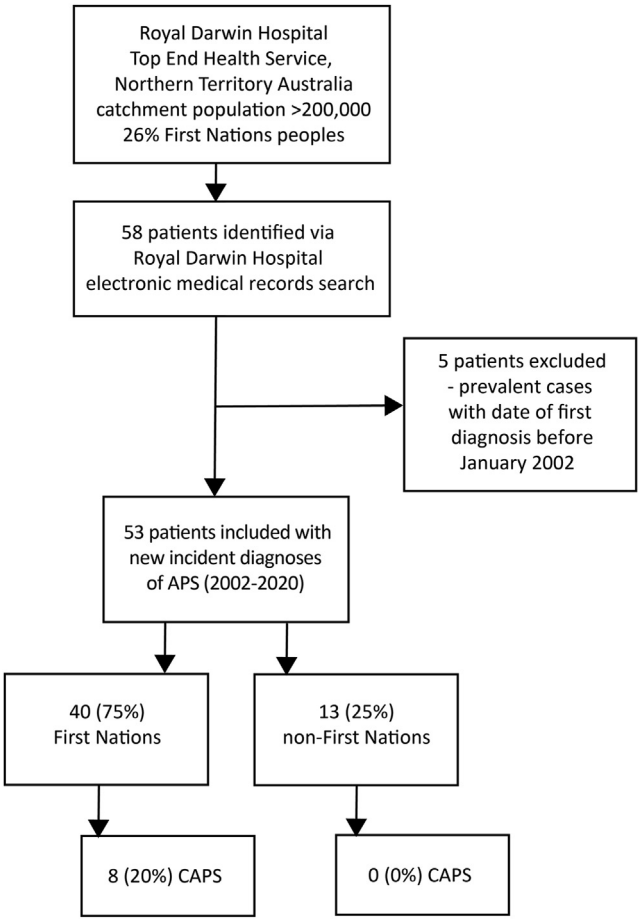

FIGURE 1 Study flow diagram of included patients with new incident APS diagnosis during the study period (2002-2020). APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome.

Of the 53 new incident cases, 46 were female (87%). Forty (75%) cases identified as First Nations, compared to an expected 26% of catchment population of Top End Health Service of NT. Median age at the time of first diagnosis was younger for First Nations patients (median, 30 years; IQR, 23-36 years) than for non–First Nations patients (median, 44 years; IQR, 32-47 years). Most First Nations patients with APS resided in Very Remote Australia (75%), and most non–First Nations patients with APS had a place of residence in Outer Regional Australia (92%) (Table 1).

Thirty-five (66%) APS cases had secondary APS, and 18 (34%) cases had primary APS. Secondary APS was more common in First Nations patients (70% vs 54%). In 34 of 35 (97%) total secondary APS cases, the underlying autoimmune disorder was SLE (Table 1), and in the remaining patient, the underlying autoimmune disorder was mixed connective tissue disease. There was a large absolute difference in the proportions of patients with CAPS between First Nations and non–First Nations patients: 8 (20%) of patients in the First Nations group had CAPS vs 0 (0%) in the non–First Nations group. Of the 46 females with APS, 4 (9%) had obstetric APS in isolation. In First Nations patients, there was a higher prevalence of

TABLE 1 Demographic data of included patients with antiphospholipid syndrome admitted to Royal Darwin Hospital in the Northern Territory (2002-2020).

Characteristics	Total (*N* = 53)	First Nations (*n* = 40)	Non–First Nations (*n* = 13)
Sex, *n* (%)			
Male	7 (13%)	4 (10%)	3 (23%)
Female	46 (87%)	36 (90%)	10 (77%)
Age at diagnosis (y), median (IQR)	33 (24-43)	30 (23-36)	44 (32-47)
Remoteness area residence, *n* (%)			
Outer Regional Australia (RA3)	20 (38%)	8 (20%)	12 (92%)
Remote Australia (RA4)	3 (6%)	2 (5%)	1 (8%)
Very Remote Australia (RA5)	30 (57%)	30 (75%)	0 (0%)
APS categorization			
Primary APS, *n* (%)	18 (34%)	12 (30%)	6 (46%)
Secondary APS, *n* (%)	35 (66%)	28 (70%)	7 (54%)
Lupus	34 (64%)	27 (68%)	7 (54%)
Lupus nephritis/ nephropathy	26 (49%)	22 (55%)	4 (31%)
Lupus with ESKD	6 (11%)	5 (13%)	1 (8%)
Catastrophic APS, *n* (%)	8 (15%)	8 (20%)	0 (0%)
Obstetric, *n*/*N* females (%)	4/46 (9%)	3/36 (8%)	1/10 (10%)
Comorbid rheumatic heart disease, *n* (%)	16 (30%)	16 (40%)	0 (0%)
Heart valve replacement	4 (8%)	4 (10%)	0 (0%)
Mitral	2 (4%)	2 (5%)	0 (0%)
Aortic	2 (4%)	2 (5%)	0 (0%)

