Favourable Functional Outcomes In Idiopathic Inflammatory Myositis- A Single Centre Experience Over 15 Years

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Abstract

Background: To describe the long term clinical outcome and prognostic factors associated with outcome in a longitudinal cohort of idiopathic inflammatory myositis (IIM).

Methods: In this retrospective cohort study, IIM patients were classified as per Bohan and Peter criteria. In those with ≥ 24 months of follow-up; treatment response, functional outcomes [health assessment questionnaire-disability index(HAQ-DI) and modified Rankin score(MRS)], Myositis damage index(MDI) at last follow-up was recorded.

Results: The cohort consists of 175 patients, with a mean age of 40.9(±12.6) years, M:F 1:3.3; the IIM subsets were dermatomyositis(DM) 78(44.6%), overlap myositis(OM) 45(25.7%), antisynthetase syndrome(ASS) 11(6.3%), polymyositis(PM) 25(14.3%) and juvenile DM/OM in 15(8.6%) patients. Mortality rate was 13.4% and disease related deaths was 9.1%.

Ninety-four patients have followed up for ≥24 months, the median (IQR) of 65(35,100.7) months. At last follow-up, 13.8% were in treatment free remission, 73.4%, 11.7% had complete clinical response and partial clinical response with treatment respectively. HAQ-DI and MRS were favourable in > 90% of patients. At last follow-up, one-third were off-steroids. Discontinuation of steroids was associated with HAQ-DI of 0 and lower MRS. Complete clinical response on/off medication at last follow-up was associated with HAQ-DI of 0[OR10.9; 95%CI(3.3,160)], better MRS[OR 3.2; 95%CI(1.4,7.3)] and lesser MDI[OR 1.7; 95% CI(1.1,2.7)] at the last follow-up as compared to partial response. Baseline parameters and IIM subsets did not significantly influence outcome.

Conclusion: Our longitudinal cohort of IIM had a good outcome in all major myositis subsets. Partial clinical response on treatment is associated with worse functional outcomes and damage accrual.

Key Messages

1. Outcome is favourable with conventional immunomodulatory treatment in majority at a median of 65 months.

2. Partial clinical response to treatment is associated with worse functional outcomes and damage accrual.

3. Mortality is early and disease related.

4. Clinicopathological subsets do not influence outcome.

Background

Idiopathic Inflammatory myositis (IIM) are a group of potentially treatable, rare heterogenous chronic systemic autoimmune disorders predominantly affecting the skeletal muscles. A multitude of immunological perturbations contribute to the pathogenesis of myositis, leading to varying severity of not only the myositis but also inflammation of extramuscular organs chiefly lung and skin.[1]

Despite the advances in understanding of immunopathogenesis of IIM, the backbone of treatment for all the subgroups remains almost similar; consisting of glucocorticoids and one or more immunosuppressants.[2] Considering the heterogeneity of IIM, treatment outcomes have been variable. Similarly, outcome measures and response criteria have been difficult to employ largely due to heterogeneity of IIM and very few large treatment trial results are available to guide clinicians.

Large cohort studies on IIM with long term outcome and its predictors can support and direct research to improve therapeutic results, however these are sparse due to its infrequent occurrence.[3–5] Moreover, with enhanced understanding of immune mechanisms; the classifications, definitions of clinical phenotype, autoantibody profiling, reporting patterns for muscle biopsy for IIM have undergone immense overhaul in last few decades. Prospective multicentric cohorts have been initiated at various centers in Europe and US, outcome data from them should be available in near future.[6] Furthermore, there is influence of distinct geographic, ethnic and or environmental factors on the clinical phenotype of IIM, and autoantibody distribution underpinning the need for long term outcome studies across the world.[7]

From Indian subcontinent, the IIM cohorts with long term follow-up are rather sparse.[8–13] Here, we describe the long term outcome, prognostic factors and mortality data of the IIM subsets over 15 years from our tertiary care referral medical college hospital, India using standard measures of clinical response and patient-reported outcomes.[14–18]

Methods

Case selection and IIM subgrouping:

This is a retrospective cohort study, using a structured case record form (CRF); clinical phenotype, treatment administered, follow up and outcomes have been recorded for all consecutive patients of inflammatory myositis from the year 2006 onwards. All patients were classified as definite/probable/possible inflammatory myositis as per Bohan & Peter criteria.[19,20] The followup information was updated and extracted till May 2020. As per the current understanding of IIM, patients were re-subgrouped into dermatomyositis (DM), polymyositis (PM), overlap myositis (OM), antisynthetase syndrome (ASS), immune mediated necrotising myositis (IMNM) and clinically amyopathic DM (CADM: includes both amyopathic and hypo myopathic subsets).[21–25] Juvenile onset myositis (onset < 16 years) were subclassified as juvenile dermatomyositis (JDM) and juvenile polymyositis based on the presence/absence of DM specific rash. Subjects with Inclusion body myositis, muscle dystrophy and metabolic myopathy were excluded. Study was approved by St. John's Medical College Institute Ethics Review Board (Approved No-80/2017).

