Do C-reactive protein and body mass index predict duration of mechanical ventilation in critically ill trauma patients?

C-reaktif protein ve vücut kitle indeksi kritik travma hastalarındaki mekanik ventilasyon süresini öngörebilir mi?

Azim HONARMAND, Mohammadreza SAFAVI

BACKGROUND

The predictive ability of body mass index (BMI) or C-reactive protein (CRP) as a simple, inexpensive, and dynamic marker of critical illness in patients requiring mechanical ventilation (MV) is unknown. This study was thus conducted to determine the incidence and presence of a relationship between the predictors of BMI or CRP and duration of MV in trauma patients admitted to the intensive care unit (ICU).

METHODS

This prospective observational study included 72 critically ill trauma patients. Admitted patients were categorized by duration of MV to Group A (≤7 days) and Group B (>7 days). The biological status of patients was assessed by the serial measurement of CRP on admission to the ICU (T1), at 48 and 72 hours after admission, and on the day of beginning (T2) or discontinuation (T3) of MV. Data on BMI, serum albumin, and the Sequential Organ Failure Assessment (SOFA) score were also collected at T2 or T3.

RESULTS

At T3, the SOFA score, BMI, albumin, and CRP were significantly higher in patients in Group B compared with Group A ($p<0.01$). The incidence of low BMI (≤20 kg/m^2) or high CRP (>10 mg/L) in patients in Group B was significantly higher at T2 or T3 compared with Group A ($p<0.05$). At T3, CRP was determined as the most powerful predictor of >7 days of MV followed by BMI.

CONCLUSION

Both BMI and CRP, comparable with the SOFA score, can be used in estimating the risk of prolonged MV.

Key Words: Body mass index; C-reactive protein; intensive care unit; mechanical ventilation; Sequential Organ Failure Assessment (SOFA) score.

AMAÇ

Mekanik ventilasyon gerektiren hastalarda kritik hastalığın basit, pahalı olmayan ve dinamik bir göstergesi olarak vücut kitle indeksi (VKİ) ve C-reaktif proteinin (CRP) öngörme değeri bilinmemektedir. Bu nedenle, bu çalışma, yoğun bakım ünitesine (YBÜ) kabul edilen travma hastalarındaki VKİ ve CRP göstergeleriyle mekanik ventilasyon süresi arasındaki bir ilişki varlığını ve insidansını belirlemek amacıyla yürütüldü.

GEREÇ VE YÖNTEM

Bu prospektif gözlemsel çalışma, 72 kritik travma hastası üzerinde gerçekleştirildi. YBÜ'ye kabul edilen hastalar, mekanik ventilasyon süresine göre Grup A (≤7 gün) ve Grup B (>7 gün) şeklinde sınıflandı. Hastaların biyolojik durumu, YBÜ'ye kabul edilişte (T1), yatırıldıktan sonraki 48. ve 72. saatte, mekanik ventilasyona başlandığı gün (T2) veya mekanik ventilasyonun kesildiği günlerde (T3) değerlendirildi. T2 veya T3'de, aynı zamanda VKİ, serum albümin ve Ardışık Organ Yetersizliğinin Değerlendirilmesi (Sequential Organ Failure Assessment-SOFA) skoru ile ilgili veriler de toplandı.

BULGULAR

T3'de, SOFA skoru, VKİ, albümin ve CRP, A grubuna kıyasla B grubunda anlamlı şekilde daha yüksek oldu ($p<0,01$). B grubu hastalarındaki düşük VKİ (≤20 kg/m^2) veya yüksek CRP insidansı (>10 mg/L), T2 veya T3'de A grubu hastalarına kıyasla anlamlı şekilde daha yüksek oldu ($p<0,05$). Yedi günden daha uzun süreli mekanik ventilasyonun en güçlü prediktörü CRP oldu ve bunu T3'de VKİ izledi.

SONUÇ

Hem VKİ hem CRP, SOFA skoru ile kıyaslanabilir şekilde uzamış mekanik ventilasyon riskinin tahmin edilmesinde kullanılabilmektedir.

Anahtar Sözcükler: Vücut kitle indeksi; C-reaktif protein; yoğun bakım ünitesi; mekanik ventilasyon; ardışık organ yetersizliğinin değerlendirilmesi (SOFA) skoru.

