Retrospective analysis of the outcome of patients with idiopathic inflammatory myopathy: a long-term follow-up study

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Abstract

Objective

Several factors have been implicated in the prognosis of idiopathic inflammatory myopathies, including age, gender, delay in diagnosis, neoplasia, creatine kinase levels and some autoantibodies. We have reviewed the main factors contributing to mortality in patients with idiopathic inflammatory myopathy (IIM) diagnosed between 1976 and 2007 who were followed for at least 5 years in the Rheumatology Unit at University College Hospital in London.

Methods

An observational retrospective study was carried out on patients with IIM diagnosed between 1976 and 2007. All the patients fullfilled at least three out of four of the Bohan and Peter criteria. The subjects were divided into the following groups: adult-onset polymyositis (APM); adult-onset dermatomyositis (ADM); juvenile dermatomyositis (JDM); overlap syndromes with another autoimmune rheumatic disease

Results

90 patients were identified. The female to male ratio was 2.5:1 and the mean age at diagnosis was 38.5 years (SD 15.03). 47.8% of the patients had APM*, 30% adult-onset ADM, 15.6% Overlap and 6.7% JDM. Among the extramuscular features, 18.9% had pulmonary involvement. In 70% the highest CK was >5 times the upper normal. Prednisolone was prescribed in 98.9%. 11.1% received rituximab. 34.4% had monophasic, 31.1% relapsing and remitting and 34.4% continuous progressive course of the disease. The median follow-up was 11.5 years (IQR 12.00). 14.4% of the patients died, 30.8% due to infection, 30.8% from a cardiovascular event and 23.1% due to neoplasia. The 1, 5 and 10-year survival was 100%, 97.8% and 91%, respectively. Male gender (Hazards Ratio (HR) 3.222; p=0.037), pulmonary involvement (HR 5.247; p=0.009), chronic progressive course (HR 3.711; p=0.030) and use of rituximab (HR 3.562; p=0.036) were the only risk factors to be statistically significantly associated (p<0.05) with death.*

Conclusion

We conclude that long-term survival in these patients is generally quite good with an estimated 10-year survival >90% in our cohort, which is even higher than previously reported.

Key words

polymyositis, dermatomyositis, idiopathic inflammatory myopathies outcome, long-term follow-up

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Received on May 6, 2013; accepted in revised form on November 12, 2013.

Competing interests: none declared.

Introduction

Idiopathic inflammatory myopathy (IIM) is a group of rare diseases, including polymyositis (PM), dermatomyositis (DM), sporadic inclusion body myositis (IBM) and, according to some authors, also necrotising autoimmune myositis (NAM) (1). The PM/DM reported incidence varies from 4 to 10 cases/million/year (2) and women are most commonly affected (2, 3). IBM is generally rarer than PM/DM and it occurs more frequently in men (4). Whereas DM has a bimodal incidence distribution, with a first peak during childhood and a second one between 50 and 70 years of age, PM occurs predominantly after the second decade of life (2). IBM is more common after the fifth decade (4). Although the Bohan and Peter criteria (1975) remain commonly accepted for diagnosis of PM/DM (5, 6), a recent study has demonstrated their poor specificity (7). The authors of the recent review concluded that the Dalakas criteria (2003) agreed best with specialist consultant diagnosis (7). The main clinical feature of both PM and DM is subacute-onset proximal, symmetric muscle weakness (3, 8-13). Respiratory and deglutition muscles may be involved in some patients (12, 14-16). The distinguishing feature of DM is the presence of cutaneous manifestations, including Gottron's lesions, an heliotrope rash, a poikilodermatous rash, "mechanic's hands" and periungual telangiectasias and erythema. Systemic symptoms and signs, notably fatigue, weight loss and fever, as well as pulmonary and cardiac involvement, may be present in both entities (12, 15). The classic IBM pattern consists of coexistent proximal leg and distal arm weakness and less common initial complaints include finger flexor weakness and atrophy, foot drop or dysphagia (17). When the IIM is accompanied by varying degrees of interstitial lung disease, arthropathy, fever, Raynaud's phenomenon, mechanic's hands and the presence of antisynthetase antibodies (Jo-1 antibody being the most common) it is referred to as the antisynthetase syndrome (18).

PM, DM and IBM may be part of an overlap syndrome with other autoimmune diseases (17, 19). There is also a well recognised association of PM and DM with malignancy (20).