APS, antiphospholipid syndrome; ESKD, end-stage kidney disease.

comorbid RHD (40% vs 0%) and heart valve replacement (10% vs 0%) (Table 1).

Of all 53 patients, 46 (87%) had laboratory APS results available to the authors confirming that laboratory APS diagnostic criteria were met (Table 2). The remaining 7 (13%) had hospital documentation available to confirm that they met the clinical criteria for APS and a specialist documented diagnosis of APS, but no positive laboratory APS antibody or LAC results available in hospital laboratory records for confirmation by the study authors. Of the 46 patients with APS with laboratory results available to the study authors for independent confirmation of APS diagnosis, 39 had full triple APS antibody results available to the authors and 7 had only partial results of the full APS panel available to the authors. Fourteen of the 39 patients with full triple laboratory results available to the authors were triple antibody positive (14/39, 36%), of which 13 of 14 (93%) were First Nations. Most patients were LAC-positive (91%, 42/46).

First Nations patients had higher prevalence of pulmonary hypertension (15% vs 0%), myocardial infarction (28% vs 8%), renal macrothrombosis (18% vs 0%), splenic thrombosis (8% vs 0%), and biopsy-proven renal thrombotic microangiopathy (15% vs 0%) (Table 3). Stroke and central venous sinus thrombosis events were similar in prevalence between both groups. Prevalence of limb deep vein thrombosis and pulmonary embolism was lower in First Nations patients than in non–First Nations patients; 30% vs 62% for pulmonary embolism and 28% vs 54% for limb deep vein thrombosis, respectively.

Obstetric history data were incomplete, with hospital records reporting gravida and parity available in only 75% (27/36) of First Nations and 70% (7/10) of non–First Nations women included in the study. There were 54 documented pregnancies in the First Nations women with 22 (41%) live births, and 21 documented pregnancies in the non–First Nations women, which included 11 (52%) live births. Obstetric comorbidity data were also incomplete; for cases with data available, there was a higher prevalence of preeclampsia in First Nations patients (5/13 [38%] vs 1/6 [17%]) (Table 3).

During the study period, 42% of patients received aspirin, 74% of patients received warfarin, and 6% of patients received rivaroxaban (Table 4). Hydroxychloroquine was the most prescribed immunosuppressant (55% of all patients). Therapeutic plasma exchange was used in 5 (13%) First Nations patients, all of whom had CAPS, vs no non–First Nations patients.

There were 13 (25%) deaths noted during the study period, of whom 11 were of First Nations patients and 2 were of non–First Nations patients. First Nations patients who died were more likely to reside in Very Remote Australia, were younger at the time of death (median [range], 36 [18-64] years vs 72 [63-80] years), and had more comorbid RHD and end-stage kidney failure compared to non–First Nations patients who died (Table 5). Sepsis was the most common cause of death (*n* = 5) in all patients. On Kaplan-Meier analysis, patients with CAPS had a median survival of 8.3 years from the date of initial APS diagnosis, compared to the non-CAPS group for whom median survival was not reached, with patients with CAPS having a significantly lower overall survival than patients without CAPS (*P* = .003) (Figure 2).

4 | DISCUSSION

We report the first cohort study of APS in the tropical Top End of the NT, Australia, in a population cohort that includes a high proportion of First Nations peoples residing in Very Remote Australia. Our study found a higher prevalence of APS in First Nations peoples admitted for tertiary care in the Top End of Australia's NT, who were younger at the time of diagnosis than non–First Nations patients. There was higher comorbidity with most cases associated with SLE, and

TABLE 2 Antibody profile of patients with antiphospholipid syndrome from total 53 patients included in the analysis.