Department of Anesthesiology and Intensive Care, Isfahan University of Medical Sciences, Isfahan, Iran.

İsfahan Üniversitesi, Tıp Fakültesi, Anesteziyoloji ve Yoğun Bakım Anabilim Dalı, İsfahan, İran.

Correspondence *(İletişim):* Azim Honarmand, M.D. Department of Anesthesiology and Intensive Care, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel: +098 - 913 - 1102327 Fax *(Faks)*: +098 - 311 - 2361594 e-mail *(e-posta):* honarmand@med.mui.ac.ir

Endotracheal intubation and mechanical ventilation (MV) is the standard supportive therapy for acute respiratory failure (ARF).[1,2] In critically ill patients suffering from ARF, weaning from ventilatory assistance is a key survival factor in intensive care units (ICUs).[3] Despite the efficacy of MV, there are still patients in whom positive pressure ventilation is not successful in preventing further deterioration of respiratory function and MV. This may be due to limitations of the device itself, how the device is applied and adjusted, or to patient characteristics and physiology.[4] Though some patient populations who clearly benefit from the application of positive pressure ventilation have been identified,[5,6] physiologic factors leading to its success or failure have not yet been fully elucidated. Established prognostic factors such as nutritional depletion as assessed by body mass index (BMI) and overall systemic inflammation as estimated by C-reactive protein (CRP) appear to be major determinants of hospitalization and death risk whatever the end-stage respiratory disease.[7] In a study by Hutter et al.,[4] the variable with the strongest association with failure of noninvasive positive-pressure ventilation (NPPV) and the need for intubation was BMI. For each l-point increase in BMI, there was a 29% decrease in the risk of endotracheal intubation and MV.[4] Similarly, the prognostic effect of low BMI has already been documented in patients with home-assisted respiratory failure and particularly during chronic obstructive pulmonary disease (COPD).[8-10] Increased CRP levels are strongly and independently associated with respiratory impairment.[11] A higher CRP value was associated with the development of respiratory failure and subsequent intubation in patients with probable severe acute respiratory syndrome (SARS).[12] Hospitalizations in patients with COPD were found to be independently determined by elevated CRP.[7] These data support the concept that a subgroup of patients with acute or chronic respiratory failure suffers from a systemic inflammation, which in turn may account for an increased morbidity and mortality. The primary cause of need for MV is ARF. Theoretically, every parameter, e.g. CRP, which predicts organ failure such as ARF, probably predicts requiring MV and in turn the duration of it. Our hypothesis is that increased CRP or decreased BMI on the day of beginning MV is associated with more prolonged duration of MV.

The severity of inflammatory response and impairment of organ function are the major determinants of the outcome in critically ill patients. Clinical trials and observational studies usually use a scoring system for the assessment of the severity of organ function impairment. One of most popular among them is the Sequential Organ Failure Assessment (SOFA) score.[13] SOFA[13] is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) graded from 0 to 4 according to the degree of dysfunction/failure (Table 1).

The predictive ability of BMI or CRP as a simple, inexpensive, and dynamic marker of critical illness in patients requiring MV is unknown. This study was thus designed to determine the incidence and presence of a relationship between the predictors of BMI or CRP and duration of MV in trauma patients admitted to the ICU and to compare their prognostic significance with the other indicators such as the SOFA score[13] or serum albumin.

MATERIALS AND METHODS

Seventy-two trauma patients (≥16 years old) admitted in the ICU at a university teaching hospital from 1 June 2005 to 1 September 2006 were included in this prospective study. The Institutional Review Board of the university approved the study. Exclusion criteria were neuromuscular disease, left ventricular dysfunction, presence of chest or abdominal trauma, death on arrival at the emergency department, history of exacerbation of chronic respiratory failure during the last 3 months, and any condition likely to affect the weaning trial outcome. The severity of illness was assessed by the RTS (Revised Trauma Score) calculated on the first ICU day. A standardized form was used to collect data from all of the charts. Body weight and height were recorded at the time of enrollment. Data collected include age, sex, BMI (kg/m^2), RTS, SOFA score, underlying disease, serum albumin, serum concentration of CRP, documentation of the need for MV, and duration of MV. Serum albumin and CRP levels were determined using conventional methods. The biological status of patients was assessed by the serial measurement of inflammatory index (CRP) on admission to the ICU, at 48 and 72 hours after admission, and on the day of beginning or discontinuation of MV. Data on BMI, serum albumin,