Disease specific evaluation and assessments:

Their initial assessments consisted of various descriptors of clinical phenotype including MMT-8, MITAX and dermatologist opinion of cutaneous manifestations.[26,27] Extramuscular organ assessment was as per clinical indication. Association with malignancy was defined by diagnosis of malignancy within 3 years of onset of myositis. However, diagnosis anytime in the past or at follow-up was recorded. Laboratory assessments include measures of muscle inflammation such as creatine kinase enzyme (CK) level, aspartate aminotransferase (AST) and lactate dehydrogenase (LDH). Autoantibody profile consisted of antinuclear antibody by indirect immunofluorescence, myositis associated antibodies (anti RNP/Sm, anti Ro-60, anti La, anti Ro-52) and anti Jo-1 (myositis specific antibody) as part of EUROIMMUN ANA profile-3 immunoblot assay. In a subset of cohort, EUROIMMUN myoblot was performed which includes anti Mi2, anti SRP, anti aminoacyl t-RNA synthetase antibodies (ARS), anti Pm-Scl and anti Ku. All immunoblot strips were analyzed with the EUROLineScan (Euroimmun) and +, ++ or +++ was considered significant. EMG was performed by a neuro physician at our centre. Muscle biopsy was performed in consenting patients and were analysed by neuropathologist at NIMHANS (National Institute of Mental Health and Neurosciences) using hematoxylin and eosin stain, modified Gomori's trichrome stain, periodic acid Schiff (PAS) and immunohistochemistry, as considered appropriate.

Treatment protocols, clinical course and outcome analysis:

Treatment protocol included methylprednisolone pulse or high dose steroids at 1mg/kg body weight for organ threatening disease or respiratory and pharyngeal muscle weakness, while others received steroids equivalent to 0.5 mg/kg body weight. All patients received immunosuppressive therapy at initial presentation alongside steroids. Steroids were tapered as per physician assessment of improvement of clinical and lab parameters. Course and outcome were analysed for those with 24 or more months of follow up. It was defined as monocyclic, chronic polycyclic and chronic continuous as per Heuber et.al.[28] Outcomes were recorded as complete/partial clinical response at 6 months and last follow-up, based on physician assessment of muscle power, status of extra muscular features, functional class and laboratory parameters. Complete clinical response was defined as no evidence of active myositis/activity in extramuscular organs for ≥6 months while receiving therapy as determined by treating physician.[29] Patients not meeting the above definition were grouped into partial clinical response as per the judgement of treating physician. Relapse was recorded in patients with >6 months of followup as clinical worsening after a period of improvement. Functional capacity at last follow-up was assessed using 2 patient reported outcome measures; MD-health assessment questionnaire (MD-HAQ) and modified Rankin score(MRS).[30,31] Damage accrual at last follow up was assessed using Myositis damage index (MDI).[26,27] Mortality was classified as myositis related if accompanying active illness, significant respiratory weakness, significant infection during initial admission or cancer related.

Statistics:

Demographic details were represented as frequency (percentage) mean (+/- standard deviation) and median (interquartile range) as appropriate. Chi-square test or Fisher exact test was used to check for association between categorical variables. Association studies for means of continuous variables were evaluated using Student's t-test or Wilcoxon rank sum test as appropriate. Factors associated with complete clinical response, steroid withdrawal and mortality were analysed using logistic regression analysis. Factors found to be significant ($p<0.05$) in univariate analysis were taken up for multivariate analysis. Survival function was analysed using Kaplan Meier estimation. STATA software version 16 was used for the above analysis, p value was kept at 5% significance.

Results

Information from a total of 190 CRFs was extracted. Of them, 15 were excluded due to incomplete information or change in diagnosis at follow up. The cohort consisted of 175 patients, with a mean age of 40.9 years (± 12.6) and a female preponderance (F:M::3.3:1). Of the cohort 133/175(76%) were classifiable as definite/probable IIM as per Peter and Bohan criteria. They were sub-classified as DM 78(44.6%), OM 45 (25.7%), ASS 11(6.3%) and PM 25(14.3%) and a single case of NAM. In the subset with DM, 5 were CADM. Juvenile onset IIM were

categorized into juvenile DM (12/15) and juvenile onset OM (3/15). The baseline demographics, disease subsets, autoantibody profile and muscle histopathology features are represented in Table 1.

Table 1
Baseline demographics, clinical phenotype, autoantibodies, treatment and mortality overview - IIM (overall and subsets).