Although the IIM pathogenesis is not yet fully understood, cellular and humoral immune (21) as well as non-immune mechanisms are believed to be involved (13). Serum creatine kinase (CK) or aldolase levels, autoantibodies, muscle biopsy, electromyogram (EMG) and magnetic resonance imaging (MRI) are part of the diagnostic evaluation (2, 22). First-line treatment consists of corticosteroids, except for IBM which is usually refractory to these drugs. However, if corticosteroids fail or cause unacceptable side-effects, other immunosupressants are used, such as azathioprine (AZA), methotrexate (MTX), cyclosporine (Cyc), cyclophosphamide (Cyclo), mycophenolate mofetil (MMF), as well as intravenous immunoglobulin (IVIg). Whereas B-cell depletion offers some promise in refractory cases, the benefit has not been confirmed in a formal clinical trial. Furthermore, the use of anti-TNF therapy is controversial (22). The 1-, 5- and 10-year survival rates of PM/DM have been reported to be, respectively, 72–95%, 52–92% and 50–89% (14-15, 23-24) and the overall mortality in published studies has varied from 12.3 to 60.1% (15). Most of the reported studies mention cancer (10–47.1%), lung (5-41.5%) and cardiac (2.9–55%) complications and infections (2.5–33.3%) as the main causes of death (15, 25). Several poor prognostic factors have been suggested, namely older age (14, 24, 26, 30), male gender (8, 30), delay in diagnosis or treatment (24, 27, 30), presence of neoplasia (10, 12, 30), normal CK levels (28, 30), presence of anti-Jo1 (8, 30) and anti-PM-Scl antibodies (11, 30) and specific MRI abnormalities (29, 30). However, there is still no clear consensus about them. In this study we analysed the mortality and reviewed the main factors contributing to it in IIM patients followed in a single centre since 1976.

Methods

We performed an observational retrospective study involving patients with Idiopathic Inflammatory Myopathy invariably diagnosed between 1976 and

2007 (1 patient was diagnosed in 1960) in our Rheumatology Department, at University College Hospital, London.

We identified in our database 114 patients with myositis followed up between 1976 and 2012. Those with myositis secondary to malignancy, infection or drugs were excluded from this study, as well as patients who had not been followed up by us for at least 5 years (patients who died before completing 5 years of follow-up, but who would have been followed at least 5 years if alive, were not excluded). There were no patients with IBM or with NAM followed up for ≥5 years. All the patients fullfilled at least three out of four of the Bohan and Peter criteria. The patients were divided into the following groups: adult-onset PM (APM); adult-onset DM (ADM); juvenile DM (JDM) and overlap syndromes with another autoimmune rheumatic disease. Using patient case-notes we completed a database and analysed the data regarding demographic features, age at diagnosis of myositis, extramuscular involvement (skin, heart, lung, gastrointestinal tract and joints), highest CK level, autoantibody pattern, EMG and needle or open muscle biopsy results, treatment, disease course, mortality and cause of death. Skin involvement was defined by the presence of one or more of the following: Gottron's lesions; an heliotrope rash; a poikilodermatous rash; "mechanic's hands"; periungual telangiectasias and erythema; cutaneous calcinosis. Cardiac involvement was defined by the *de novo* presence of one or more of the following (as a clinical manifestation or in noninvasive studies such as ECG, echocardiography and cardiac MRI): arrhythmia; conduction abnormalities; congestive heart failure; myocarditis; pericarditis; angina and fibrosis. Pulmonary involvement was defined by any persistent respiratory complaints in the presence of abnormal pulmonary function tests, chest computed tomography scan and/or arterial blood gas tests. Gastrointestinal involvement was defined as *de novo* dysphagia (liquids/solids) and/or regurgitation. Joint involvement was considered to be present if the patient complained of arthralgias or if an inflammatory arthritis was diagnosed during the course of the disease.

The ANA (HEp-2) was considered to be positive if the titre was ≥1:80.

The patients were further subclassified into those who had a monophasic illness (a single episode of active disease), a relapsing–remitting disease (episodes of active disease and disease-free periods) and a chronic progressive disease (evidence of active disease despite treatment).

