Initial Predictors for Short-termprognosisin Anti-melanoma Differentiation-associated Protein-5 Positive Patients

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Abstract

Background: Anti-melanoma differentiation-associated protein-5 (anti-MDA5) positive patients are characterized by the high mortality rate caused by interstitial lung disease (ILD). We conducted a retrospective study to summarize the clinical features and identify the initial predictors for death in anti-MDA5 positive patients.

Methods: We designed a retrospective cohort of anti-MDA5 positive patients.The demographic and clinical data recorded on first admission, as well as the outcomes during the first six months follow-up were collected. Risk factors for death were identified using multivariate analyses.

Results: A total of 90 anti-MDA5 positive patients were included in this study. Eighty-one (90%) patients presentedILD on admission and 35(38.9%) patients developed rapidly progressive ILD (RP-ILD) subsequently.During the first six months of follow-up, 22 (24.4%) patients died of respiratory failure at an average time of 6.6 ± 5.9 weeks.Univariate analysis identified several factors associated with death, including demographic, clinical, laboratory and image variables. Multivariate analysis showed that total CT GGO score≥4(HR 4.8, 95%CI 1.3-17.9,*P*=0.020), KL-6>1600U/ml (HR3.7, 95%CI 1.5-9.1, *P*=0.004) and CRP>5.8mg/L (HR3.7, 95%CI 1.0-12.8, *P*=0.044) were poor prognostic risk factors, however initial combined treatment(HR 0.3, 95%CI 0.1-0.8, *P*=0.019) predicted good prognosis in anti-MDA5 positive patients.

Conclusion: Anti-MDA5 positive patients demonstrated a high prevalence of ILD on admission, leading to a high short-term mortality rate. Higher total GGO score, higher levels of initial KL-6 and CRP predict poor outcome in anti-MDA5 positive patients. However, in tial intensive treatment may improve the prognosis.

Background

In 2005, anti-melanoma differentiation-associated protein-5 (anti-MDA5) was identified as a novel autoantibody by Sato [1], in patients diagnosed of clinically amyopathic dermatomyositis (CADM), which was defined as having a manifestation of typical skin lesions of dermatomyositis (DM) without clear evidence of myopathy. Since then, a lot of studies have verifiedthe association between anti-MDA5 and CADM [2, 3]. Accumulating evidences have demonstrated that patients with anti-MDA5 often have a high mortality rate caused byrapidly progressive interstitial lung disease (RP-ILD) [2-6]. While immunosuppressive treatment has improved the outcome of anti-MDA5 positive patients [7, 8], therestill were patients failing to respond and dying of respiratory failure shortly after the diagnosis was established.

Risk factors predicting poor prognosis have been established in polymyositis(PM)/DMpatients includingage, serum ferritin level, skin ulcers, peripheral capillary oxygen saturation (PaO_2) and anti-MDA5 antibody [2, 9-11], among which anti-MDA5 antibody was consistently reported as poor prognostic risk factor in most studies [12]. Of note, in the studycontaining all types of myositis, anti-MDA5 has such a strong association with poor prognosis, that it dominates the analysis and makes other potential poor

prognostic factors even tendto be a protective factor [11]. While in the subgroup of anti-MDA5 positive patients, the reported risk factors varied in different reports, possibly due to small sample size [5, 9, 13].

Therefore, we conducted a retrospective cohort of 90 anti-MDA5 positive patients, which involved in different departments including rheumatology,pneumonologyand dermatology. This study was designed to summarize the clinic-biological characteristicsand identify the prognostic factorsin anti-MDA5 positive patients.

Methods

Patients

We conducted a retrospective study of patients who visited the First Affiliated Hospital of Zhengzhou University and were diagnosed with anti-MDA5 positive DM/CADM or PM for the first time, from September, 2018 to December, 2019. The exclusion criteria included: 1) age<16years old, 2)complicated with other connective tissue diseases, 3) complicated with lethal carcinoma that occurred before,4) incomplete clinical or laboratory data necessary for this study. The diagnosis of classical DM and PM were based on Bohan and Peter criteria [14, 15], and CADM was based on Sontheimer criteria [16]. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2020-KY-194).