Antibody	Total	First Nations	Non–First Nations
LAC-positive[a], *n/N* (%)	42/46 (91%)	34/36 (94%)	8/10 (80%)
aCL-positive[a], *n/N* (%)	24/49 (49%)	19/38 (50%)	5/11 (45%)
β2GPI-positive[a], *n/N* (%)	20/41 (49%)	18/33 (55%)	2/8 (25%)
Triple-positive[a], *n/N* (%)	14/39 (36%)	13/32 (41%)	1/7 (14%)

aCL, anticardiolipin; β2GPI, β2 glycoprotein-I; LAC, lupus anticoagulant.
[a]*N* represents the total number of cases for which data were available, of the total 53 patients included in the study.

comorbidity with RHD and end-stage kidney failure, as has been well characterized and previously described in the NT's First Nations patient population [9,13].

In contrast to non–First Nations patients, most First Nations patients with APS in our cohort resided in Very Remote Australia and were overrepresented in the group of patients with CAPS, which was associated with significantly shortened overall survival. Non–First Nations patients predominantly resided in the relatively more metropolitan Outer Regional Australia—and thereby closer to the Top End of the NT's single tertiary care center in Darwin. Of note, however, one limitation of our cohort study design is its inpatient admission setting, which may have excluded First Nations patients with milder APS living very remotely and not referred to Royal Darwin Hospital for tertiary inpatient care during the study period.

The proportion of First Nations patients with CAPS in our cohort was much higher than that reported in studies globally (20% vs <1%), although given our small cohort size and the tertiary hospital–based recruitment of our cohort, this finding may reflect selection bias. In our patients with CAPS, patients were typically treated with combined full-dose anticoagulation plus high-dose corticosteroids, plus plasma exchange, and/or intravenous immunoglobulins (so-called triple therapy), as is typically used and recommended internationally to improve survival [7,8,19]. The aim of these treatments is to address precipitating factors, suppress the cytokine storm, and prevent and treat

TABLE 3 Clinical features of patients with antiphospholipid syndrome.

Clinical features	Total (*N* = 53)	First Nations (*n* = 40)	Non–First Nations (*n* = 13)
Clinical manifestation, *n* (%)			
Pulmonary embolism	20 (38%)	12 (30%)	8 (62%)
DVT limb	18 (34%)	11 (28%)	7 (54%)
Stroke (large vessel)	14 (26%)	11 (28%)	3 (23%)
Central venous sinus thrombosis	4 (8%)	3 (8%)	1 (8%)
Pulmonary hypertension	6 (11%)	6 (15%)	0 (0%)
Myocardial infarction	12 (23%)	11 (28%)	1 (8%)
Renal macrothrombosis	7 (13%)	7 (18%)	0 (0%)
Splenic thrombosis	3 (6%)	3 (8%)	0 (0%)
Liver thrombosis	1 (2%)	1 (3%)	0 (0%)
Vertebral thrombosis	3 (6%)	2 (5%)	1 (8%)
Biopsy-proven renal TMA	6 (11%)	6 (15%)	0 (0%)
Skin ulcers	1 (2%)	1 (3%)	0 (0%)
Obstetric manifestations, *n/N* (%), where *N* = cases with data available			
Women with gravida parity available	34/46 (74%)	27/36 (75%)	7/10 (70%)
Total pregnancies	75	54	21
Live births/total pregnancies	33/75 (44%)	22/54 (41%)	11/21 (52%)
Preeclampsia (women)	6/19 (32%)	5/13 (38%)	1/6 (17%)

DVT, deep vein thrombosis; TMA, thrombotic microangiopathy.

TABLE 4 Therapeutics used in patients with antiphospholipid syndrome.

Treatment	Total (N = 53)	First Nations (n = 40)	Non–First Nations (n = 13)
Aspirin	22 (42%)	16 (40%)	6 (46%)
Warfarin	39 (74%)	29 (73%)	10 (77%)
Rivaroxaban	3 (6%)	2 (5%)	1 (8%)
Enoxaparin	2 (4%)	2 (5%)	0 (0%)
Antenatal enoxaparin only	4 (8%)	2 (5%)	2 (15%)
Immunosuppressants			
Hydroxychloroquine	29 (55%)	23 (58%)	6 (46%)
Mycophenolate	9 (17%)	8 (20%)	1 (8%)
Corticosteroids	25 (47%)	23 (58%)	2 (15%)
Rituximab	12 (23%)	12 (30%)	0 (0%)
Therapeutic plasma exchange	5 (9%)	5 (13%)	0 (0%)
Intravenous immunoglobulin	7 (13%)	5 (13%)	2 (15%)
Eculizumab	1 (2%)	1 (3%)	0 (0%)

