Clinical Characteristics and Poor Predictors of Anti-NXP2 Antibody-Associated Chinese JDM Children

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Abstract

Background. Juvenile dermatomyositis (JDM) is a rare and sometimes fatal disease in children. The subtype of anti-NXP2 antibody-associated JDM is the leading cause of death in JDM, but there are no reports about clinical characteristics and high risk factors of poor prognosis. For the first time, we introduced the clinical characteristics and poor predictors of anti-NXP2 antibody-associated juvenile dermatomyositis in Chinese children.

Methods. Twenty-six patients with anti-NXP2 antibody-related JDM from 85 JDM patients diagnosed from January 2016 to November 2019 were involved. Logistic regression was used to analyze the risk factors for refractory cases and death.

Results. The ratio of male to female was 9:17. The median age of onset was 4.5 (1–13) years. Twenty-four cases (92.3%) had rash and muscle weakness. Treatments included glucocorticoids, immunosuppressive agents, biological agents (7 cases), plasma exchange, Janus kinase inhibitor (7 cases) and autologous stem cell transplant (1 case). Eleven cases (11/26, 42.3%) were refractory JDM associated with edema, skin ulcer, muscle strength < = grade 3, CD4/CD8 ratio < 1.4 and SF > 200ug/ml. Among 6 cases (6/26, 23.1%) with severe gastrointestinal involvement, 5 cases died and 1 case survived after ASCT. The risk factors for gastrointestinal involvement and death were edema, skin ulcer, severe muscle weakness (Dysphagia/Hoarseness/Lower voice), BMI < 15 and ANA positive.

Conclusions. Anti-NXP2 antibody-positive JDM of Chinese children was characterized by rash and severe muscle weakness. Edema, skin ulcer and severe muscle weakness predicted refractory and poor prognosis. Decreased CD4/CD8 ratio and high SF related with refractory cases, and very low BMI and ANA (+) predicted high risk of gastrointestinal involvement and death.

Background

Juvenile dermatomyositis (JDM) is an autoimmune vasculitis, mainly characterized by proximal muscle weakness and typical rash. The incidence rate is (2 ~ 4/100,000). China has a population of about 1.4 billion, among which 250 million are children under the age of 16. However, there are few reports on the incidence and clinical features of JDM in Chinese children.

JDM is a highly heterogeneous disease, involving not only muscles and skin, but also other organs including cardiovascular, respiratory, and gastrointestinal systems and even cause considerable mortality. Although many treatments have been applied to improve the prognosis of JDM,its mortality rate has almost become the leading cause of death of children with rheumatic and immunological diseases. In recent years, myositis-specific autoantibodies (MSAs) were found to be closely associated with distinct clinical features and prognosis of the DM sub-types. It is reported that anti-NXP2 antibody might be one of the most common and poor prognosis in JDM, which characterized by younger age, serious muscle weakness, atrophy, typical rashes and calcinosis.[1,2] Some case reports suggested that gastrointestinal involvement was a serious complication in anti-NXP2 antibody-related JDM .[2,3]

However, up to date, the predictors of refractory cases and risk factors for death of anti-NXP2 antibody-positive JDM have not been clearly identified. In order to determined the high risk factors associated with refractory cases and death in JDM, for the first time, we presented retrospective analysis of anti-NXP2 antibody-related

Chinese JDM cases. This would finally allow stratifying treatment regimens based on the risk factors of poor response and prognosis.

Patients And Methods

Patients

We performed a prospective study of Chinese children who were diagnosed as JDM with positive anit-NXP2 autoantibody at Capital Institute of Pediatrics (CIP) from January 2016 to November 2019. The inclusion criteria: (1) age <18 years old; (2) diagnosed as JDM based on the Bohan and Peter criteria for myositis;[4] (3) anti-NXP2 antibody positive. The exclusion criteria: Patients with other diseases that cause weakness or rash, or a clear alternative diagnosis and with unwillingness were excluded from the study. The age of disease onset was defined as the earliest age that the typical symptoms of JDM appeared. Duration before diagnosis indicates the time from onset to diagnosis. Refractory was defined as the ineffectiveness of glucocorticoids combined with more than two immunosuppressive agents, and (or) need more aggressive treatment like biological agents. This study was approved by Ethics Committee of CIP（KSSHERLL2017068）.