Data collection

A standard form was used to collect demographic, clinical and laboratory data from medical records. Data collection includedthe age of disease onset, gender, duration, symptom of fever, mechanic's hands, Raynaud phenomenon, Gottron's papules, heliotrope rash, skin ulcer, neck Vsign, arthritis, malignancy. The laboratory data included the serum levels of creatine kinase(CK), lactate dehydrogenase(LDH), Krebs von den Lungen-6(KL-6), ferritin,ESR, CRP and the titerof ANA.All patients were tested for a panel ofmyositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs)including anti-MDA5 andTIF1-γ antibodies using ELISA kits (MBL, Japan), andanti-OJ, EJ, PL7, PL12, SRP, Jo-1, Mi-2, Ku and Ro52antibodies using lining immunofluorescence (Euroimmun, Germany)by following the manufacturer's instructions.

The initial treatment regimens were also recorded according to medical records, including glucocorticoid (GC), calcineurin inhibitors (CNI) such as tacrolimus and cyclosporineA, cyclophosphamide (CYC), and intravenous immunoglobulin (IVIG). High-dose GC is defined of a prednisolone equivalent of 1mg/kg daily. Initial combined treatment is defined as a combination of high dose GC and at least one immunosuppressant starting immediatelyafter diagnosis. The main outcome was death. Survival status was respectively or prospectively confirmed by hospital records or the follow-up calls.

HRCT findings

All patients were subjected to high-resolution computed tomography (HRCT) scan on admission. After excluding infections, RP-ILD was defined as following: deteriorating dyspnea on exertion, decrease in PaO_2 levels by >10 mmHg within 4 weeks, or expanding GGO on HRCT within 4 weeks. HRCT findings were assessed both in GGO score and fibrosis score using the method proposed byKazerooni*et al*. [17]Every patient's HRCT was evaluated in three limited levels: themid-aortic arch, left tracheal bifurcation, and 1cm above the diaphragm. Each lobe (right upper, middle, and lower, and left upper and lower lobes) was scored at the three sites on a scale of 0-5as follows: GGO scores for GGO involving the lobe: 0, none;1,≤5%; 2, 5% to <25%; 3, 25% to 49%; 4, 50% to 75%; and 5, >75%. Similarly, fibrosis scores were assessed according to honeycombing involving the lobe: 0, none; 1, interlobular septal thickening without discrete honeycombing; 2, <25%; 3, 25-49%; 4, 50-75%; and 5,>75%. The images were independently reviewed by a pulmonary radiologist and a respiratory specialist (C. Y and W.SJ) blinded to the patients' clinical information. Disagreement between two observers was solved by consensus. TotalGGO scores and fibrosis scores were calculated by summing the scores of the five lobes.

Statistical analysis

The normality of continuous variables was tested using the Shapiro-Wilk test. Hypothesis testing was performed for comparing continuous variables in different outcome groups using *t*-test or Mann-Whitney U test. Categorical variables were assessed by the Chi-squared test or Fisher's exact test. Risk factor analysis was performed using univariate and multivariate Cox regression analyses. All continuous variables were converted to dichotomous variables for analysis, and cut-off values were determined by receiver operating characteristics(ROC) [18]. Variables with $P< 0.1$ in the univariate analysis weresequentially included in the multivariate Cox regression analysis, and the forward stepwise (likelihood ratio) method was used to select the variables that were eventually included in the model. Kaplan-Meier analysis with the log-rank test was used for factors selected by final model for predictors for mortality. Statistical analysis was performed using SPSS software (ver 20.0, USA) andMedcCalc software (ver 18.2.1, Belgium). The significance levels were computed for 2-tailed testing and the cutoff of significance was set at $P< 0.05$.

Results

Baseline features and outcomes of anti-MDA5 positive patients

A total of 90 anti-MDA5 positive patients were included in our study. The demographic features, antibody variables and treatment regimens on admission, and the clinical outcomes were recorded in Table1. The average ageat disease onset was51.9 ± 12.1 years, and female accounted for 63.3% of the cohort. This cohort consisted of 70(77.8%) CADM,19(21.1%) DMand 1(1.1%) PM cases, among whom the CADM patients accounted for the majority.All the patients were negative for other MSAs except anti-MDA5 antibody. Meanwhile, 64(71.1%) patients were also positive for anti-Ro52 antibody, indicatingthe necessity to testMSAs in patients positive for anti-Ro52.