thrombotic events [8]. Even with optimization of therapy, CAPS is associated with a high mortality rate of between 37% and 50% [8,19]. A 1000 patient European cohort (the Euro-Phospholipid project) reported a CAPS occurrence in 0.9% of their cases and death in 55.6% [5]. In a CAPS international registry, a study of 500 patients with CAPS showed that the majority (65%) were triggered by a precipitating factor, most commonly infection, with 37% mortality overall and 48% mortality in CAPS associated with SLE [20]. In APS more broadly, survival has been shown to be comparable to the normal population in European and US cohort studies, for example, in the European APS 1000-person cohort, in which overall survival at 5 years was 94.7% and at 10 years was 90.7% [5,21].

Most of the First Nations patients in our cohort had secondary APS in association with SLE, and there was a significant comorbid burden of RHD. Our prevalence of secondary APS in First Nations patients in particular differs from other global studies generally showing lower proportions of secondary APS. In a Korean population–based study (n = 3088), 27% of cases were SLE-associated [22], and in a US-based cohort study of incident APS cases (n = 33), the proportion of cases associated with SLE was 18% [21]. In a smaller single-center Malaysian retrospective cohort study (n = 17), mean age of onset of APS was 24 ± 5 years, 82% of the participants were female, and primary APS was present in 65% [23]. Among our study's First Nations patients with APS, comorbid RHD and heart valve replacements were disproportionately over-represented: 40% of our cohort had RHD and 10% had received a heart valve replacement. This compares to a reported total of 2308 RHD cases in the NT as of 2019, equivalent to an overall prevalence of approximately 0.9% in the NT, Australia [24].

Our 53 new incident cases, most of whom were female, over an 18-year cohort study from a catchment population of approximately 200,450 are comparable to those reported in other studies. The estimated incidence of APS is approximately 1 to 5 new cases per 100,000 person-years, with a prevalence of 6 to 50 per 100,000 persons (depending on ethnicity), female predominance, and 85% of patients being young- to middle-aged (15-50 years of age) [1,3,21,22]. Our findings compare to data from a large UK population–based study reporting a 4.1:1 ratio of females to males in cases and a peak incidence of APS in women of 7.5 new cases per 100,000 person-years at an age of 35 to 39 years and a peak incidence of APS in men of 2 new cases per 100,000 person-years at an age of 55 to 59 years [25]. These data compare to a large population-based Korean study (n = 3088 incident cases over 10 years), in which new incident cases of APS were observed at a mean age of 44.6 ± 16.6 years, with a bimodal peak incidence among women at ages 30 to 39 and 70 to 79 years and a single peak in men at 70 to 79 years [22].

Other findings in our study are somewhat limited by the retrospective approach of this study, potential selection bias due to the cohort being defined by tertiary hospital inpatient admissions rather than an ambulatory setting, reliance on routinely collected medical records information, and (being a rare disease) the small size of the cohort. Our other findings included higher triple aPL antibody positivity in First Nations patients; however, data were incomplete. Many studies have demonstrated the stronger risk of thrombosis with LAC positivity compared to either aCL or β2GPI [2,26] and for triple aPL antibody positive patients [1,3]. In women with APS in our study, we found lower live birth rates (41% and 52% in First Nations vs non–First Nations pregnancies) compared to those in other published studies [4]; however, data were incomplete, with obstetric history only available for 74% of women in the cohort. Moreover, reliance on tertiary hospital records for pregnancy outcomes may have conferred bias toward adverse pregnancy outcomes. Most of our included patients were anticoagulated with warfarin, with a small number on rivaroxaban. There are clear data on the reduced efficacy of direct oral anticoagulants such as rivaroxaban in APS [27], and further prospective studies are recommended to explore factors associated with anticoagulant choice and outcomes in our patient population. Prescribing of immunosuppressants reflected the presence of associated autoimmune disease, namely, SLE.

