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Multiple Organ Dysfunction Syndrome (MODS): Is It Preventable or Inevitable?*

Ayman El-Menyar[1,2#], Hassan Al Thani[3], El Rasheid Zakaria[4], Ahmad Zarour[3], Mazin Tuma[3], Husham AbdulRahman[3], Ashok Parchani[3], Ruben Peralta[3], Rifat Latifi[2,3,5]

[1]The Clinical Research, Trauma Surgery, Hamad Medical Corporation (HMC), Doha, Qatar; [2]Clinical Medicine, Weill Cornell Medical School, Doha, Qatar; [3]Trauma Surgery, Hamad Medical Corporation (HMC), Doha, Qatar; [4]Medical Research Center, Hamad Medical Corporation (HMC), Doha, Qatar; [5]Department of Surgery, University of Arizona, Tucson, Arizona, USA.
Email: #aymanco65@yahoo.com

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ABSTRACT

Multiple organ dysfunction syndrome (MODS) is a systemic, dysfunctional inflammatory response that requires long intensive care unit (ICU) stay. It is characterized with high mortality rate depending on the number of organs involved. It has been recognized that organ failure does not occur as an all-or-none rule, but rather a range of organ dysfunction exists resulting in clinical organ failure. In the absence of a gold standard scoring or tool for early diagnosis or prediction of MODS, a novel bio-clinical scoring is mandatory. Moreover, understanding the pathophysiology of MODS in medical, surgical and trauma, ICUs should take a priority to achieve a favorable outcome. Herein we reviewed the literatures published in English language through the research engines (MEDLINE, Scopus, and EBASE) from 1982 to 2011 using key words: "multiorgan dysfunction", "organ failure", "intensive care units" to highlight the definition, mechanism, diagnosis and prediction of MODS particularly at its earliest stages. Bring up new bio-clinical scoring to a stage where it is ready for field trials will pave the way for implementing new risk-stratification strategy in the intensive care to reduce the morbidity and mortality and save resources. Prospective studies are needed to answer our question and to shift MODS from an inevitable to a preventable disorder.

Keywords: Multiorgan Dysfunction; Failure; Intensive Care Units

1. Introduction

Multiple organ dysfunction syndrome (MODS) is a systemic, dysfunctional inflammatory response that requires long intensive care unit (ICU) stay and has high mortality rate of 27% - 100% depending on the number of organs involved [1-3]. However, there is no gold standard scoring system for MODS and also, the available registries and studies are not enough to understand, diagnose or predict the occurrence of MODS across the different types of ICUs. Herein we reviewed the literatures published in English language through the research engines (MEDLINE, Scopus, and EBASE) from 1982 to 2011 using key words: "multiorgan dysfunction", "organ failure", "intensive care units" to highlight the definition, mechanism, diagnosis and prediction of MODS particularly at its earliest stages. Non-English articles, case reports, outdated abstracts, and unpublished data were excluded.

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#Corresponding author.

2. Mechanism of Multiple Organ Dysfunction Syndrome

MODS is the leading cause of mortality in patients who survived the initial hours after trauma [2]. Moreover, MODS represents the most common cause of utilization of hospital resources. Initially MODS was thought to be an overwhelming, uncontrolled sepsis response, this was modified with the realization of the bimodal model of MODS (**Figure 1**) and the recognition that early MODS was unrelated to sepsis. In general, the cause of post injury MODS involves a mixed layering of patient, injury and treatment factors (**Figure 1**). The dysregulated immunological response is the crucial factor in the pathophysiology of post injury MODS [3].

3. Cycle and Stages of MODS

Patients with a heterogeneous trauma load and clinical picture are resuscitated into a similar state of systemic hyperinflammation, termed systemic inflammatory response syndrome (SIRS). This might be both beneficial