Although almost all patients were diagnosed in early stage at a median timeof 3.7months, 81(90%) patients already presented ILD on admission and 35(38.9%) patients developed RP-ILD subsequently. During the first six months follow-up,a high mortality rate of 24.4% was observed in our cohort. Patients all died of respiratory failure caused by RP-ILD, some of whom werecomplicated with infections in the end stage,atan average time of 6.6 ± 5.9 weeks(range 1-24weeks)after diagnosis.

During the first six months follow-up, malignancieswere found inthreeCADM patients:one withesophageal cancer, one with lung adenocarcinoma andonewith thyroid carcinoma. However, no patient died of malignancy in the first six months.

Treatment Regimens

All patients were treated with high-doseGCat diagnosis, of whom 58 cases were initially combined with CNIand/orCYC and 32 cases were step-up treated (Table 1). In our cohort, CNI was a preferable choice than CYCbut without significant difference（41.1% vs.31.1%, *P*=0.16）. Only seven patients(7.8%) were treated with a triple combination of high-dose GC with CYC and CNI, due to the concern of serious infections. Additional IVIG(0.4g/kg daily) was administered in 43 cases based on physician's decision after comprehensive assessment of patients' condition.

Comparison of clinical features between survivors and non-survivors

No significant difference was observed in other demographic features, exceptthenon-survivorswere significantly older at theage of disease onset than the survivors (Table 2). Clinically,asignificant higher incidence of fever anda lower incidence of DM rashes,such asheliotrope sign and neck V sign,were observedin the death group. As to the laboratory data, the death group presented a significant higher initial serum levels of ferritin, KL-6, LDH, ESR and CRP,suggesting a more intensiveinflammation inside, than the survival group. The non-survivors had a significant higher incidence of anti-Ro52 positivity than the survivors, reminding physicians to pay attention to the patients double-positivefor anti-MDA5 and anti-Ro52. Not surprisingly, the non-survivors had significant worse HRCT presentations on admission, both in total CT fibrosis score and total GGO score. Initial combination therapy was more common in the survivors, butthe use of IVIG was of no significant difference between the two groups.

Initial prognostic factors in anti-MDA5 positive patients

To identify the prognostic factors associated with death in anti-MDA5 positive patients, we performed univariate analysis using all the initial variables. The cut-off points were determined using the ROC analysis, and then all continuous variables were converted to dichotomous variables for analysis.In the univariate analysis, several variables, including demographic, clinical, laboratory and image parameters, were found significantly related to death, while initial combination related to survival (Table 3).Variables with *P*< 0.1 in the univariate analysis were sequentially included in the multivariate Cox regression analysis. After adjusting covariates, we identifiedtotal CT GGO score≥4（HR 4.8, 95%CI 1.3-17.9, *P*=0.020）, initial KL-6>1600U/ml (HR3.7, 95%CI 1.5-9.1,*P*=0.004), CRP>5.8mg/L(HR 3.7,95%CI 1.0-12.8,*P*=0.044)as

independent risk factors for death, and initial combination（HR 0.3, 95%CI 0.1-0.8,*P*=0.019）as independentrisk factor for survival.

Survival curves of anti-MDA5 positive patients in different groups divided by independent risk factors

To further testify the prognostic value of the aforementioned risk factors, we examined survival curves of patients divided by these independent risk factors. As shown in Fig. 1, the survival curve ofpatients with total CT GGO score≥4was significantly worse than those with GGO<4 (*P*<0.001) (Fig.1A). Similarly, significant differences were observed in the survival curves between patients with KL-6>1600U/ml(*P*<0.001) (Fig.1B), CRP>5.8mg/L (*P*<0.001) (Fig.1C) than those without respectively. In addition, compared to the patients treated with step-up regimens, those treated with initial combination had a significant superior survival curve (*P*<0.001)(Fig.1D).