	Overall	DM	OM	PM	JM	ASS
N (%)	175	78(44.6)	45(25.7) 20/11/10/4(SSc,MCTD,UCTD,SLE)	25(14.3)	15(8.6)	11(6.3)
Median age in Years (IQR)	38(27.5,48.5)	39.5(30,50)	37(34,44)	45(29.5,50)	12.5(10,15)	46(43,55)
F:M	3.3:1	2.9: 1	6.5:1	3.2:1	2:1	1.2:1
Median(IQR) duration of illness(months)	4(1,7)	3(1,8)	4(1,5)	4(1,6)	2(1,6)	3(2,14.5)
Median MMT-8 (baseline) n = 133	61(49,69)	61(50,67)	61(49,72)	55(39,61)	61.5(45.5,71)	66(61.5,75)
MITAX (baseline) n = 75	12(7,16)	12.5(7,18)	12(6.75,12)	9(5,12)	13(8.5,15.5)	0
Dysphagia (%)	51 (29.1)	27(34.6)	14 (31.1)	6 (24)	3 (20)	0 *
Dysphonia (%)	14 (8)	5 (6.4)	4 (8.8)	2 (8)	2 (13.3)	0
Respiratory weakness(%)	6 (3.4)	2(2.5)	4 (8.8)	0	0	0
ILD (%)	24 (13.7)	6 (7.7)	10 (22.2)*	1 (2.4)	1 (6.6)	6(54.5)***
DM specific rash(%)	70 (40)	54 (69.2)	3 (6.6)	1 (2.4)	10 (66.6)	2(18.2)
Cardiac (%)	11 (6.3)	1 (1.3)	6 (13.3)*	0	1(6.6)	3(27.3)**
Calcinosis (%)	13 (7.4)	5 (6.4)	2 (4.4)	1(2.4)	3 (20)	2(18.2)
Malignancy (%)	7 (4)	6 (7.7)	0	1(2.4)	0	0
ANA (n = 154)(%)	98 (63.6)	28 (38.9)	34 (87)	10(41.6)	9 (60)	8 (80)
MSA (n = 111)(%)	12 (10.8)	2(4.4)	-	1(6.6)	1 (7.6)	8 (72.7)
Jo-1	8 (7.2)	4 (8.8)	-	1 (6.6)	-	3 (27.2)
Non Jo-1 ARS	10 (9)	8 (17)	1 (4.3)	-	1 (7.6)	-
MI-2(α&β)	3 (2.7)	1 (2.2)	2 (8.6)	-	-	-
SRP						
MAA (n = 137) (%)	41 (29.9)	9 (16.3)	25 (62.5)**	5 (26.3)	2 (15.4)	0
U1RNP	50 (36.5)	14 (25.4)	22 (55)#	4 (21)	3 (23)	7 (63)**
Ro-52	7 (6.3)	3 (5.4)	3 (7.5)	1 (5.2)	-	-
Ku	10 (9)	4 (7.2)	2 (5)	1 (5.2)	3 (23)	-
Pm-Scl	5 (3.6)	1 (1.8)	4 (10)	-	-	-
Scl 70	9 (6.5)	2 (3.6)	2 (5)	3 (15.7)	2 (15.4)	-
SSA	4 (2.9)	2 (3.6)	2 (5)	-	-	-
CENP						
Muscle Histopathology	n = 77	n = 34	n = 14	n = 14	n = 8	n = 4

Statistically significant- *p = .03(ASS vs rest & OM vs rest); #-.01(OM vs rest); **p = .02(ASS vs rest & OM vs rest);*** p = .001(ASS vs rest).

DM- Dermatomycosis, PM - polymyositis, OM - overlap myositis, SSc- systemic sclerosis, MCTD - Mixed connective tissue disease, UCTD - undifferentiated CTD, SLE - systemic lupus erythematosus, ASS- antisynthetase syndrome, JM- Juvenile Myositis, ILD- Interstitial Lung Disease, MMT8- Manual Muscle Testing, MITAX- myositis intention to treat activity index, PFA - Perifascicular atrophy, HCQ- Hydroxychloroquine, PLEX-Plasma Exchange, IVIg- Intravenous Immunoglobulin, MP- Methylprednisolone

	Overall	DM	OM	PM	JM	ASS
PFA	22	16	2	0	4	0
Endomysial inflammation	3	1	0	1	0	1
Perivascular inflammation	44	21	8	9	4	2
Necrosis	29	14	8	4	2	0
No features of myositis	4	0	1	1	1	1
Treatment	165(94.2)	75(96.1)	45(100)	22(88)	12(80)	10(90.9)
Steroid	58(33)	27(34.6)	13(28.8)	8(32)	5(33.3)	5(45.4)
MP pulse	90 (52)	40(51.2)	26(57.7)	8(32)	10(66.6)	6(54.5)
Immunosuppressants	52 (29.7)	24 (30.7)	17(37.7)	8(32)	2(13.3)	1(9)
Methotrexate	33 (18.9)	13(16.6)	9(20)	5(20)	2(13.3)	4(36.3)
Azathioprine	12 (6.8)	5(6.4)	4(8)	1(4)	-	2(18.2)
Mycophenolate mofetil	19 (10.8)	8(10.2)	5(11)	-	1(6.6)	5(45.4)
Cyclophosphamide	28 (16)	13(16.6)	9(20)	-	3(20)	3(27.2)
Rituximab	7 (4)	2(2.5)	3(6.6)	-	1(6.6)	1(9)
HCQ	4 (2.2)	1(1.2)	2(4.4)	-	-	1(9)
Tacrolimus	4 (2.3)	3(3.8)	-	1(4)	-	-
Leflunomide	2 (1.1)	1(1.2)	-	1(4)	-	-
IVIg						
PLEX						
Death	24 (13.7)	15(19.2)	2(4.4)	4(16)	2(13.3)	1(9)