Laboratory examinations

We used immune dot blot to determine the presence of anti-NXP2 antibody in human serum (D-TEK, Belgium). Creatine kinase (CK) were tested by automated biochemical analyzer (Siemens, Germany). Serum ferritin (SF) was measured by quantitative chemiluminescence assay (Abbott Laboratories, US). Anti-nuclear antibodies (ANA) and anti-Ro-52 antibodies were measured by immunofluorescence assay (Euroimmun, US) and immunoblotting (Euroimmun, US) respectively. We assessed CD4/CD8 ratio by flow cytometry and immunofluorescence (Becton, Dickinson and Company, US).

Statistical analyses

Characteristics of patients were compared with four kinds of outcomes. Indicators include age at onset, duration, BMI, muscle force, childhood myositis assessment score (CMAS), CK, SF and CD4/CD8 ratio. Continuous variables are expressed as median and range (minimum-maximum) and categorical variables were expressed as frequency and percentage. Associations between the risk factors for poor outcomes were evaluated by univariate logistic regression analysis. Adjusted odds ratio (OR) and 95% confidence interval (95% CI) were calculated. In addition, follow-up time was compared using Wilcoxon's signed rank test and each variable was evaluated by Spearman correlation test. P values <0.05 (two-

sided) were considered as statistically significant. All statistical analyses were performed with R 3.2.3 (http://www.r-project.org/).

Results

Patients

Twenty six cases of 85 patients diagnosed as JDM were proved to be with anti-NXP2 autoantibody. Among the 26 patients, 13 cases including 4 severe patients were transferred from other hospitals. Ages at onset of these patients ranged from 1 to 13 years with the median age of 4.5 years. Table 1 presented the demographic and clinical characteristics of the patients.

Table 1
Demographic and clinical data of 26 patients with anti-NXP2 autoantibody positive JDM

Baseline Characteristics	n (%) or Median (range)
Diagnosis	
JDM	23(88.5%)
JPM	1(3.8%)
Overlap myositis	2(7.7%)*
Gender	
Male	9(34.6%)
Female	17(65.4%)
Age at onset (y)	4.5(1–13)
Duration from onset to diagnosis (m)	2.0(1.0–42.0)
First symptom	
Rash	8(30.8%)
Muscle weakness	5(19.2%)
Rash & muscle weakness	13(50%)
Proximal muscle strength	
<= grade 3	18(69.2%)
> grade 3	8(53.8%)
CMAS	7(0–47)
Dysphagia/Hoarseness/Lower Voice	15(57.7%)
Other signs	
Cutaneous ulceration	10(38.5%)
Periorbital edema	5(19.2%)
Calcification	3(11.5%)
Other organ systems	

JDM: juvenile dermatomyositis; JPM: juvenile polymyositis; CMAS: childhood myositis assessment score; ANA: antinuclear antibody; MRI: magnetic resonance imaging; EMG: electromyography; HRCT: high-resolution computed tomography; * overlapping with systemic sclerosis and juvenile idiopathic arthritis respectively. **GC: glucocorticoids including methylprednisolone and prednisolone; IA: immunosuppressive agents; $IA^{\leq 2}$: two or less than 2 types of immunosuppressive agents; $IA^{>2}$: more than 2 types of immunosuppressive agents; IVIG: intravenous immunoglobulin; BA: biological agents, including monoclonal antibodies and JAK inhibitors like Tofacitinib.

