Supplementary Tables

Table S1. Model 1: Regression analysis and model summary of fatigue score with BDCAF scores in BD patients. **Model 2**: Regression analysis and model summary of fatigue scores with systemic activity in BD patients. **Model 3**: Regression analysis and model summary of PSQI with BDCAF scores in BD patients. **Model 4**: Regression analysis and model summary of PSQI with systemic activity in BD patients.

	Coefficients				
Model 1 (Dependent variable[a]: BDCAF score combined with predictor variable[b]: fatigue score)	Unstandardized Coefficients		Standardized Coefficients	t	*p* value
	B	Std. Error	Beta		
Fatigue score	.117	.019	**.554**	6.031	**.001***
R value= **0.554** R Square value= 0.307 ANOVA test; *p*= **0.001***	a. Dependent Variable: BDCAF score. b. Predictors: Fatigue score. **c.** Fatigue had significant impact to increase BDCAF score in BD cohort by percentage of 55%.				
Model 2 (Dependent variable[a]: system. activity combined with predictor variable[b]: fatigue score)	Unstandardized Coefficients		Standardized Coefficients	t	*p* value
	B	Std. Error	Beta		
Fatigue score	.023	.005	**.500**	5.064	**.001***
R value= **0.500** R Square value= 0.25 ANOVA test; *p*= **0.001***	a. Dependent Variable: Systemic activity. b. Predictors: Fatigue score. c. Fatigue had significant impact to increase systemic activity in BD patients by percentage of 50%.				
Model 3 (Dependent variable[a]: BDCAF scores combined with predictor variable[b]: PSQI)	Unstandardized Coefficients		Standardized Coefficients	t	*p* value
	B	Std. Error	Beta		
Quality of sleep scores	.202	.058	**.432**	3.455	**.001***
R value= **0.43** R Square value= 0.19 ANOVA test; *p*= **0.001***	a. Dependent Variable: BDCAF scores. b. Predictors: PSQI. c. Quality of sleep had significant impact to increase BDCAF score in BD cohort by percentage of 43%.				
Model 4 (Dependent variable[a]: system. activity combined with predictor variable[b]: PSQI)	Unstandardized Coefficients		Standardized Coefficients	t	*p* value
	B	Std. Error	Beta		
Quality of sleep score	.037	.014	**.37**	2.656	**.011***
R value= **0.37** R Square value= 0.14 ANOVA test; *p*= **0.01***	a. Dependent Variable: Systemic activity. b. Predictors: PSQI. c. Quality of sleep had significant impact to increase systemic activity in BD cohort by percentage of 37%.				

**p* value is significant at level< 0.05.

Table S2. Regression analysis of fatigue score and quality of sleep questionnaire.

Fatigue score	Unstandardized Coefficients		Standardized Coefficients	*p* value
	B	Std. Error	Beta	
Sleep quality	4.086	2.146	**.333**	**.046***
Sleep Latency	.632	.966	.073	.516
Sleep duration	-.872	1.388	-.077	.533
Habitual sleep efficiency	1.538	1.305	.158	.244
Sleep disturbances	.767	1.628	.052	.639
Use of sleeping medications	-.077	1.114	-.007	.945
Daytime dysfunction	4.111	1.508	**.355**	**.009***
Model (dependent outcome and independent variables integration) R= 0.749 R^2 = 0.561 ANOVA; *p*=**.001***				

Dependent variable: Fatigue score. Predictor variables: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction.
**p* values<0.05.

Table S3. Model 5: Regression analysis and model summary of fatigue scores with alpha-MSH in BD patients. **Model 6:** Regression analysis and model summary of fatigue scores with VIP in BD patients. **Model 7**: Regression analysis and model summary of alpha-MSH with quality of sleep in BD patients. **Model 8**: Regression analysis and model summary of VIP and quality of sleep in BD patients.

	Coefficients				
Model 5 (Dependent variable[a]: fatigue score combined with predictor variable[b]: alpha-MSH)	Unstandardized Coefficients		Standardized Coefficients	*t*	*p* value
	B	Std. Error	Beta		
alpha-MSH concentration (ng/ml)	6.993	1.630	**.44**	4.291	**.001***
R value =**0.44** R Square value =0.193 ANOVA test; *p*=**0.001***	a. Dependent Variable: Fatigue score. b. Predictors: alpha-MSH concentration. c. alpha-MSH had significant impact to increase fatigue in BD patients by percentage of 44%.				
Model 6 (Dependent variable[a]: fatigue score combined with predictor variable[b]: VIP)	Unstandardized Coefficients		Standardized Coefficients	*t*	*p* value
	B	Std. Error	Beta		
VIP concentration (pg/ml)	.024	.016	.168	1.446	.152
R value =0.168 R Square value =0.028 ANOVA test; *p*=0.152	a. Dependent Variable: Fatigue score. b. Predictors: VIP concentration. c. VIP did not have significant impact to increase fatigue in BD patients.				
Model 7 (Dependent variable[a]: PSQI combined with predictor variable[b]: alpha-MSH)	Unstandardized Coefficients		Standardized Coefficients	*t*	*p* value
	B	Std. Error	Beta		
alpha-MSH concentration(ng/ml)	2.236	.860	**.35**	2.599	**.012***
R value =**0.35** R Square value =0.121 ANOVA test; *p*=**0.012***	a. Dependent Variable: PSQI. b. Predictors: alpha-MSH concentration. c. alpha-MSH had significant impact to increase score of PSQI in BD patients by percentage of 35%.				
Model 8 (Dependent variable[a]: PSQI combined with predictor variable[b]: VIP)	Unstandardized Coefficients		Standardized Coefficients	*t*	*p* value
	B	Std. Error	Beta		
VIP concentration (pg/ml)	.024	.010	**.343**	2.452	**.018***
R value =**0.343** R Square value =0.112 ANOVA test; *p* =**0.018***	a. Dependent Variable: PSQI. b. Predictors: VIP concentration. c. VIP had significant impact to increase score of PSQI in BD patients by percentage of 34%.				