Table 1
Baseline data and treatment regimens of 90 anti-MDA5 positive patients

Variables(n=90)	Value
Demographic features	
Female, n (%)	57 (63.3)
Age, yrs, mean±SD	51.9±12.1
Disease duration, months, median (IQR)	2.0 (1.0, 3.8)
CADM, n (%)	70 (77.8)
Antibody variables	
Anti-Ro52, n (%)	64 (71.1)
Anti-MDA5, U/ml, median (IQR)	188.5 (158.5, 206.3)
ANA≥1:320, n (%)	15 (16.7)
Initial treatment regimens	
High dose GC, n (%)	90(100)
CNI, n (%)	37(41.1)
CYC, n (%)	28(31.1)
Initial combination therapy, n (%)	58(64.4)
IVIG, n (%)	43(47.8)
Malignancy (within 6 months), n (%)	3(3.3)
Prognosis	
Death, n (%)	22(24.4)

CADM clinically amyopathic dermatomyositis; anti-MDA5 anti-melanoma differentiation-associated protein-5; ANA anti-nuclearantibody; CNI calcineurin inhibitors; CYC cyclophosphamide; IVIG intravenous immunoglobulin; SD standard deviation; IQR interquartile rang

Table 2
Comparison of clinical features and treatment regimens between the survival group and the death group

	Survival group (n = 68)	Death group (n = 22)	*P* value
Demographic features			
Female, n (%)	43 (63.2)	14 (63.6)	0.973
Age, yrs, mean ± SD	49.5 ± 11.4	59.2 ± 11.6	0.001*
Disease duration, months, median (IQR)	2.0 (1.0, 4.0)	1.0 (1.0, 2.8)	0.086
Clinical features			
CADM, n (%)	51 (75.0)	19 (86.4)	0.380
Fever, n (%)	33 (48.5)	19 (86.4)	0.002*
Raynaud's phenomenon, n (%)	7(10.3)	2(9.1)	1.000
Neck V sign, n (%)	18(26.5)	1(4.5)	0.035*
Gottron's papules, n (%)	46(67.6)	15(68.2)	1.000
Heliotrope sign, n (%)	47 (69.1)	10 (45.5)	0.045*
Skin ulcer, n (%)	1 (1.5)	1 (4.5)	0.431
Laboratory test			
Serum ferritin, ng/ml, median (IQR)	734.5 (426.2, 1255.5)	2198.5 (1008.8, 2923.5)	<0.001*
KL-6, U/ml, median (IQR)	857.0 (640.8, 1202.2)	1736.0 (830.0, 2958.5)	0.002*
LDH, U/L, median (IQR)	314.0 (268.2, 427.8)	491.5 (320.0, 715.5)	0.009*
CK, U/L, median (IQR)	64.5 (34.0, 114.5)	72.5 (41.8, 132.2)	0.508
CRP, mg/L, median (IQR)	4.4 (1.7, 16.5)	23.0 (11.2, 44.7)	<0.001*
ESR, mm/h, median (IQR)	30.5 (19.8, 45.0)	37.0 (27.2, 71.8)	0.043*

Lymphocyte, $\times 10^9$/L, median (IQR)	0.8 (0.6, 1.2)	0.6 (0.4, 0.9)	0.014*
Anti-Ro52, n (%)	44 (64.7)	20 (90.9)	0.018*
Anti-MDA5, U/ml, median (IQR)	187.5 (155.5, 206.0)	192.3 (165.8, 205.0)	0.333
ANA ≥ 1:320, n (%)	11 (16.2)	4 (18.2)	1.000
HRCT findings			
Total CT GGO score, median (IQR)	0.5 (0.0, 4.0)	11.0 (5.0, 14.8)	<0.001*
Total CT fibrosis score, median (IQR)	2.0 (0.0, 4.0)	6.0 (2.2, 12.0)	0.001*
Treatment			
Initial combination therapy, n (%)	53 (77.9)	5 (22.7)	<0.001*
IVIG, n (%)	31 (45.6)	12 (54.5)	0.465