Table 1. The SOFA scoring system (PaO_2 arterial oxygen tension, FiO_2 fractional inspired oxygen, MAP mean arterial pressure)

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FiO_2 (mmHg)	>400	≤400	≤300 with respiratory support	≤200	≤100
Coagulation					
Platelets x $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(µmol/l)	<20	20-32	33-101	102-204	>204
Cardiovascular					
Hypotension	No hypotension	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norephinephrine >0.1[a]
Central nervous system					
Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal					
Creatinine (mg/dl)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
(µmol/l)	<110	110-170	171-299	300-440	>440
or urine output				or <500 ml/day	or <200 ml/day

[a] Adrenergic agents administered for at least 1 h (does given are in µg/kg per min).

and the SOFA score were also collected on the day of starting or discontinuation of MV.

The procedure of weaning from MV began when a patient's condition showed visible improvement or there was a resolution of the underlying cause of respiratory failure. To start the weaning procedure, the following criteria had to be met: spontaneous respiration rate (f) <35/min, spontaneous respiratory volume (Vt) >5 ml/kg body weight, maximum spontaneous inspiratory effort (Pi max) >25 cm H_2O, heart rate <140/min, body temperature <38.5°C, hemoglobin >100 g/L, partial arterial oxygen pressure (PaO_2) >60 mmHg, breathing a fraction of inspired oxygen (FiO_2) <0.4 with a positive end expiratory pressure (PEEP) <5 cm H_2O, no need of vasoactive or inotropic support, PaO_2/FiO_2 ratio >200, and f/Vt ratio <100. The procedure of weaning started with 5 minutes of spontaneous breathing through a T-tube circuit, with the FiO_2 set at the level used during MV. During the 2-h trial, the patient had to meet the following objective criteria: spontaneous respiratory frequency <35/min, arterial blood oxygen saturation (SaO_2) >90% at FiO_2 <0.4, heart rate <140/min or >20% change from the baseline, systolic blood pressure <200 mmHg or not <80 mmHg, PaO_2 >60 mmHg, pH <7.30, and stable clinical condition. The patients who fulfilled these criteria at the end of the 2-h trial were extubated. The weaning procedure was considered successful if reintubation was not required within 48 h of extubation.

Statistical analysis

Analysis of our data showed that MV of 7 days duration had the best sensitivity and specificity for BMI or CRP to predict MV duration. Thus, patients were categorized by duration of MV to Group A (≤7 days) and Group B (>7 days). Differences in durations of MV, BMI, CRP, serum albumin, and the SOFA score between the defined groups were assessed using the Mann-Whitney nonparametric test and between time points were analyzed by the Wilcoxon signed rank test. The nonparametric Spearman ranked sign procedure was used to assess the significance of associations. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive or negative likelihood ratios (±LR) for BMI, CRP, serum albu-

Table 2. Demographics and laboratory data of the study population

	All patients	Group A (n=24)	Group B (n=48)	p
Sex				
Male, n (%)	48 (66.7)	16 (66.7)	32 (66.7)	1.000
Female, n (%)	24 (33.3)	8 (33.3)	16 (33.3)	
Age (year)	39.9±14.4	40.4±21.1	39.7±11.8	0.847
Weight (kg)	72.1±10.3	71.8±10.5	72.2±10.3	0.872
Height (cm)	170.6±10.6	171.9±10.5	170.3±10.8	0.770
RTS	6.4±0.8	6.4±0.70	6.35±0.8	0.817
Duration of MV (day)	9.7±3.9	6.0±0.83	11.6±3.4	0.000
At start of MV				
SOFA	18.7±3.7*	16.2±5.7	16.7±4.4	0.710
BMI (kg/m^2)	22.4±4.0*	25.3±2.2	24.7±2.2	0.324
CRP (mg/L)	15.5±6.6*	11.5±5.5	12.7±6.7	0.400
Albumin (g/L)	33±6.0*	34.4±0.73	3.4±0.6	0.700
At discontinuation of MV				
SOFA	16.1±3.2	14.1±2.3	19.7±2.7	0.000
BMI (kg/m^2)	26.1±3.6	26.4±2.3	21.1±2.4	0.000
CRP (mg/L)	13.0±5.6	12.7±3.5	16.8±6.5	0.003
Albumin (g/L)	36±0.4	38.3±0.4	33.6±0.3	0.000