Baseline Characteristics	n (%) or Median (range)
Arthritis	8(30.8%)
Interstitial lung disease	7(26.9%)
Gastrointestinal involvement	6(23.1%)
Laboratory testing	
ANA (+) only	8(30.8%)
Anti-Ro52 antibody (+) only	3(11.5%)
ANA (+) & Anti-Ro52 antibody (+)	4(15.4%)
Other examination	
MRI: myositis	26
EMG: myogenic damage	18(81.8%)
HRCT: interstitial lung disease	7(28%)
Treatment**	
GC + IA$^{\leq 2}$ +(IVIG)	8(30.8%)
GC + IA$^{\geq 2}$ +(IVIG)	8(30.8%)
GC + IA$^{\leq 2}$+IVIG + BA	4(15.4%)
GC + IA$^{>2}$+IVIG + BA	6(23.1%)
Follow-up(m)	27.5(1.0-106.0)
Refractory JDM	11(42.3%)
Death	5(19.2%)

JDM: juvenile dermatomyositis; JPM: juvenile polymyositis; CMAS: childhood myositis assessment score; ANA: antinuclear antibody; MRI: magnetic resonance imaging; EMG: electromyography; HRCT: high-resolution computed tomography; * overlapping with systemic sclerosis and juvenile idiopathic arthritis respectively. **GC: glucocorticoids including methylprednisolone and prednisolone; IA: immunosuppressive agents; IA$^{\leq 2}$: two or less than 2 types of immunosuppressive agents; IA$^{\geq 2}$: more than 2 types of immunosuppressive agents; IVIG: intravenous immunoglobulin; BA: biological agents, including monoclonal antibodies and JAK inhibitors like Tofacitinib.

Laboratory results

Initial CK was recorded in 22 patients (4 cases transferred from other hospitals lost their testing results). Two cases (2/22, 9.1%) were normal, 12 cases (12/22, 54.5%) varied from 1 to 10 times the normal levels and 8 cases were higher than 10 times the normal level. ANA and anti-Ro-52 antibody were showed in Table 1. Results of imaging examinations including Magnetic resonance imaging (MRI) and High-

resolution CT (HRCT) were also showed in Table 1. Pulmonary function was characterized by mild obstructive ventilation dysfunction, decreased small airway function, and 3 cases had mildly increased residual volume.

Treatment and prognosis

Treatment started promptly upon diagnosis. Regimens were showed in Table 1. Glucocorticoid (GC) was the first-line therapy, except one case started with biological agent because parents refused to use GC. If GC plus two immunosuppressive agents failed, more immunosuppressive agents or (and) biological agents were be given. One case received autologous stem cell transplantation (ASCT) for severity and poor response to medicine. Tofacitinib or Ruxolitinib (Janus-kinase inhibitors, JAKi) was used in 7 cases. Two were treated with JAKi due to intractable rash at 4 months and 1 year respectively; four were treated with JAKi because of the aggravation or no remission with GC and immunosuppressive agents; and one was treated with JAKi after ASCT for refractory rash. Twenty-five patients were followed up for 27.5 (1.0-106.0) months (one case was lost to follow-up). Twenty patients improved and five died of gastrointestinal perforation; One patient with gastrointestinal involvement (intestinal edema) survived after ASCT.

Statistical analyses results

Comparison between refractory and non-refractory groups

Among 26 patients, 11 cases (11/26, 42.3%) were refractory and 15 were non-refractory. The differences of muscle force, CMAS, SF and CD4/CD8 ratio between refractory and non-refractory group were showed in Fig. 1. There was no significant difference in BMI and CK between the two groups (supplement 1). Furthermore, we analyzed the predictors of refractory JDM by univariate logistic regression (Table 2). Edema ($P < 0.0001$), skin ulcers ($P = 0.0003$), severe muscle weakness (Dysphagia/Hoarseness/Lower voice, $P = 0.0089$; muscle strength < = grade 3, $P = 0.0041$), CD4 / CD8 ratio < 1.4 ($P = 0.0255$) and SF > 200 ng / ml ($P = 0.0361$) were considerably associated with refractory JDM. ANA positive might be correlated with refractory JDM, but the difference was not significant ($P = 0.0521$). BMI and Ro-52 might not be the risk factors of refractory cases ($P > 0.05$).