Statistically significant- *p = .03(ASS vs rest & OM vs rest); #-.01(OM vs rest); **p = .02(ASS vs rest & OM vs rest);*** p = .001(ASS vs rest).

DM- Dermatomycosis, PM - polymyositis, OM - overlap myositis, SSc- systemic sclerosis, MCTD - Mixed connective tissue disease, UCTD - undifferentiated CTD, SLE - systemic lupus erythematosus, ASS- antisynthetase syndrome, JM- Juvenile Myositis, ILD- Interstitial Lung Disease, MMT8- Manual Muscle Testing, MITAX- myositis intention to treat activity index, PFA - Perifascicular atrophy, HCQ- Hydroxychloroquine, PLEX-Plasma Exchange, IVIg- Intravenous Immunoglobulin, MP- Methylprednisolone

Myositis autoantibodies:

Antinuclear antibody was detected in 98(57.25%). MSAs were demonstrated in 26/111(23.4%), most commonly Jo-1 12/137(8.8%), Mi-2 10/111(9%), non Jo-1 ARS 8/111(7.2%) and SRP 3/111(2.7%). MAAs were detected in 81/137(59.1%) while 16(11.7%) were negative for both MSA & MAA. Multiple MSA positivity was seen in 6/111(5.4%), overlap of MSA and MAA was noted in 11/111 (9.9%). These have been detailed in Table 1.

Clinical response and functional outcome

Table 2
Outcome parameters at > 24 months of follow up in IIM subsets (n = 94)

	Overall(94) n(%)	DM(35) n(%)	OM(33) n(%)	PM(13) n(%)	JM(8) n(%)	ASS(5) n(%)
Course	13(13.8)	4(10.8)	5(15.2)	3(23.07)	1(12.5)	0
Monocyclic	35(37.2)	14(40)	11(33.3)	4(30.7)	4(50)	2(40)
Polycyclic	46(48.9)	17(45.9)	17(51.5)	6(46.1)	3(37.5)	3(60)
Chronic continuous						
Response	69(73.4)	28(80)	25(75.7)	7(53.8)	5(62.5)	4(100)
Complete Response on Rx	13(13.8)	4(10.8)	5(15.2)	3(23.07	1(12.5)	0
Complete Response off Rx	11(11.7)	3(8.6)	3(9.1)	3(23.07)	2(24)	0
Partial						
Steroid (mg)/ day at last FU(n = 87)	35(40.2)	14(42.4)	13(43.3)	5(38.5)	3(42.8)	0
0	45(51.7)	18(51.5)	14(46.7)	6(53.8)	3(42.8)	0
≤ 7.5	7(0.08)	2(6.1)	3(10)	1(7.7)	1(14.3)	4(100)
> 7.5						
HAQ(n = 79)	51(64.6)	19(65.5)	18(64.3)	5(45.5)	6(100)	3(60)
0	24(30.4)	10(34.5)	9(32.1)	4(36.4)	0	1(20)
≤ 1	4(5)	0	1(3.6)	2(18.2)	0	1(20)
> 1						
MDI(n = 90)	38(42.7)	17(48.6)	11(34.4)	4(36.4)	4(50)	2(50)
0	36(40.4)	13(37.1)	13(40.6)	6(54.5)	2(25)	2(50)
1–2	16(17.7)	5(14.3)	8(25)	1(9.1)	2(25)	
> 2						
MRS (n = 84)	61(72.6)	26(72)	19(65.5)	7(58.3)	6(100)	4(80)
0–1	19(22.6)	7(28)	9(31)	3(25)	0	0
2	4(4.8)	0	1(3.5)	2(16.7)	0	1(20)
> 2						

HAQ-Health Assessment questionnaire's; MDI – Myositis Damage Index; MRS-Muscle Ranking Score; FU- Follow Up; Rx- Treatment

Table 3
Prognostic factors for clinical response, steroids discontinuation and mortality