Corticosteroids were generally used as first line drugs unless there was any absolute contraindication or intolerance and the doses ranged invariably between 0.5 and 0.75mg/kg of oral prednisolone. Pulse steroids were only used on rare occasions if patients presented with profound weakness.

The IBM® SPSS® Statistics Version 21 was used for statistical analysis.

The Kolmogorov-Smirnov test was used to accept or reject Normality. The continuous variables with a distribution similar to Normal were described by the mean and standard deviation whereas the remaining were described by the median and interquartile range (P25-P75). The categorical variables were described by relative frequencies/percentages. The 1- and 5-year survival rates were calculated by the direct method. A Kaplan-Meier analysis was performed in order to estimate survival over time. The Cox proportional hazards regression was used to establish the relationship between the categorical predictor variables and the dichotomous outcome death/non-death. The independent variables shown to be statistically significant in univariate regression were further submitted to multivariate analysis. The Chi-square test and the Student *t*-test were used to compare, respectively, proportions and means from unpaired samples. Whenever there were missing values (those not reported in the database), these were reported and excluded from the analysis. A p-value <0.05 was considered statistically significant.

Results

Ninety patients were identified. The female to male ratio was 2.5:1. The mean age at diagnosis was 38.5 years (95% CI 35.4–41.6) with a standard deviation of 15.03 years, a minimum of 5 and a maximum of 67 years. 11 patients (12.2%) were <20, 39 (43.3%) were 20 to 39, 30 (33.3%) were 40 to 59 and 10 (11.1%) were ≥60 years old. Ethnically, 56 (62.2%) patients were White, 16 (17.8%) Afro-Caribbean, 16 (17.8%) Asian and 2 (2.2%) Black. In relation to diagnosis, 43 (47.8%) had adult-onset PM (APM), 27 (30.0%) had adult-onset DM (ADM), 14 (15.6%) had an overlap syndrome and 6 (6.7%) had juvenile DM (JDM). Excluding 13 cases in which the notes did not provide sufficient clarity, delay in diagnosis varied between 1 week and 108 months after clinical presentation, with a median of 5.0 months and an interquartile range of 9.00 months. Furthermore, 75.3% of the patients were diagnosed <12 months after clinical presentation. The median duration of follow-up was 11.5 years with an interquartile range of 12.00 years.

Among the extramuscular features, 18 (20.0%) had joint, 17 (18.9%) pulmonary, 6 (6.7%) cardiac and 3 (3.3%) gastrointestinal involvement. In relation to the highest CK level during follow-up, in 12 patients (13.3%) it was always normal whereas in 3 (3.3%) it was <2 times the upper normal limit, in 12 (13.3%) 2-5 times and in 63 (70.0%) >5 times the upper limit of normal and in 47 patients (52.2%) it was >10 times the upper normal. 47 patients (52.2%) were ANA positive. Excluding 5 missing values, 18 patients (21.2%) had positive Jo-1 antibody and 3 (3.5%) had positive SRP antibody. Although EJ and Mi-2 antibodies were positive, respectively, in 1 and 3 patients, these tests were only undertaken in <30% of the cohort.

All the patients received treatment. 89 patients (98.9%) were prescribed prednisolone and 79 patients (87.8%) were prescribed one or more DMARDs (either AZA, MTX, CycA, Cyclo or MMF). 11 patients (12.2%) had Cyclo and 5 (5.6%) MMF, 30 patients (33.3%) had IVIg and 3 (3.3%) were subjected to plasma exchange. 10 patients (11.1%) were prescribed rituximab. Tacrolimus was used systemically in 2 patients (2.2%). 31 patients (34.4%) had a monophasic, 31 (34.4%) a continuous progressive and 28 (31.1%) a

relapsing and remitting course of the disease (Table I).