CADM: clinically amyopathic dermatomyositis; KL-6: Krebs von den Lungen-6; LDH: lactate dehydrogenase; CK: creatine kinase; CRP: C-reactive protein; ESR:erythrocyte sedimentation rate; anti-MDA5: anti-melanoma differentiation-associated protein-5; ANA: anti-nuclear antibody; HRCT: high-resolution CT; GGO:ground-glass opacity; CNI: calcineurin inhibitors; CYC: cyclophosphamide; IVIG: intravenous immunoglobulin; SD: standard deviation; IQR: interquartile range; * significant

Table 3
Initial parametersassociated with death significantly using a Cox regression model

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*value	HR	95% CI	*P* value
Age>55yrs	5.1	1.9-13.9	0.001*	-	-	-
Fever	5.5	1.6-18.8	0.006*	-	-	-
Heliotrope sign	0.4	0.2-1.0	0.051	-	-	-
Serum ferritin>2000ng/ml	6.7	2.8-16.1	<0.001*	-	-	-
KL-6>1600U/ml	6.8	2.9-15.8	<0.001*	3.7	1.5-9.1	0.004*
LDH>500U/L	4.7	2.0-10.9	<0.001*	-	-	-
CRP>5.8mg/L	7.1	2.1-24.1	0.002*	3.7	1.0-12.8	0.044*
ESR>23mm/h	9.6	1.3-71.0	0.028*	-	-	-
Lymphocyte<0.6×10^9/L	0.4	0.2-1.0	0.057	-	-	-
Anti-Ro52	4.7	1.1-19.9	0.038*	-	-	-
Total CT GGO score≥4	12.2	3.6-41.2	<0.001*	4.8	1.3-17.9	0.020*
Total CT fibrosis score≥10	7.0	2.9-16.4	<0.001*	-	-	-
Initial combined treatment	0.1	0.04-0.3	<0.001*	0.3	0.1-0.8	0.019*

KL-6: Krebs von den Lungen-6; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR:erythrocyte sedimentation rate; GGO:ground-glass opacity; * significant

Figure 1. Survival curves of anti-MDA5 positive patients in each group based on initial KL-6, CRP level, total GGOscore and initial combined treatment.

KL-6: Krebs von den Lungen-6; CRP: C-reactive protein; GGO:ground-glass opacity

Discussion

It has been reported that there are two waves of fatal events in PM/DM patients, and the first wave of mortality is caused by ILD and infections in the early stage [19]. Our study has revealed a high prevalence of ILD inanti-MDA5 positive patients, consistentwith previous studies in Europeans and Japanese [2, 20]. The short-term mortality rate of anti-MDA5 positive patients was especially high within the first 6-12 months [5, 9, 13]. Based on these findings, we set to analyze the first six months living situation and identify the predictive factors for death in anti-MDA5 positive patients. The multivariate analysis has confirmed that higher total GGO score, higher levels of initial KL-6 and CRP are poor prognostic factors, and that initial combined treatment predicts favorable outcome in anti-MDA5 positive patients.

It has been widely accepted that MSAs, especially anti-MDA5 antibody,have an important role in predicting prognosis of PM/DM patients. When the cohort contains patients with all types of myositis, the significance of anti-MDA5 antibody in predicting death is dominating, leading to other potential risk factors ignored [11]. However, the predictive value may be reduced when MSAs were not completely examined in the cohort [21]. We would like to emphasize that every patient in our cohort was tested for a panel of important MSAs and MAAs, and that anti-MDA5 positive patients were recruited from different specialties to avoid a potential selection bias.