Data are presented as mean ± SD unless otherwise indicated; RTS: Revised trauma score; MV: Mechanical ventilation; SOFA: Sequential Organ Failure Assessment; BMI: Body mass index; CRP: C-reactive protein.
* p<0.01 vs on the day of discontinuation from mechanical ventilation.

min, and the SOFA score in predicting MV of >7 days were calculated. Also, receiver operator characteristics (ROC) curves were constructed for each of the predictive variables and the areas under the ROC curves (AUC) were compared. The analyses were facilitated with the use of the MedCalc 9.0.1.1 software packages. Stepwise logistic regression analysis was used to determine which of the above variables was an independent risk factor for duration of MV of >7 days. Differences were considered significant if the p value was <0.05.

RESULTS

There were 84 consecutive trauma patients admitted to the ICU during the study period. Of these, 12 patients were excluded: 5 had abdominal or chest trauma and 7 died on arrival at the emergency department. A total of 72 trauma patients were studied. Demographic and laboratory data of study patients are given in Table 2. There was no significant difference between the two groups in demographic characteristic or RTS. On the day of discontinuation from MV, the SOFA score (SOFA-2), BMI (BMI-2), albumin (albumin-2), and CRP (CRP-2) were significantly lower in the population study compared with these variables at the beginning of MV (p<0.05). On the day of disconnection from MV, there was also significant difference in these variables between patients in Groups A and B (p<0.01). In comparison with Group A, duration of MV was significantly increased in Group B (p= 0.000). The incidence of low BMI (≤ 20 kg/m^2) or high CRP (>10 mg/L) on the day of beginning MV was 72.2% (52/72) and 81.9% (59/72), respectively (Tables 3, 4). The incidence of low BMI or high CRP in patients in Group B was significantly higher on the day of starting MV compared with Group A (p<0.05). On the day of discontinuation from MV, the incidence of BMI >20 kg/m^2 or CRP ≤10 mg/L was significantly higher in patients in Group A compared with Group B (p<0.05) (Tables 3, 4). For all patients, >7 days duration of MV was significantly associated with the SOFA score, BMI, CRP, and albumin on the day of discontinuation from MV (p<0.05) (Table 5). The highest correlation was with the SOFA score (rs= 0.73). The association was negative with BMI or serum albumin concentration. On the day of beginning MV, the

Table 3. Incidence of body mass index ≤20 kg/m^2 for the study population

Variable	All patients		Group A		Group B		RS	p
	n (%)		n (%)		n (%)		(95%CI)	
	BMI ≤20	BMI >20 kg/m^2	BMI ≤20	BMI >20 kg/m^2	BMI ≤20	BMI >20 kg/m^2		
BMI-1	52 (72.2)	20 (27.8)	13 (54.2)	11 (45.8)	39 (81.3)	9 (18.8)	0.33 (0.09-0.80)	0.025
BMI-2	19 (26.4)	53 (73.6)	2 (8.3)	22 (91.7)	17 (35.4)	31 (64.6)	0.17 (0.03-0.80)	0.022

BMI-1, -2: Body mass index on the day of beginning or discontinuation of mechanical ventilation, respectively; RS: Risk estimate; CI: Confidence interval.

Table 4. Incidence of C-reactive protein >10 mg/L for the study population

Variable	All patients		Group A		Group B		RS	p
	n (%)		n (%)		n (%)		(95%CI)	
	CRP ≤10	CRP >10 mg/L	CRP ≤10	CRP >10 mg/L	CRP ≤10	CRP >10 mg/L		
CRP-1	13 (18.1)	59 (81.9)	8 (33.3)	16 (66.7)	5 (10.4)	43 (89.6)	4.3 (1.2-15.1)	0.030
CRP-2	21 (29.2)	51 (70.8)	11 (45.8)	13 (54.2)	10 (20.8)	38 (79.2)	3.21 (1.11-9.30)	0.030

CRP-1, -2: C-reactive protein on the day of beginning or discontinuation of mechanical ventilation, respectively; RS: Risk estimate; CI: Confidence interval.