Table 2
Comparison between refractory and non-refractory groups of anti-NXP2 autoantibody positive JDM

		Outcome ratio (%)	N	β	OR	95%CI	P-values
Gender	male	33.33	26	0.5534	1.739	0.257 ~ 14.451	0.8037
	female	47.06					
BMI (kg/m^2)	>=15	33.33	25	1.5396	4.663	0.558 ~ 62.967	0.2032
	< 15	71.43					
Muscle force	> 3	0	26	2.6654	14.373	2.461 ~ > 999.999	0.0041*
	<=3	61.11					
Edema	No	11.76	25	3.926	50.705	8.086 ~ > 999.999	< .0001*
	Yes	100					
Skin ulcer	No	12.5	26	3.8559	47.27	3.869 ~ > 999.999	0.0003*
	Yes	90					
Dysphagia/Hoarseness/Lower voice	No	9.09	26	2.8634	17.521	1.691 ~ 952.094	0.0089*
	Yes	66.67					
Symptom	No	10	26	2.5977	13.433	1.308 ~ 721.398	0.0219*
	Yes	62.5					
ILD	No	27.78	25	1.7855	5.963	0.698 ~ 82.561	0.1237
	Yes	71.43					
ANA (+)	No	21.43	26	1.9024	6.702	0.987 ~ 61.614	0.0521
	Yes	66.67					
Anti-Ro-52 (+)	No	31.58	26	1.6178	5.042	0.609 ~ 67.675	0.1696
	Yes	71.43					
CD4/CD8 ratio	>=1.4	18.75	24	2.4221	11.269	1.26 ~ 171.48	0.0255*
	< 1.4	75					
SF (ng/ml)	<=200	16.67	24	2.1876	8.914	1.115 ~ 123.379	0.0361*
	> 200	66.67					

Outcome ratio: the ratio of outcomes in different condition; Symptom: at least one of edema, skin ulcer or Dysphagia/Hoarseness/Lower voice; BMI: body mass index; ILD: interstitial lung disease; ANA: antinuclear antibody; SF: serum ferritin. *: significantly statistic difference, $P < 0.05$.

Comparison between Survival and death groups

BMI (P = 0.0325), muscle force (P = 0.0495) and CD4 / CD8 ratio (P = 0.0481) were significantly different between death and survival groups (Fig. 2). There was no significant difference in CMAS scores, CK and SF (supplement 2). Univariate logistic regression analysis found that BMI < 15 (P = 0.012) and ANA positive (P = 0.0245) were highly correlated with death (Table 3). Regarding the cause of death, 5 cases of children died of gastrointestinal involvement; and the factors of gastrointestinal involvement were generally consistent with the death factors (supplement 3).

Table 3

Comparison between survival and death groups of anti-NXP2 autoantibody positive JDM

		Outcome ratio (%)	N	B	OR	95%CI	P value
Gender	Male	11.11	26	0.8695	2.386	0.188 ~ 136.137	0.8394
	Female	23.53					
BMI (kg/m2)	>=15	5.56	25	2.9305	18.737	1.328 ~ > 999.999	0.0245*
	< 15	50					
Muscle force	> 3	0	26	1.2982	3.663	0.585 ~ > 999.999	0.1303
	<=3	27.78					
Edema	No	0	25	2.8369	17.062	2.562 ~ > 999.999	0.0055*
	Yes	50					
Skin ulcer	No	0	26	2.8358	17.045	2.722 ~ > 999.999	0.0038*
	Yes	50					
Dysphagia/Hoarseness/Lower Voice	No	0	26	1.8624	6.439	1.044 ~ > 999.999	0.0457*
	Yes	33.33					
Symptom	No	0	26	1.6794	5.362	0.867 ~ > 999.999	0.0664
	Yes	31.25					
ILD	No	5.56	25	2.4074	11.105	0.696 ~ 707.076	0.1051
	Yes	42.86					
ANA (+)	No	0	26	2.4202	11.248	1.819 ~ > 999.999	0.012*
	Yes	41.67					
Anti-Ro-52 (+)	No	15.79	26	0.7253	2.065	0.136 ~ 24.28	0.8215
	Yes	28.57					
CD4/CD8 ratio	>=1.4	6.25	24	2.0877	8.066	0.517 ~ 502.932	0.1818
	< 1.4	37.5					