**p* value is significant at level <0.05.

Table S4. The differences of cytokines concentrations between fatigue groups and PSQI groups in BD.

	BD. Fatigue groups	Mean ± SD	Mean Rank	*p* value	BD. PSQI groups	Mean ± SD	Mean Rank	*p* value
IL-1β	Low fatigue	1.26 ± 2.17	13.00	0.639	PSQI <5	0.39 ± 0.64	7.00	0.684
	High fatigue	0.58 ± 0.68	11.56		PSQI >5	-0.14 ± 0.18	6.14	
IL-6	Low fatigue	3.02 ± 2.19	33.93	**0.007***	PSQI <5	1.71 ± 1.04	17.43	0.184
	High fatigue	1.32 ± 1.34	20.62		PSQI >5	2.08 ± 0.303	12.80	
IL-10	Low fatigue	3.65 ± 3.07	17.06	0.255	PSQI <5	-3.45 ± 1.95	9.67	0.58
	High fatigue	5.06 ± 5.30	22.54		PSQI >5	10.98 ± 1.03	11.79	
TNF-α	Low fatigue	2.09 ± 1.79	9.58	**0.074**	PSQI <5	1.25 ± 0.68	6.67	**0.08**
	High fatigue	13.47 ± 22.96	14.64		PSQI >5	1.24 ± 1.83	10.86	

**p* value is significant at level <0.05.

Table S5. The association of cytokines concentrations with α-MSH and VIP.

Spearman's Correlation Coefficient		IL-1 β	IL-6	IL-10	TNF-α	α-MSH	VIP
IL-1 β	R	1.00					
	p value						
	N	23					
IL-6	R	.232	1.00				
	p value	.299					
	N	22	48				
IL-10	R	.259	.219	1.00			
	p value	.300	.174				
	N	18	40	42			
TNF-α	R	.007	.073	.118	1.00		
	p value	.980	.760	.700			
	N	15	20	13	23		
α-MSH	R	-.357	**-.368**	-.079	**.495**	1.00	
	p value	.146	**.030***	.682	**.023***		
	N	18	35	29	21	83	
VIP	R	-.366	.169	-.028	-.008	.213	1.00
	p value	.164	.348	.886	.974	**.063**	
	N	16	33	28	19	77	77

Statistical analysis of the associations between detectable cytokine levels in serum with α-MSH and VIP. **p* value is significant at level <0.05.

Supplementary figures

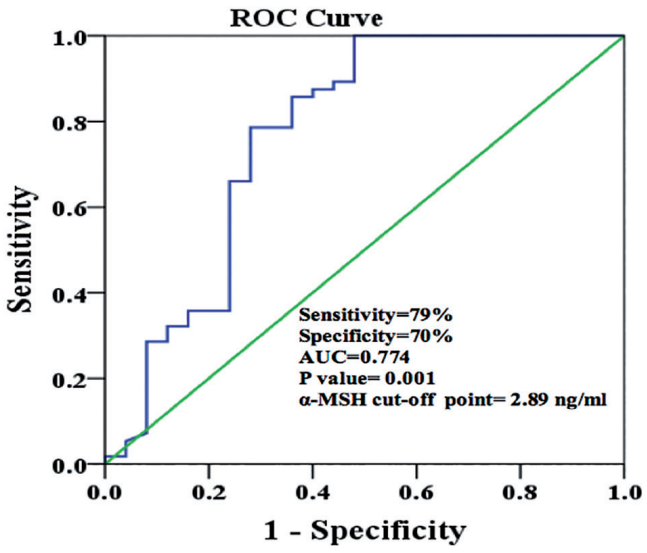

Fig. S1. Receiver operating characteristic (*ROC*) curve of α-MSH concentration for predicting high fatigue in BD patients. Accuracy is measured by the area under the ROC curve (*AUC*). An area of 1.0 represents a perfect test; an area of 0.5 represents a worthless test. *AUC*, in this cohort= 0.774.

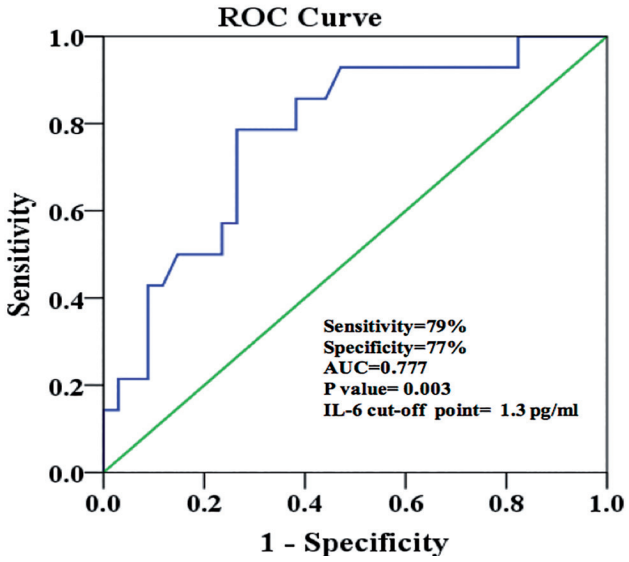

Fig. S2. Receiver operating characteristic (*ROC*) curve of IL-6 concentration for predicting low fatigue in BD patients. Accuracy is measured by the area under the ROC curve (*AUC*). An area of 1.0 represents a perfect test; an area of 0.5 represents a worthless test. *AUC* in this cohort= 0.777.