association with these variables was not significant. There was significant association between BMI and serum albumin (r= 0.560, p= 0.000), and between the SOFA score with CRP (rs= 0.467, p= 0.000) or BMI (rs= -0.371, p= 0.000) on the day of weaning from MV. This correlation shows that increased SOFA score on the day of weaning was accompanied with increased CRP and decreased BMI or serum albumin. The sensitivity, specificity, PPV, NPV, positive or negative LR, and area of the ROC curve (AUC) at the best cutoff point for >7 days duration of MV are presented in Table 6. CRP-2 or BMI-2 had high specificity or PPV for predicting >7 days of MV. The SOFA-2 score had 100% sensitivity or NPV for this purpose. SOFA-2, serum albumin-2, CRP-2, and BMI-2 provided significantly good discrimination (AUC >0.5) in descending order, as shown in Table 6. The AUC for BMI-2 or CRP-2 was not significantly different (p>0.05). BMI-2 <23.3 kg/m^2 or CRP-2 >10 mg/L increases the probability of >7 days duration of MV by factor 3.50 or 8.0, respectively. The trend of serum CRP changes during ICU days is shown in Fig. 1. Mean serum CRP level at 72 h after admission to the ICU or on the day of discontinuation from MV was significantly higher in patients in Group B compared with Group A (p<0.01). By performing stepwise binary logistic regression analysis, it was shown that the most powerful predictor of >7 days of MV was CRP-2 followed by BMI-2. An increase of 1 in CRP-2 or BMI-2 significantly increased the relative probability of >7 days of MV by a factor 1.454 (95% CI, 1.112-2.520, p= 0.011) or 1.201 (95% CI, 1.001-1.798, p= 0.017), respectively. The model

Table 5. Associations of SOFA score, BMI, CRP, and serum albumin with more than seven days duration of mechanical ventilation for all patients (Spearman ranked correlations)

	At start of MV	At discontinuation of MV
SOFA score	rs= +0.02, p= 0.83	rs= +0.73, p= 0.000
BMI (kg/m^2)	rs= -0.12, p= 0.22	rs= -0.41, p= 0.000
CRP (mg/L)	rs= +0.08, p= 0.50	rs= +0.23, p= 0.030
Albumin (g/L)	rs= -0.10, p= 0.51	rs= -0.50, p= 0.000

SOFA: Sequential Organ Failure Assessment; BMI: Body mass index; CRP: C-reactive protein; MV: Mechanical ventilation; rs: Ranked Spearman.

Table 6. Predictive ability of BMI, CRP, albumin, and the SOFA score for more than seven days duration of mechanical ventilation

Variable	Cutoff Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	+LR	-LR	p
BMI-1 (kg/m^2)	27.2	89.6	33.3	72.9	61.5	0.588	1.34	0.31	0.2254
BMI-2 (kg/m^2)	23.3	29.2	91.7	87.5	39.3	0.610*	3.50	0.77	0.0402
CRP-1 (mg/L)	12.0	20.8	87.5	76.9	35.6	0.546	1.67	0.90	0.5203
CRP-2 (mg/L)	12.0	33.3	95.8	94.1	41.8	0.633	8.00	0.70	0.0440
Albumin-1 (g/L)	31.0	45.8	70.8	75.9	39.5	0.547	1.57	0.76	0.5170
Albumin-2 (g/L)	36.0	85.4	75.0	87.2	72.0	0.841	3.42	0.19	0.0001
SOFA-1	12.0	72.9	33.3	68.6	38.1	0.514	1.09	0.81	0.8432
SOFA-2	16.0	100	83.3	81.4	100	0.941†	6.00	0.00	0.0001

BMI: Body mass index; CRP: C-reactive protein; SOFA: Sequential Organ Failure Assessment; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under curve; LR: Likelihood ratio; MV: Mechanical ventilation; 1: On start of MV; 2: On disconnection from MV.
* p<0.001 vs Albumin-2 and SOFA-2; † p<0.001 vs CRP-2.

used implies that these factors can be combined multiplicatively so that they change the relative probability of this variable by 1.75 (1.454 times 1.201).