Outcome ratio: the ratio of outcomes in different condition; Symptom: at least one of edema, skin ulcer or Dysphagia/Hoarseness/Lower voice; BMI: body mass index; ILD: interstitial lung disease; ANA: antinuclear antibody; SF: serum ferritin. *: significantly statistic difference, P < 0.05.

Discussion

JDM is a rare idiopathic inflammatory myopathy. Studies showed that more than 2 third of patients developed a chronic course and 4.1% of patients died, [5,6]which seriously affected the children's health. MSA is potentially useful biomarker for it is associated with different clinical phenotypes.[7, 8] In children with JDM, anti-MDA5, anti-TIF-1γ and anti-NXP2 are the most common MSAs.[9–13] The reports from UK and Argentina showed anti-NXP2 antibody were detected in 23% and 25% respectively of patients with JDM.[14, 15] In our study, anti-NXP2 seemed to be the most common antibody (30.6%). The ratio of anti-NXP2 antibody in JDM was higher than that in western countries, [4, 15, 16] which may be because the severe patients from all over the country concentrated to our department. The present study reported the characteristics and high risk factors of poor response to the treatment and death of anti-NXP2 antibody-related JDM in Chinese.

Twenty-six patients with anti-NXP2 antibody out of 85 JDM patients were involved. The female to male ratio was 17:9, which was different from reports of adult DM patients that anti-NXP2-antibodies were predominantly found in men. [18,19] The median age at onset is 4.5 years, which was younger than the average age of whole JDM cases.[20]

As to the onset symptoms, muscle weakness and skin rash were the most common clinical manifestations of the JDM patients in this cohort (92.4%). The skin lesions in this study included rashes (96.2%), skin ulcer (38.5%), edema (19.2%) and calcification (11.5%). Calcification was reported to be highly associated with the anti-NXP2 antibodies (33), [21]while only 11.5% of patients showed calcification in our cohort, that might be related to active treatment due to the severe weakness. [22] In the cohort, 96.2% of patients manifested muscle weakness during the course of disease. Serious weakness (strength < = grade 3) was found in 69.2% of patients. In the 15 patients with a CMAS < 10, 9 cases were found CMAS < = 2 and all manifested symptoms of central muscle group including dysphagia/hoarseness/lower voice and bucking. MRI showed muscle involvement in all 26 patients including those without muscle weakness. There was a girl, whose MRI revealed significant abnormalities but she had not muscle weakness at all, suggesting the importance of MRI in evaluating muscle involvement. Electromyography (EMG) showed myogenic damage in 69.2% of cases, suggesting it was not as sensitive as MRI.

The level of serum muscle enzymes plays an important role in the diagnosis of JDM. At the onset of the disease, 9.1% cases were normal, 54.5% of cases varied from 1 to 10 times the normal levels and 36.4% of cases were higher than 10 times the normal levels. It was interesting that the CK level were almost normal in some patients who died of severe JDM; While in some cases who were sensitive to therapy or with mild symptoms, CK was significantly increased (> 10000U/L). The phenomenon suggested that the level of CK was not associated with disease severity. As shown in previous studies, [9] 50% of cases in the study were found with mildly elevated level of ALT, but whether it was liver dysfunction or not remains to be validated.