During follow-up, 6 patients (6.7%) fully recovered and 13 patients died (14.4%), 4 of them (30.8%) due to an infection, 4 (30.8%) due to a cardiovascular event, 3 (23.1%) due to neoplasia (lung, endometrium and one of unknown origin), 1 (7.7%) due to respiratory failure and 1 (7.7%) due to trauma. Analysing each diagnostic category subgroup, the mortality was 22.2% in patients with ADM, 14.3% in those with an Overlap syndrome, 11.6% in APM and 0% in JDM. 15.4% (2 patients) died between >1 and ≤5 years of follow-up and 53.8% (7 patients) died ≤10 years after diagnosis. The observed 1- and 5-year survival was, respectively, 100% and 97.8%. The estimated cumulative proportion survival at 10 and 20 years was 91% and 79.7% (Fig. 1). Among the patients who died: the age at diagnosis was 20–39 years in 53.8% and 40–59 years in 30.8%; 53.8% were male and 61.5% were white; 46.2% had ADM, 38.5% APM, 15.4% Overlap and none had JDM; in 84.6% the highest CK was >5x the upper normal limit; 61.5% had positive ANA and 41.7% had a positive Jo1 antibody (1 missing value in the later); 38.5% (5 patients) had pulmonary involvement and 15.4% (2 patients) had cardiac involvement; all of them were administered prednisolone and 84.6% of them were also administered one or more DMARDs; 23.1% had cyclo, 46.2% IVIg, 30.8% rituximab and 7.7% plasma exchange; 23.1% had a monophasic, 7.7% a relapsing and remitting and 69.2% a continuous progressive course of the disease (Table II).

In our sample, the age at diagnosis, ethnic group, delay in diagnosis, highest CK level, presence of Jo1 antibodies or ANA, diagnostic category and cardiac involvement were not statistically significantly related to the outcome death/non-death. Nevertheless, in univariate analysis, male gender (hazards ratio (HR) 3.222; 95% CI: 1.075–9.652; p=0.037), pulmonary involvement (HR 5.247; 95% CI: 1.502–18.330; p=0.009), chronic progressive course (HR 3.711; 95% CI: 1.138–12.100; p=0.030) and use of rituximab (HR 3.562; 95% CI: 1.088–11.662; p=0.036) were associated with an increased risk of death. When adjusted to gender, the HR for pulmonary involvement slightly decreased to 5.037 (95% CI 1.432–17.712; p=0.012). Furthermore, when adjusted for gender, chronic progressive course of the disease was no longer a statistically significant predictor of death (HR 2.859; 95% CI 0.822–9.950; p=0.099). In multivariate analysis, pulmonary involvement (HR 4.711; 95% CI 1.314–16.892; p=0.017) was the only independent statistically significant predictor factor of worse prognosis.

Table I. Descriptive analysis of the 90 patients.

Gender, n (%)	Female	64 (71.1)
	Male	26 (28.9)
Age at diagnosis (yrs), mean (SD)	38.5 (15.03)	
Ethnic group, n (%)	White	56 (62.2)
	Afro-Caribbean	16 (17.8)
	Asian	16 (17.8)
	Black	2 (2.2)
Diagnostic category, n (%)	APM	43 (47.8)
	ADM	27 (30.0)
	Overlap syndrome	14 (15.6)
	JDM	6 (6.7)
Delay in diagnosis (months), median (IQR)	5.0 (9.00) (13 missing values)	
Extramuscular involvement, n (%)	Joints	18 (20.0)
	Lung	17 (18.9)
	Heart	6 (6.7)
	GI	3 (3.3)
Duration of follow-up (yrs), median (IQR)	11.5 (12,00)	
Highest CK, n (%)	Normal	12 (13.3)
	<2x upper limit	3 (3.3)
	2-5x upper limit	12 (13.3)
	>5x upper limit	63 (70.0)
ANA, n (%)	Positive	47 (52.2)
Other autoantibodies, n (%)	Jo1+	18 (21.2)
	SRP+ (5 missing values)	3 (3.5)
Treatment, n (%)	Prednisolone	89 (98.9)
	DMARDS (one or more)	79 (87.8)
	Cyclo	11 (12.2)
	MMF	5 (5.6)
	IVIg	30 (33.3)
	Plasma exchange	3 (3.3)
	Rituximab	10 (11.1)
	Tacrolimus (systemic)	2 (2.2).
Course of the disease, n (%)	Monophasic	31 (34.4)
	R&R	28 (31.1)
	Chronic progressive	31 (34.4)
Full recovery, n (%)	6 (6.7)	
Death, n (%)	13 (14.4)	