DISCUSSION

This study of critically ill trauma patients admitted to the ICU suggests a high incidence of BMI ≤20 kg/m^2 (72.2%) or CRP >10 mg/L (81.9%) on the day of beginning MV. The incidence of low BMI or high CRP was significantly higher in patients in Group B compared with Group A on day of disconnection from MV. In all patients admitted to the ICU, the SOFA score, BMI, albumin, and CRP were significantly lower on the day of discontinuation from MV compared with these variables on the day of beginning MV. These variables were also significantly lower in patients in Group A compared with Group B. In a study by Cano et al.,[7] the two major determinants of outcome in patients with end-stage respiratory disease were BMI and CRP. Hutter et al.'s[4] study showed that the group of patients that failed NPPV had a mean BMI of 23 kg/m^2, which is relatively underweight. In another study by Celli et al.,[14] low BMI in outpatients with COPD was shown to be a predictor of poor prognosis. That lower muscle mass makes it more likely that a patient will become dependent on MV and less likely that the patient will have an effective cough. In fact, in critically ill patients, it has been shown that patients in overweight and obese categories may actually have a better survival and discharge functional status.[15] It may also be that patients with lower BMI require a different approach and methodology for the application of positive pressure ventilation or NPPV[4] Menzies and colleagues[16] showed that in COPD patients with ARF who required MV, the serum albumin concentration was associated with survival and weaning success. In our study, both BMI and serum albumin were significantly low on the day of weaning from MV in patient Group B compared with Group A.

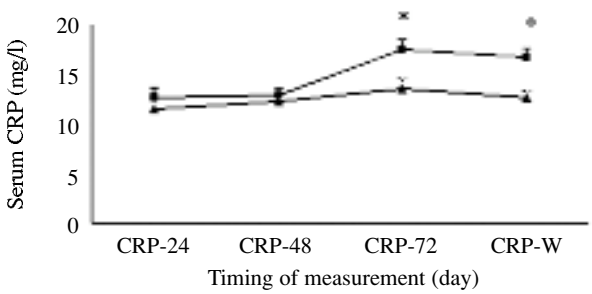

Fig. 1. Change in serum C-reactive protein on the day of admission to the intensive care unit (ICU) (CRP-24), 48 (CRP-48) and 72 (CRP-72) hours after admission to the ICU, and on the day of discontinuation from mechanical ventilation (CRP-W) for patients with less or more than 7 days of mechanical ventilation (VD <7 or VD >7). Data are presented as mean ± SE. * p<0.01. ■= Patients with VD >7; ▲= Patients with VD ≤7.

The strong and independent association of increased CRP and respiratory failure was shown in Kony et al.'s[11] study. In evaluation of prognostic factors in patients with SARS in a SARS center in

Taiwan,[12] development of respiratory failure was associated with higher CRP. The relationship between CRP and prognosis is also well recognized in chronic respiratory failure.[17] Malo and colleagues[17] showed that the circulating blood levels of several inflammatory cytokines and acute phase proteins were higher in patients with stable COPD. These data confirm the association of systemic inflammation with respiratory failure. Our data showed that the more severe the organ injury, as implicated by the SOFA score calculation, the higher the CRP, the lower the BMI, and the greater the duration of MV that can be expected.

The severity of inflammatory response and impairment of organ function are the major determinants of the outcome in critically ill patients.[18-21] As implicated from these studies, respiratory failure, the primary cause of the need for MV, was more common in patients with higher SOFA score during the days of admission to the ICU. Thus, it is logical that the duration of MV in these patients become more prolonged and persistent.

In our study, the trend of serum CRP changes during ICU days showed that the serum CRP level was significantly high in patients with more than seven days duration of MV. Lobo et al.'s[22] study showed that in critically ill patients, elevated concentrations of serum CRP were correlated with a risk of multiple organ failure (MOF) and death, especially when these persist over time. There is an increasing body of evidence supporting the critical role of the vascular endothelium in the pathogenesis of MOF in critically ill patients.[23,24] CRP can act directly on endothelial cells, inducing the production of inflammatory cytokines.[25] These data show that measuring serum CRP level during the ICU stay acts as a marker for predicting risk of organ failure (e.g. respiratory failure) and subsequent risk of the need for MV and its duration.

In conclusion, we found high incidence of low BMI or high CRP in critically ill trauma patients. BMI-2 less than 23.3 kg/m^2 or CRP-2 more than 10 mg/L is an independent predictor of more than seven days duration of MV. Future studies need to be conducted to determine the optimal timing as well as the threshold reference value for the BMI or CRP in a heterogeneous adult ICU population. Thereafter, large-scale multiple-center, prospective epidemiologic studies must be conducted to confirm and validate the findings of these preliminary studies.

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