A study of Caucasus reported that none of those cases with anti-NXP2 antibody JDM had any lung involvement.[2, 3] However, in the study, HRCT revealed 26.9% of patients had mild ILD, while the corresponding pulmonary manifestations such as dyspnea and cough were not obvious. ILD quickly disappeared after treatment, which was not same as anti-MDA5 antibody-related JDM.

As to treatment of JDM, the first-line treatment is GC combining immunosuppressant. If the response to the treatment is not ideal, another immunosuppressant or biological agents will be added. In the study, all cases were initially treated with GC and immunosuppressive agents except one girl. During the follow up, 6 patients' CMAS were significantly increased. Nine severe cases including those with gastrointestinal involvement received biological agents treatment, such as rituximab and infliximab. JAKi was used in 7 cases because of no response to conventional therapy. All 7 cases showed good response on JAKi. A severe case, with skin ulcer, edema, muscle weakness and gastrointestinal involvement, received salvage treatment with ASCT. After ASCT, her situation was significantly improved; two years later, she went to

kindergarten and no longer needed any medicine. Therefore, ASCT might be an ideal/alternative therapeutic regimen for those refractory and severe cases.

According to response to treatment, we divided the cases into refractory and non-refractory, death group and survival group. Eleven cases were belong to refractory group and 15 cases were belong to no-refractory group. Statistical analysis showed muscle force, edema, skin ulcer, Dysphagia/Hoarseness/Lower voice, CD4/CD8 ratio and SF were significantly different between the two groups. In these factors, the CD4/CD8 ratio (< 1.4) related to refractory cases was firstly reported by the study. Serum SF has been considered to be an indicator for monitoring JDM activity and prognosis prediction. In the study, SF≥200 ng/ml was found in 46.2% of patients with lower CMAS, and was a predictive factor of refractory JDM.

Of the 26 cases, 5 died of gastrointestinal perforation, which accounted for the vast majority of 6 deaths (6/85), suggesting that anti-NXP2 antibody accounted for almost all causes of death in Chinese children with JDM. Among the death group, the ratio of female to male was 4:1 which implied that female cases are more prone to poor prognosis. Statistical analysis showed significant differences of BMI, edema, skin ulcer, Dysphagia/Hoarseness/Lower voice, ANA (+) were found between death group and survival group as well as in groups with and without gastrointestinal involvement.

Among the 5 deaths, very low BMI (< 13) could be seen in 4 children. Univariate logistic regression analysis found BMI < 15 (P = 0.012) was highly correlated with death. The very low BMI was found before they had abdominal pain, so we speculated that the lower BMI might be a result of chronic gastrointestinal vasculitis activity before perforation. Five patients who died of gastrointestinal perforation were found to be with ANA (+) though the dilution was not very high, suggesting positive ANA might be related with gastrointestinal involvement and mortality.

Conclusions

Combined with risk factors of refractory cases and death, we observed that patients present with edema, skin ulcer and dysphagia/hoarseness/lower voice, may have a poor response to medicine and a high risk of death. Decreased CD4/CD8 ratio and high SF related with refractory cases, Further more, if patients present with very low BMI and ANA (+), the risk of gastrointestinal involvement and death might be significantly increased. ASCT might be a salvage therapy to reduce mortality from gastrointestinal involvement. Although the study provided the predictive factors, the monocentric cohort restricted the number of patients, thus further research is needed to confirm.

List Of Abbreviations

NXP2
nuclear matrix protein 2
TIF-1γ

transcriptional intermediary factor 1γ

MDA5

me lanoma differentiation associated gene

JDM

juvenile dermatomyositis

JPM

juvenile polymyositis

IIM

idiopathic inflammatory myopathies

MSA

myositis-specific autoantibody

ASCT

autologous stem cell transplant

JAKi

Janus kinase inhibitor

IVIG

intravenous immunoglobulin

BMI

body mass index

ANA

anti-nuclear antibody

HRCT

high-resolution computed tomography

IVIG

intravenous immunoglobulin

MRI

magnetic resonance imaging

ILD

interstitial lung disease

EMG

electromyography

CMAS

childhood myositis assessment score

CK

creatine kinase

SF

serum ferritin

Declarations

Ethics approval and consent to participate

This study was approved by Ethics Committee of CIP□KSSHERLL2017068□.