Discussion

The cohort of patients we have studied does not differ significantly from the earlier reports as far as demographic features are concerned. Importantly, though, we have followed the patients up for rather longer periods. Although with variable percentages (53.2%–72.7% (3, 8, 10, 12, 14, 24, 26)), there was an higher prevalence of female patients in all the previous studies, as it was in our cohort (71.1%). The overall mean age at diagnosis varied from 39.2 to 47.2 years (3, 8, 12, 14) or, in other reports, from 49.2 to 56 in PM and from 44 to 53 in DM (10, 24). In spite of our patients being younger, the difference was not statistically significant [mean (SD): 38.5 (15.03) *vs*. 39.2 (13.6), p=0,7065]. Similar to most of the previous studies (12, 14, 24, 26), our cohort showed a predominance of PM over DM (including juvenile and adult-onset). In relation to extramuscular features, the percentage of pulmonary involvement was not different from the

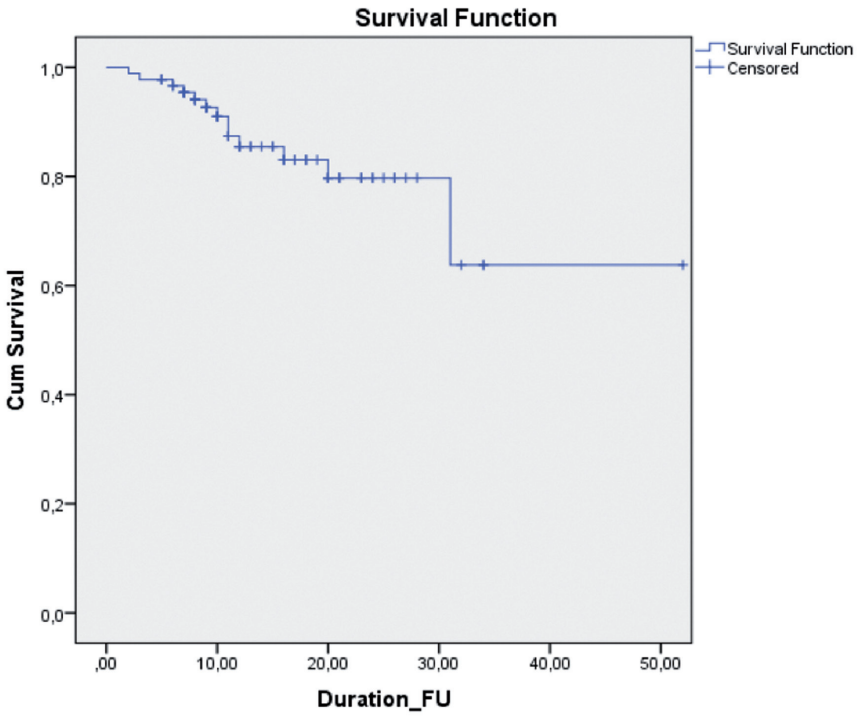

Fig. 1. Estimated cumulative proportion survival (Kaplan-Meier curve). [Duration FU: Duration of follow-up, in years].

other reports, except for Dankó *et al*. (14), who had a statistically significant higher incidence (38.2% *vs*. 18.9%; *p*=0.0025). Our median delay in diagnosis (5 months) was similar to previous studies. Apart from the report on patients with PM/DM with anti-PM-Scl antibody (11), no other study has divided the course of the disease into monophasic, relapsing and remitting and continuous progressive. Although not all of the previous studies describe treatment, the percentage use of steroids in our sample (98.9%) was similar to that of Marie *et al*. (26) (98.9% *vs*. 98.7%; *p*=0,5549), but it was higher than the reported by Bronner *et al*. (8) (98.9% *vs*. 76%; *p*<0,0001) and Yu *et al*. (12) (98.9% *vs*. 68.2%; *p*<0,0001). Most of other reports had a short median follow-up, of 3 to 5 years (3, 8, 12), except for one study with 11 yrs (IQR 16) (24). Nevertheless, the median follow-up of our patients (11.5 yrs) was statistically significantly longer (*p*=0.0032), which arguably makes our data interpretation more reliable.