In the current study,both total GGO and total fibrosis score were significantly higher in the deceased group than the survival group.However, only total GGO scorewas identified as an independent predictor in the multivariate analysis.This may be caused by the fact that honey combing, an important component of fibrosis scoring, is less common in the early stage of anti-MDA5 associated ILD. On the contrary, GGO was a quitecommon pattern in the early stage.Similarly, in a prospective study, patients with GGO in all six lung fields at baselineall died of respiratory failure during follow-up[5]. Fujiki*et al*. [22]also reported the prognosis of patients with right middle lung lobe GGO score≥2 was poor.Different from the wide consensus on the utility ofCT score, the effect ofinitial KL-6 level was still controversial in different reports [9, 11, 13, 21-23]. In our cohort, we found the cut off value of initial KL-6>1600U/mlas an independent poor prognostic predictor and the cumulative six-months survival rate differed significantly. In addition,Ye *et al*. [13]reported initial KL-6 of 792U/ml as the cut-off for discriminating between survivors and non-survivors in anti-MDA5 positive patients.Moreover,dynamic change of KL-6 level, like markedincrease of serum KL-6 during the first four weeks, has also been reported as apoor prognosticpredictor inPM/DM patients [23]. We inferred that higher total GGO score and KL-6 level both indicated a more rapid progression of ILD and wider extent of lung involvement, resulting in respiratory failure in the early stage.

The value of CRP in predicting death in anti-MDA5 positive patients was rarely reported before.CRP is a general reflection of inflammatory which has been widely tested clinically. In a large multicenter myositis-

associated ILD cohort, CRP>10mg/L was revealed as an independent poor prognostic risk factor [11]. Moreover,a meta-analysis indicated that higher CRP level is associated with an increased risk of developing ILD in PM/DM patients [24].Consistent with these findings, our study identified initial CRP of 5.8mg/L as the cut-off for discriminating between survivors and non-survivors in anti-MDA5 positive patients.

Different from previous studies, we didn't findany association between CADM and poor prognosis in our study. This discrepancy was caused by the strong connection between CADM and anti-MDA5 antibody in the cohortsincluding all types of myositis, which apparently doesn't exist in our cohort. Althoughinitial serum ferritin wasn't identified as an independent predictor for death, it was still significantly associated with poor prognosis, consistent with previous studies [9].

More than half of the patients were treated with initial combination regimens, and it turned out the initial combination treatmentsignificantly improve the prognosis,which was in accordance witha prospective study[7].Owing to its nature of retrospective study, treatment regimens relied on attending physician's decision, instead of a pre-determined protocol. Some of the patients with diffuse GGO on HRCT, which was difficult to be distinguished from infections, were treated with step-up regimens due to the concern of severe infections. This may lead to exaggeration of the advantages of initial combined treatment. Although IVIG was reported effective in treating PM/DM associated ILD[25], such efficacy was not observed in our study.

There are several limitations of this study. First, patients were all recruited from a single center of a tertiary hospital which may lead to a bias of a more severe form of this disease.Second, pulmonary function test, which has been reported as a potentialprognostic factor, was not included into analysis, since many patients suffered a severe chest congestion and were unable to complete the lung function tests.

Conclusions

In conclusion, we observed that anti-MDA5 positive patients presented a high prevalence of ILD on admission, resulting in a high short-term mortality rate. Higher total GGO score, higher levels of initial KL-6 and CRP were identified as poor prognostic factors in anti-MDA5 positive patients, however initial intensive treatment may improve the prognosis.

List Of Abbreviations

ANA: anti-nuclear antibody;anti-MDA5: anti-melanoma differentiation-associated protein-5; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; CNI: calcineurin inhibitors; CRP: C-reactive protein; CYC: cyclophosphamide; DM:dermatomyositis; ESR:erythrocyte sedimentation rate; GGO:ground-glass opacity; HR: hazard ratio; HRCT: high-resolution CT; ILD: interstitial lung disease;IQR: interquartile range; IVIG: intravenous immunoglobulin;KL-6: Krebs von den Lungen-6; LDH: lactate dehydrogenase;

PaO_2; peripheral capillary oxygen saturation; PM: polymyositis; RP-ILD: rapidly progressive interstitial lung disease; SD: standard deviation;

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2020-KY-194).

Consent for publication

Not applicable.

Availability of data and materials

Data can be requested from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YQ, LS, and YZ designed the study. YQ, ZX and LK collected the data. WS and CY scored all radiographs. LK analyzed the data. YQ and LT interpreted the data. YQ,LT, and LK wrote the manuscript. All authors reviewed and approved the manuscript.