Prognostic factors for clinical response, steroid withdrawal and death	n	Odds ratio(95% CI)	P value	Adjusted odds (95% CI)	P value
CR on or off Rx (n = 93)					
No Relapses	93	4.9(1.2, 19.8)	0.02	12.9(0.9,188)	0.06
HAQ ≤ 1 at last f/u	76	10.9 (3.3, 160)	0.008	6.7(0.8,51.8)	0.06
MRS	90	3.2(1.4,7.3)	0.004	1.7(0.4,6.6)	0.4
MDI	90	1.7(1.1,2.7)	0.01	1.7(0.9,2.9)	0.07
Steroid withdrawal (n = 93)					
Myositis associated antibody	67	5.7(1.8,17.4)	0.002	4.6(0.69,30.6)	0.14
Ro 52	69	3.2(1.1,9.5)	0.03	1(0.14,6.9)	0.9
Follow-up duration	93	0.9(0.96,0.99)	0.001	0.9(0.96,0.99)	0.02
HAQ < = 1 at last f/u	76	3.3(1.3,8.6)	0.01	1.8(0.2,14.7)	0.5
MRS at last f/u	80	1.7(1,3)	0.03	1.2(0.3,4.7)	0.7
Mortality (n = 175)					
DM vs non DM		2.52(0.9,6.3)	0.052		
Baseline MMT-8	131	0.97(0.93,1)	0.05	0.9(0.9,1.1)	0.1
Dysphagia		2.5(1.03,6.2)	0.04	1.5(0.3,6.8)	0.6
Dysphonia		5.3(1.6,17)	0.005	3.4(0.3,35.8)	0.3
Respiratory weakness		6.3(1.8,22)	0.004	2.5(0.2,28.3)	0.4
Malignancy		6(1.9,18.3)	0.002	1.5(0.2,10.5)	0.7
RNP/Sm positivity	140	0.12(0.02,0.9)	0.002	0.1(0.02,1.2)	0.07
Factors analysed in univariate analysis were age, sex, diagnosis, time to presentation, baseline MMT-8, oropharyngeal weakness, ILD, MSA positivity, MAA positivity, Ro-52positivity, RNP/Sm positivity, time to 0–15 mg/kg steroids, response at 6 months, relapsing disease, HAQ-DI ,MRS,MDI at last follow-up. Significant factors (p = < 0.05) only are represented in the table.					
DM- Dermatomycosis, MMT8- Manual Muscle Testing, MRS-Muscle Ranking Score, MITAX- myositis intention to treat activity index, HCQ-Hydroxychloroquine, CR-Complete Response					

Steroids were used in all patients except one, the majority [157(89.7%)] required high dose steroids, 58/175 (33.1%) required pulse steroids in addition. All patients received simultaneous steroid sparing agents. The distribution of steroid sparing immunomodulators are represented in Table 1. Median number of steroid sparing immunomodulators used in management of these patients were 1(1,2). Methotrexate was the most common immunomodulator prescribed in 91 (52%) of patients. Nineteen (10.9%) patients in this cohort required rituximab due to either relapse or lack of adequate response to steroids and or steroid sparing immunomodulators.

Follow up information of 24 months or more was available in 94 (54.9%) patients, the median (IQR) followup in this subset was 65(35,100.7) months. Of them, 13(13.8%) had monocyclic illness (treatment free remission), 37(38.5%) polycyclic and 46(47.9%) chronic continuous course. At the last follow up, 69(73.4%) were in complete clinical remission (CR) on medications, 11(11.7%) had partial response(PR). Overall, complete discontinuation of steroids could be achieved in 35(36.5%) and another 46(47.9%) were on low dose prednisolone < 7.5mg/day. Complete discontinuation of steroids[35(38.9%)] was associated with a longer follow-up duration(OR 0.9(0.96,0.99)), MAA positivity[OR 5.7(1.8,17.4)]), Ro-52 positivity [(3.2(1.1.9,5)] better HAQ-DI (OR 3.3(1.3,8.6)) and MRS[OR 1.7(1,3)]) scores as compared to those who were on some dose of steroids[52(61.1%)].

Complete clinical response on/off treatment at last follow-up[82(87.2%)] were less likely to have a relapse (OR 4.9(1.2,19.8), more likely to have HAQ-DI of 0 at last follow-up[OR 10.9(3.3,160)], better MRS [3.2(1.]4,7.3)), lesser MDI scores[1.7 (1.1,2.7)]) as compared to those who had partial response[11(11.7%)] at last follow-up. Treatment free remission was attained by 13(13.8%) individuals, after a median(IQR) of 60(36,89) months; they had a longer median duration of follow-up[OR 0.9(0.97,0.99)], were less likely to have dysphagia at presentation [OR

0.3(0.09,0.9)], were associated with Ro-52 positive [OR 8.5(1,70)]. They had a moderate severity at presentation [median(IQR)MMT 8 of 52.5(50,59)], other baseline factors and response and functional outcomes were not different from the rest of the cohort.