Consent for publication: Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

Dr Jianguo Li and Zhixuan Zhou substantially contributed to study design, analysis and interpretation of data and revised the article for important intellectual content. Dr Xinning Wang and Yuchuan Ding analyzed and interpreted the patient data and were major contributor in writing the manuscript. Dr Jun Hou and Yingjie Xu contributed to acquisition, analysis and interpretation of data and revise the article critically. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be pubulised.

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Figures

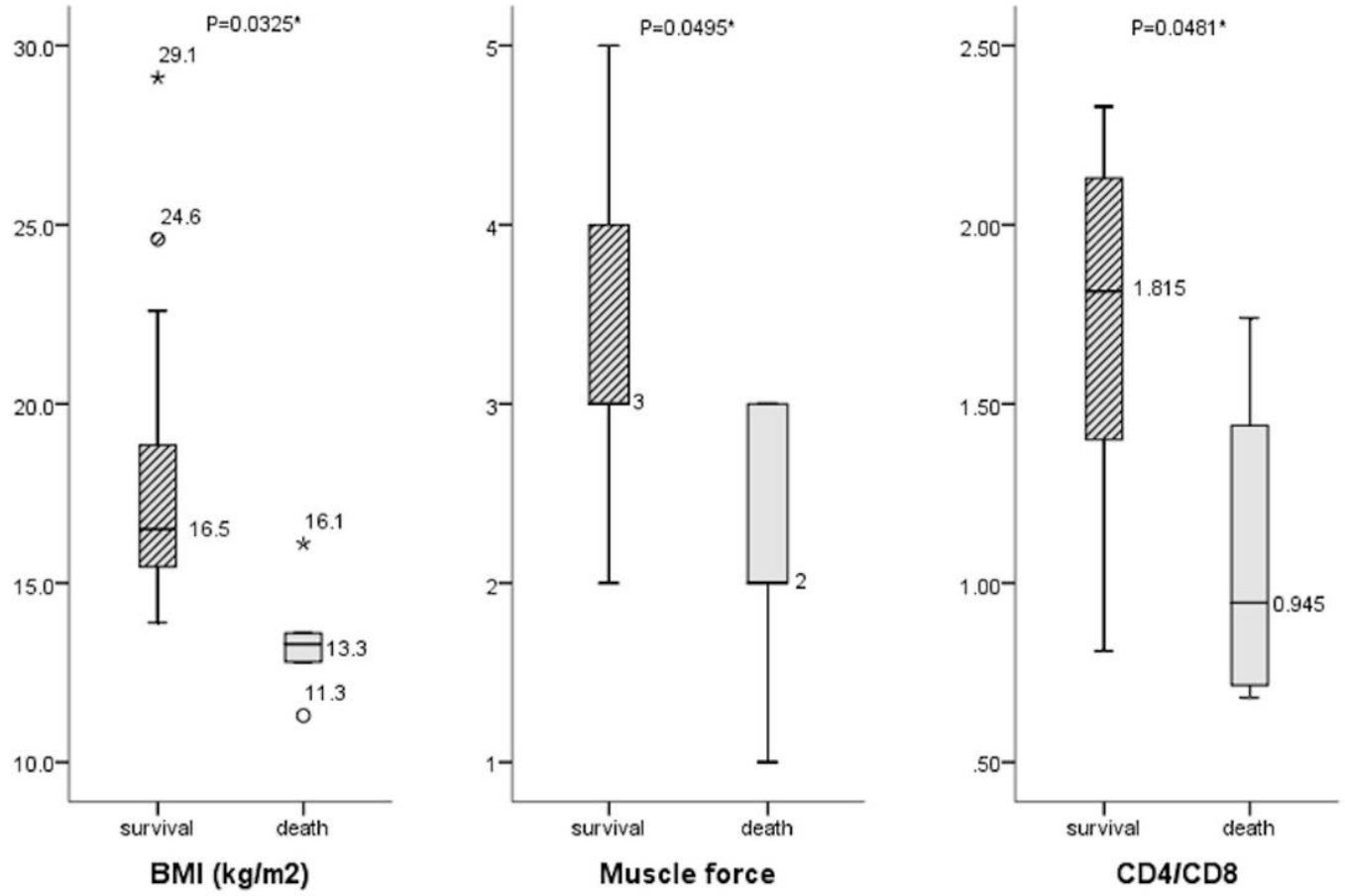

Figure 1

The difference of muscle force, CMAS, SF and CD4/CD8 ratio between refractory JDM and non-refractory JDM.

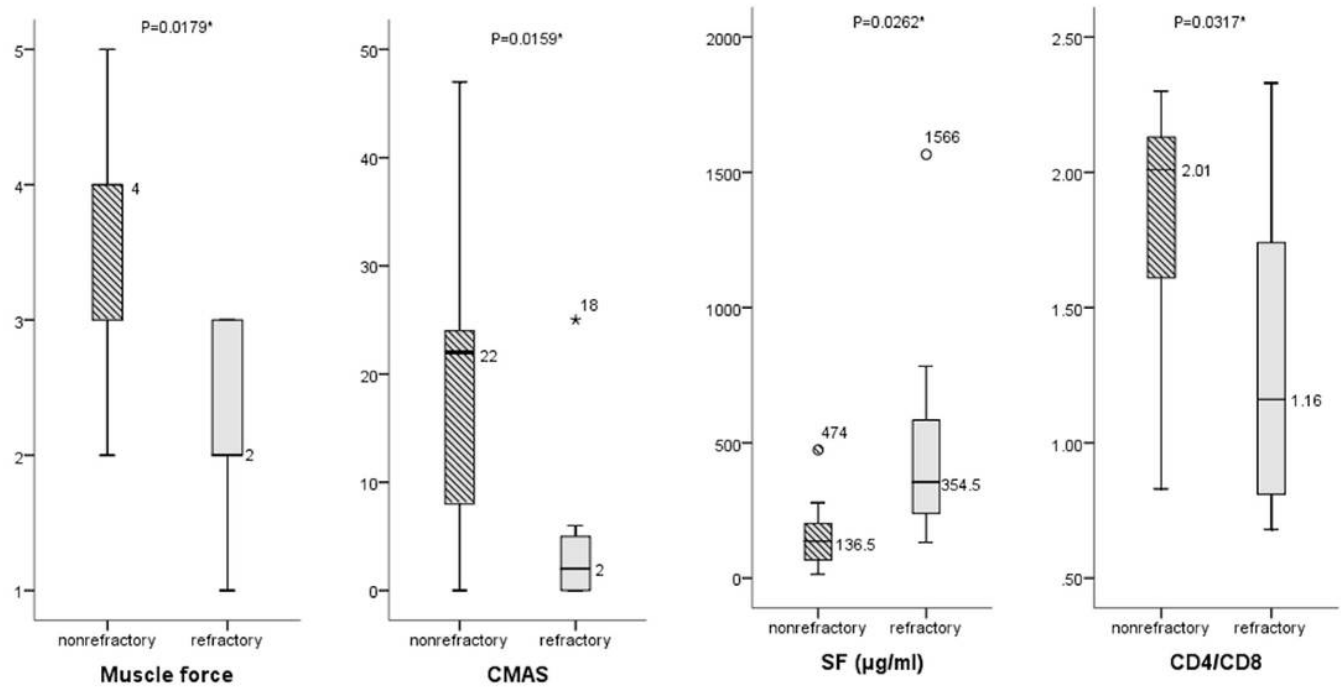

Figure 2

The difference of BMI, muscle force and CD4/CD8 ratio between survival and death

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