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Figures

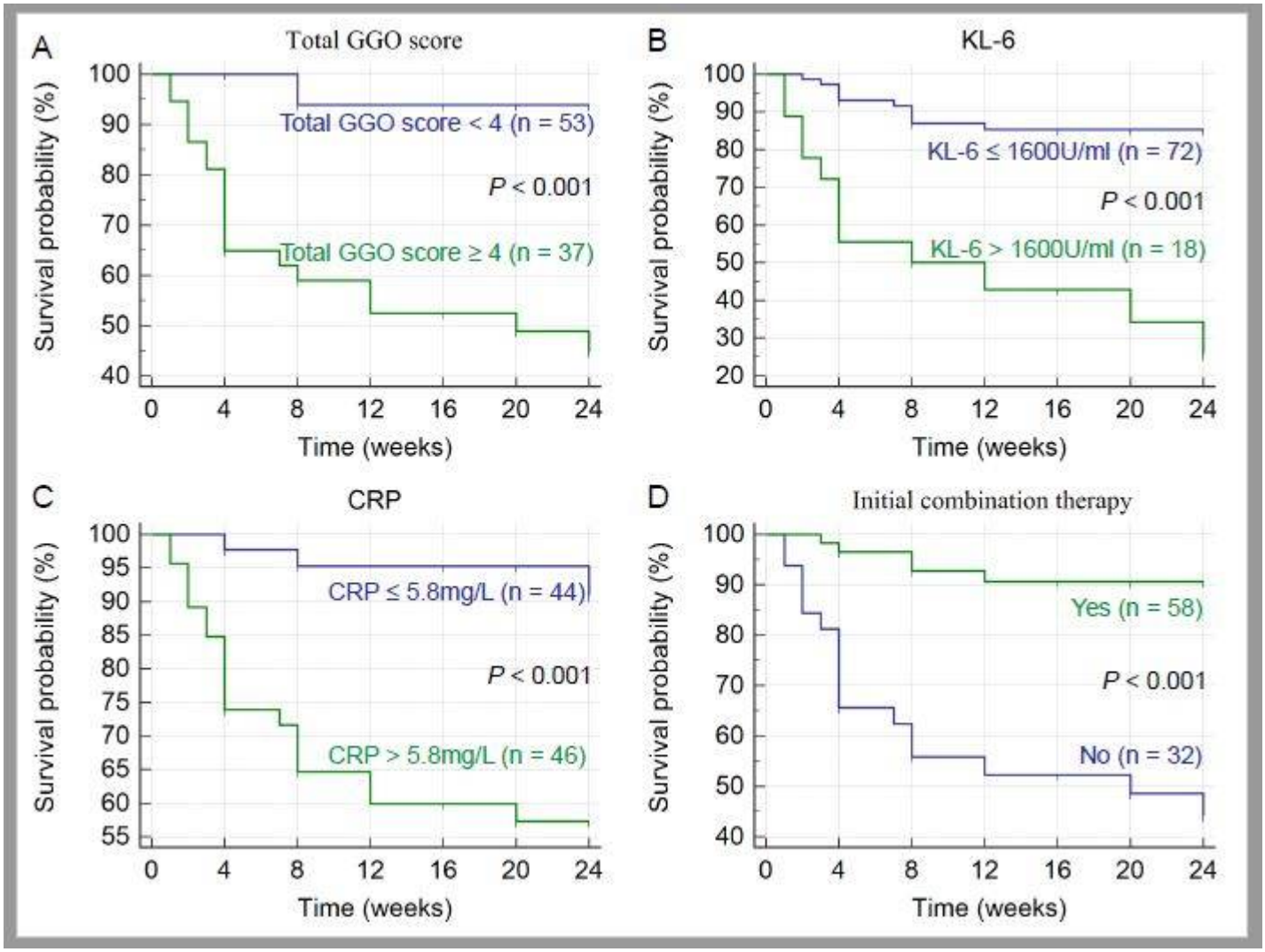

Figure 1

Survival curves of anti-MDA5 positive patients in each group based on initial KL-6, CRP level, total GGOscore and initial combined treatment. KL-6: Krebs von den Lungen-6; CRP: C-reactive protein; GGO:ground-glass opacity