Median HAQ score (n = 79) recorded at last follow-up was 0(0,0.2) and was recorded 0 in 51(63.7%). Another 24(31.2%) patients had mild to moderate disability (HAQ > 0 ≤ 1) and only 4 reported moderate to severe (HAQ > 1) disability (Fig. 1). Correspondingly, MRS scores (84) were favorable in our cohort with median scores of 0(0,2) ; 61(70.4%) having no residual symptoms or no significant disability(score-0,1); 19(21.6%) having slight disability (score-2) and 4(5.7%) having moderate disability respectively. Median MDI scores of the cohort (n = 89) was 1(1,2).

In view of the majority having a favourable outcome, factors influencing outcome were not further explored. The common complications observed during followup included infections, metabolic and cardiovascular events. These are represented in supplementary table2.

Relapse:

Among patients who have followed up for longer than 6 months (n = 125), a single relapse has occurred in 45(36%) while more than one relapse has occurred in 21(16.8%). Median relapse free survival rate of our cohort is 121(CI 88–153) months. Survival curve based on relapse free survival is represented in Fig. 2. Factors such as IIM subtype, dysphagia, ILD, MAA, complete vs partial response at 6 months, median HAQ, median MRS and median MDI were not different in the subgroups who had at least one relapse versus those who had no relapse.

Malignancy:

Association with malignancy was noted in 7 patients (DM-5, CADM-1, PM-1). The median duration between diagnosis of malignancy and myositis was 2.5(0,5) months except for a single patient developing malignancy 59 months after diagnosis of myositis. Features of muscle disease / DM skin lesions persisted in 4 even after the treatment of malignancy, requiring steroids and immunomodulatory agents over long term. The malignancies noted were carcinoma of breast (2), papillary carcinoma of thyroid (1), lung carcinoma (2) and adenocarcinoma of ovary(2).

Mortality:

In our cohort, 24 (13.7%) patients have died. Disease specific mortality rate was 9.1%. One year, 5 years and 10 years cumulative survival rate of our cohort was 89.1%, 86.9% and 86.3% respectively. Majority of deaths (15/24) occurred during the initial 6 months of illness and were related to disease (45.8%) or infectious complications(16.6%). The median duration from diagnosis to death was 3.5 (1,10.5) months. The mean survival time of the cohort was 239 (CI 220,258) months(Fig. 3).

Acute coronary syndrome (ACS, n = 2) leading to deaths were attributed to IIM both were young (< 50 years) and had no other adverse cardiac risk factors. Of the 7 patients with malignancy, 4 have died during follow up. Two were directly related to malignancy and occurred soon after diagnosis itself. Survival curve based on the above data is depicted in Fig. 2. Univariate regression analysis of factors associated with mortality were baseline MMT-8[OR 0.97(0.9,1)], dysphonia[5.3(1.6,17)], dysphagia[2.5(1,6.2)], respiratory weakness[6.3(1.8,22)], malignancy[6(1.9,18.3)], and absence of RNP/Sm[0.1(0.02,0.9)], however none of the factors were found to be significant in multivariate analysis (Table 3).

Discussion

We present here the largest single centre prospective longitudinal data on inflammatory myositis from the Indian subcontinent in a real-life setting. Clinical phenotype of our cohort is similar to the published reports across the world, however, we report a lower prevalence of extramuscular manifestations(Supplementary table 1).[3,11,32,33] Higher female preponderance, lesser mean age in our cohort as compared to EuroMyositis cohort is likely contributed by higher prevalence of OM subset in our cohort, however it is comparable to the other Indian and Chinese cohort.[3,11,32] Polymyositis proportion(14.3%) is higher than in other published cohorts, probably attributable to prevalent understanding of IIM at that time. As we have learnt since the discovery of MSA and recognition of MAA, that more and more PM can be classified either as DM or ASS or IMNM or IBM.[34]

Clinical response and functional outcome:

The induction and maintenance immunosuppressive treatment is in line with other published cohorts. However, the median number of steroid sparing immunomodulatory medications used is less in our cohort as compared to the Euro Myositis cohort. Hallmark of our cohort is discontinuation of steroids in almost one-third of patients and the ability to reduce it to ≤ 7.5 mg/day prednisone in close to half (47.9%) of the patients. There are very few studies discussing this matter, however it is comparable to the large Chinese cohort of Xio Ming Shu et.al.[3] Complete discontinuation of steroids is associated with better HAQ and MRS scores, hence, this target should be pursued in all IIM patients.

Complete clinical response on or off medication is associated with absence of relapse, better functional outcomes in terms of HAQ-DI and MRS, and reduced damage accrual in our cohort. Relapse related to a refractory disease needs a consideration for revision of the immunomodulatory therapies as a target of complete clinical response needs to be pursued.

Treatment-free remission differs in various cohorts. Treatment free remission was around 20% in the Netherland cohort, and was not associated with any of the factors studied.[31] Another Indian Cohort by Ramesha et al. have described a medication free remission in 39/68 (57%) of their cohort, however their cohort size is much smaller with lesser duration of follow-up.[35] Treatment free remission in our cohort was 13.8%; it was associated with longer duration of followup, absence of baseline dysphagia and Ro52 positivity. Treatment free remission is a subset which needs a dedicated study in future prospective cohorts.