We report the first cohort study outlining the clinical features, outcomes, and overall survival of patients in the tropical North of Australia with APS, which included a significant proportion of First Nations patients residing in Very Remote Australia. Patients were more likely to be female, of First Nations background, and from a remote primary place of residence, and patients with CAPS specifically had poorer survival. In First Nations patients, there was marked prevalence of comorbid diseases, including SLE and RHD, and being from a more remote residence, being at an increased distance from tertiary hospital specialist care. Our findings underscore the burden of disease for APS in First Nations Australians and the need for prospective studies in both hospital and ambulatory care settings to better understand factors behind the prevalence of CAPS in this patient cohort with a focus on modifiable risk factors. Future studies should inform best models of

TABLE 5 Features of patients with antiphospholipid syndrome who died during the study period.

Features of APS patients who died	Total (*N* = 13)	First Nations (*n* = 11)	Non–First Nations (*n* = 2)
Female sex	11 (85%)	10 (91%)	1 (50%)
Age at time of diagnosis (y), median (range)	36 (18-71)	28 (18-57)	57 (44-71)
Age at time of death (y), median (range)	38 (18-80)	36 (18-64)	72 (63-80)
Remoteness area of residence[a]			
Outer Regional Australia (RA3)	4 (31%)	3 (27%)	1 (50%)
Remote Australia (RA4)	1 (8%)	0 (0%)	1 (50%)
Very Remote Australia (RA5)	8 (62%)	8 (73%)	0 (0%)
Obstetric APS only	0 (0%)	0 (0%)	0 (0%)
Secondary APS	10 (77%)	8 (73%)	2 (100%)
SLE-associated APS	9 (69%)	7 (63%)	2 (100%)
MCTD	1 (8%)	1 (9%)	0 (0%)
CAPS	5 (38%)	5 (45%)	0 (0%)
Comorbid RHD	6 (46%)	6 (55%)	0 (0%)
Comorbid ESKD	3 (23%)	3 (27%)	0 (0%)
Cause of death			
Sepsis	5 (38%)	4 (36%)	1 (50%)
CAPS	2 (15%)	2 (18%)	0 (0%)
Intracerebral hemorrhage	1 (8%)	1 (9%)	0 (0%)
Acute coronary syndrome	1 (8%)	1 (9%)	0 (0%)
Cancer	2 (15%)	1 (9%)	1 (50%)
Not recorded	2 (15%)	2 (18%)	0 (0%)

APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; ESKD, end-stage kidney disease; MCTD, mixed connective tissue disease; RHD, rheumatic heart disease; SLE, systemic lupus erythematosus.

[a]Remoteness area of residence classified as per the 2016 Australian Bureau of Statistics Australian Statistical Geography Standard Remoteness Structure [18].

care for First Nations patients living with APS that are culturally safe and fit for purpose in the remote Australian context with a view to improving long-term patient outcomes.

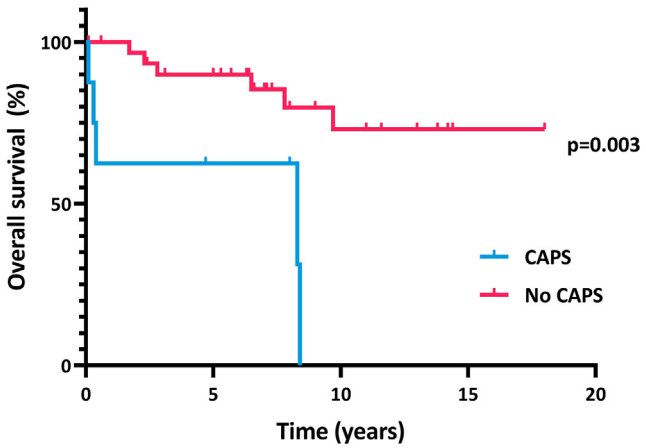

FIGURE 2 Kaplan-Meier survival curve of overall survival for patients with a diagnosis of catastrophic antiphospholipid syndrome (CAPS) vs no CAPS.

FUNDING

No funding was received for this research.

ETHICS STATEMENT

This study has ethics clearance from the Human Research Ethics Committee of Northern Territory Health and the Menzies School of Health Research (approval no. 2018-3246). A waiver for patient consent was granted for this study in accordance with the Australian National Statement on Ethical Conduct in Human Research (2018) Section 2.3.10, available online: https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018#toc__156, accessed on 1 December 2022. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

AUTHOR CONTRIBUTIONS

E.A. and T.N. conceived the study, extracted data, performed statistical analyses, and interpreted data. E.A. drafted the manuscript. All authors were involved in subsequent manuscript critical review and revision and approved the final version for submission.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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