Although within the expected range, the overall mortality in our sample was low. Our observed 1 and 5-years survival was superior to the highest previously reported, though not statistically significant (respectively: 100% *vs*. 95%, *p*=0.0745; 97.8% *vs*. 92%, *p*=0.1119) (14-15, 23-24). The estimated cumulative proportion survival at 10 and 20 years was 91% and 79.7%. Considering studies in which 10-year survival was estimated, ours (91%) was statistically significantly higher than previous reports (Yu *et al*. (12): 66.2%, *p*<0.0001; Schiopu *et al*. (3): 62%, *p*<0.0001; Airio *et al*. (24): 50%, *p*<0.0001), except for that of Dankó *et al*. (14), who described a similar outcome (91% *vs*. 89%, *p*=0.7761). Airio *et al*. (24) had the lowest 10-year survival. They searched in the National Discharge Registry of Finland for patients with PM or DM diagnosed between 1969 and 1985, fulfilling Bohan and Peter criteria and who had available medical records. The 176 PM and 72 DM patients were then followed up until death or till 1995, with an overall median follow-up of 11 years (IQR10-26). The 10-year survival rates for both PM and DM were about 50% only. Statistically significant predictors of outcome included older age at diagnosis and, in PM, delay of diagnosis and the presence of cancer. The higher mean age of this cohort of patients – 56(14) in PM and 53(17) in DM – may, in part, help to explain the higher mortality. The authors do not specify if neoplasia, when present, was diagnosed before, concomitantly or after myositis, which might also lead to a misinterpretation of the results.

The main causes of death in our study had a similar frequency to those in other studies and included infection, cardiovascular events, neoplasia and respiratory failure.

Male gender, pulmonary involvement, chronic progressive course of the disease and use of rituximab were significantly associated with an increased probability of death in our sample. As far as the later is concerned, it is probably related to the fact that rituximab was only used in severe cases, which were refractory to treatment. In fact, in multivariate analysis, pulmonary involvement (HR 4.711; 95% CI 1.314–16.892; *p*=0.017) was the only independent statistically significant predictor factor of worse prognosis.

Our low mortality might be due to timely referral by General Practitioners, leading to rapid treatment onset, and a regular follow-up by the Rheumatology Department. Additionally, few patients in our cohort had pulmonary involvement, a predictor of worse outcome, which could also help to explain the good survival.

It is not easy, though, to compare the conclusions of the studies, mainly due to the discrepancies with regard to inclusion criteria. For example, some authors included cancer-associated myositis (10, 12, 26, 27), which inevitably leads to a higher mortality.

Our study has some limitations. It is observational, retrospective and single-centred, it includes patients with varying lengths of follow-up and some data are missing. Autoantibodies, notably the rarer anti-synthetase antibodies, were among the main missing values, especially in patients diagnosed before 1990. This led to a suboptimal analysis of the contribution of autoantibodies to prognosis.

Further studies are necessary to understand the course and prognosis of PM/DM, based on more complete patient

Table II. Descriptive analysis of the patients who died during follow-up.

Gender, n (%)	Female	6 (46.2)
	Male	7 (53.8)
Age at diagnosis (yrs), mean (SD)	40.3 (12.90)	
Ethnic group, n (%)	White	8 (61.5)
	Afro-caribbean	2 (15.4)
	Asian	2 (15.4)
	Black	1 (7.7)
Diagnostic category, n (%)	APM	5 (38.5)
	ADM	6 (46.2)
	Overlap syndrome	2 (15.4)
	JDM	0 (0)
Extramuscular involvement, n (%)	Lung	5 (38.5)
	Heart	2 (15.4)
	GI	0 (0)
Highest CK, n (%)	Normal	1 (7.7)
	<2x upper limit	0 (0)
	2-5x upper limit	1 (7.7)
	>5x upper limit	11 (84.6)
ANA, n (%)	Positive	8 (61.5)
Other autoantibodies, n (%)	Jo1+	5 (41.7)
	SRP+	0 (0)
	(1 missing value)	
Treatment, n (%)	Prednisolone	13 (100)
	DMARDS (one or more)	11 (84.6)
	Cyclo	3 (23.1)
	MMF	0 (0)
	IVIg	6 (46.2)
	Plasma exchange	1 (7.7)
	Rituximab	4 (30.8)
	Tacrolimus (systemic)	0 (0)
Course of the disease, n (%)	Monophasic	3 (23.1)
	R&R	1 (7.7)
	Chronic progressive	9 (69.2)
Cause of death	Infection	4 (30.8)
	Cardiovascular event	4 (30.8)
	Neoplasia	3 (23.1)
	Respiratory failure	1 (7.7)
	Trauma	1 (7.7)

records and multicentre prospective analyses. However, as far as we are aware, our study has the longest follow-up reported and predicts a better than expected 10-year survival.

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