Significant disability at last follow-up is seen in only < 5% of patients in our cohort, which is significantly different from the Netherland(24%) and Hungarian cohorts(47%).[31.36] Furthermore, in comparison to the Chinese cohort as well, the median HAQ-DI score in our cohort is lesser even though the number of patients with mild disability is higher, thereby demonstrating overall good outcome. Both the Caucasian cohorts were published a decade and half earlier, the improved outcomes in ours and the Chinese cohort, may be reflective of early referral, better understanding in the management over the last 2 decades. Amongst those who have survived, unless there is a recent relapse (< 10%), patients have remained quiescent on or off medications, which is similar to the Chinese and Hungarian cohort.[3,36]

Mortality:

Disease specific mortality rate (9.1%) in our cohort over a median duration of 26.5(6,72) months of follow up is comparable to other large cohorts.[3,31] Mortality rate and etiologies of death varies in various cohorts depending on definition of cause of death, inpatient vs population based mortality data. Majority of deaths (62.5%) occurred early (< 6 months since diagnosis); due to active disease and /or infections. Similar observation has been noted in recent publications from India too.[10,15]

Furthermore, infections as a major cause of mortality has also been highlighted in most large cohorts viz. Chinese, US, Mexico, Japanese, and Spanish (20–60%) cohorts too.[37–40] However, it is not a significant cause of mortality in some other cohorts (Hungarian, Swedish and Netherland cohorts), where active disease leading cardiorespiratory involvement and malignancy forms the leading cause of death.[39,40] Higher infections in our IIM cohort may possibly be related to the intense immunosuppression, during initial management of IIM and the general living conditions of our population. Although factors such as diagnosis of DM, oropharyngeal weakness, MMT-8, respiratory weakness and malignancy were found in association with mortality in univariate analysis in our cohort, none of these factors remained significant in multivariate analysis. Age at onset, malignancy, cardiopulmonary and respiratory muscle involvement appeared as risk factors to death in few cohorts.[3,31,41] Overall, contributing factors for mortality in IIM deserves attention on a larger scale, to ascertain and ameliorate modifiable factors. With more ease of availability of extended autoantibody profiling in IIM, this association may prove to be the most determining factor.

Limitations

Over the last few decades, understanding of interrelationship between clinical phenotypes, autoantibody associations, immunopathogenesis and therapeutic options for IIM have undergone a substantial transformation. The autoantibody assays and the therapeutic choices have been variable as per prevalent opinions and consensus in this real-life experience cohort. In the subgroup with relapse, structured review of compliance has not been performed. Similarly, in the mortality subgroup, information about terminal events and its treatment is unclear in some.

Conclusions

IIMs are potentially treatable diseases, requiring long term treatment and follow up. Through our study, we emphasize that good long term functional outcomes as determined by low HAQ, MRS can be achieved in majority. Complete clinical response on /off treatment and discontinuation of steroids is associated with better functional outcomes. Damage accrual is more in those who are unable to achieve complete clinical response with treatment. Infection remains an important cause of early mortality second only to active disease.

Declarations

Ethics approval and consent to participate: Study is approved by Institutional Ethics Committee St. John's Medical College, St. John's National Academy of Medical Sciences (Approved No-80/2017).

Consent for publication: Yes

Availability of data and materials: The data and materials are available to all authors

Competing interest: None of the authors has any conflict of interest to disclose.

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Authors Contribution:

1) Conception and design of the study- Dr.RJ, Dr.VS

2) Analysis and interpretation of data- Dr.RJ, Dr.VS, Mr.JMR

3) Data acquisition - All authors

4) Drafted the work and revised it critically for important intellectual content – Dr.RJ, Dr.VS, Dr.R N, Dr.AM

5) Approved the version to be published- All authors

6) Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved- All authors

Ethical Publication: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figures

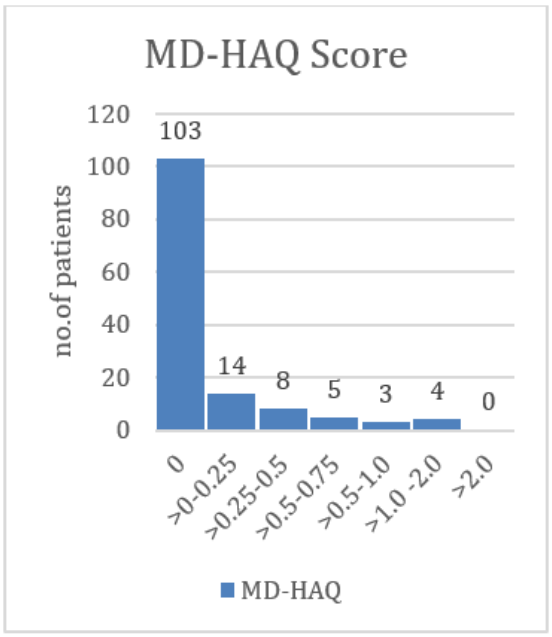
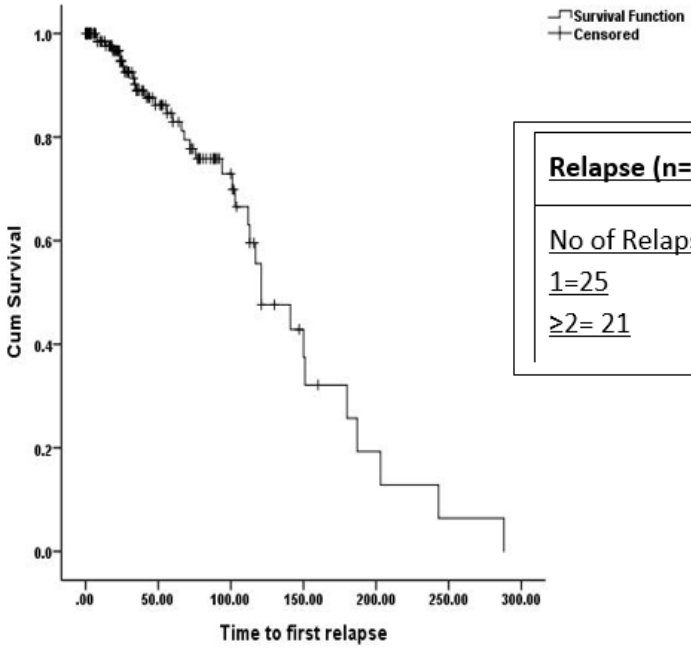


Figure 1

MD- HAQ score at last follow up

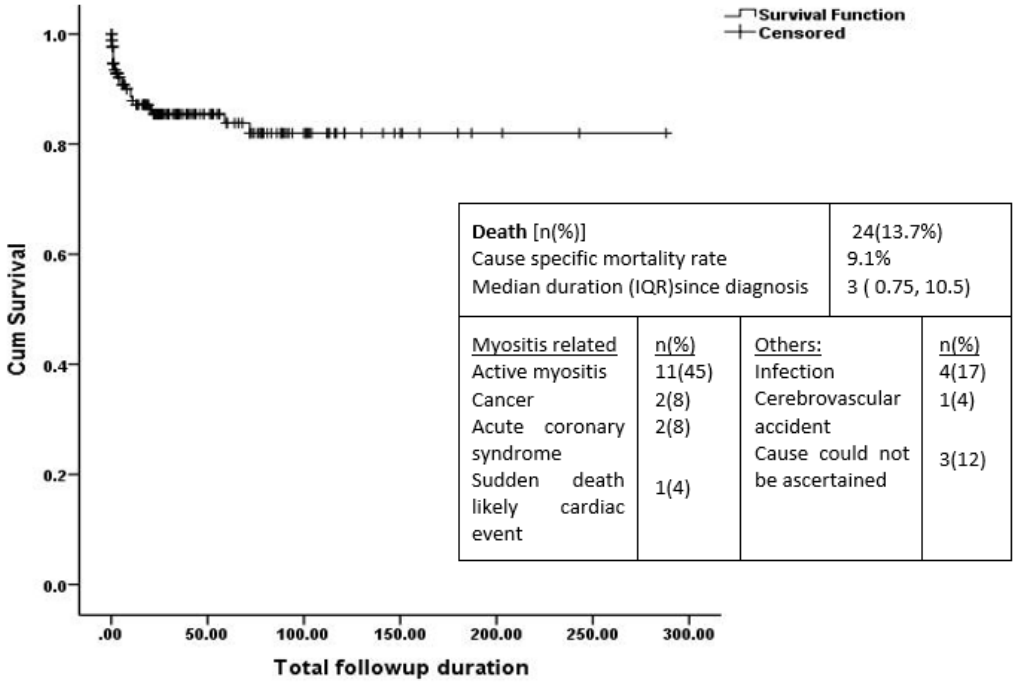


Relapse (n=125)	Reason for Relapse:
No of Relapses: 0 = 41 1=25 ≥2= 21	Refractory disease -7 Steroid taper <5 mg/day-23 Non-compliance-16

Median relapse free survival of the cohort is 121(CI 88-153) months

Figure 2

Relapse free survival curve



Death [n(%)]			24(13.7%)
Cause specific mortality rate			9.1%
Median duration (IQR)since diagnosis			3 (0.75, 10.5)
Myositis related	n(%)	Others:	n(%)
Active myositis	11(45)	Infection	4(17)
Cancer	2(8)	Cerebrovascular accident	1(4)
Acute coronary syndrome	2(8)	Cause could not be ascertained	3(12)
Sudden death likely cardiac event	1(4)		

Mean survival time of cohort = 239 (CI 220,258) months.

Figure 3

Cumulative survival curve of the cohort

Supplementary Files

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- SupplementaryTable.docx