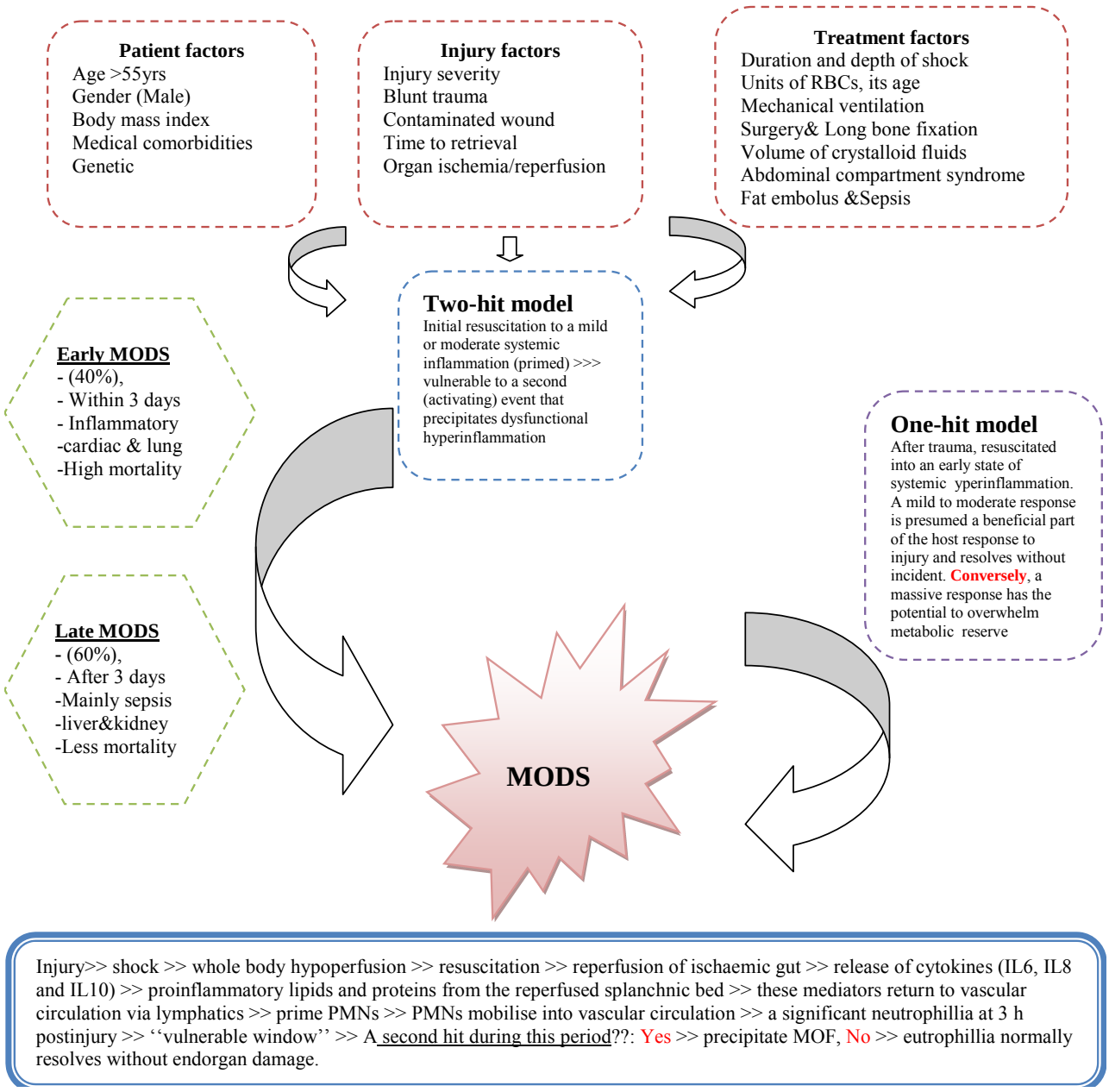

Figure 1. Causes, mechanism and types of multiorgan dysfunction syndrome.

and compensatory mechanism in the early stage of the disease, resolving in the majority of patients as they recover. However, organ failure may occur if this inflamematory response is exaggerated or sustained, eventually resulting in MODS. The initial magnitude of postinjury inflammatory response is depend on the amount of tissue injury, the degree of shock and the presence of host factors [4]. Patients who develop MODS frequently have early respiratory dysfunction, which is the major contributor to early MODS, occurring in 99% of postinjury MODS. Lung dysfunction precedes cardiac, hepatic and renal dysfunction [1,5]. The other dysfunctional organ systems can be associated with or without sepsis, and occur generally after 72 hrs of the primary insult (Late MODS). Late MODS patients require a second hit to progress to organ failure, and this hit is often sepsis. Nosocomial pneumonia, a common ICU complication, is the major infection associated with or precipitate late MODS [1,6].

4. MODS-Related Studies

Most of studies have included heterogonous population including medical and surgical patients who developed organ failure from a wide range of causes [7]. It is now recognized that organ failure does not occur as an all-or-

none phenomenon, but rather that a range of organ dysfunction exists leading up to clinical failure [7]. It has been suggested that this continuous process of varying levels of organ function is designated "MODS" [8]. This change in the understanding of organ failure as a continuous process has led to the development of a number of scoring systems that attempt to quantitate the degree of organ failure [9,10]. These variations in the definition of organ failure and the study of heterogeneous patient populations have made it difficult to establish the accurate incidence of organ failure in a given homogeneous population. **Figure 2** shows the incidence of single and multiorgan failure (SOF and MOF) in various studies [11-15].

5. Independent Predictors for MOF

For early risk stratification (12 hrs postinjury), several modifiable and non-modifiable predictors have been reported: high injury severity, amount of red blood cell transfusion, age of transfused products, age greater than 55 years old, high base deficit, uncorrected lactate at 12 - 24 hrs postinjury, obesity, male gender and abdominal compartment syndrome [1]. However, even during this early period, MOF already has been triggered and may be inevitable [1,16].

6. Scoring and Criteria

The pathophysiology of MODS is varying according to the mechanism of injury in the medical versus non-medical (trauma and surgical) ICUs. Certain criteria should be taken into consideration when assessing the value of any scoring system in clinical practice [17,18]. These criteria should include reliability, validity and the ability of a scoring system to unmask temporal changes in organ dysfunction if measured sequentially [18,19]. Studies evaluated the comparative prognostic value of the commonly used organ dysfunction scoring systems concluded that some standardization of the included variables is needed before introducing a scoring tool in everyday practice [20,21]. In the absence of a gold standard scoring or tool for diagnosis or prediction of MODS, validation is required to evaluate the association of different scores with objective, adverse outcomes, clinical status and resource utilization. **Table 1** shows the diver sity of scoring systems for MOF [10,12,13,15-20]. Sauaia *et al.* [21] reported that both Denver and Marshall MOF scores perform reasonably well as indicators of unfavorable outcomes in critically ill patients; with the Denver MOF

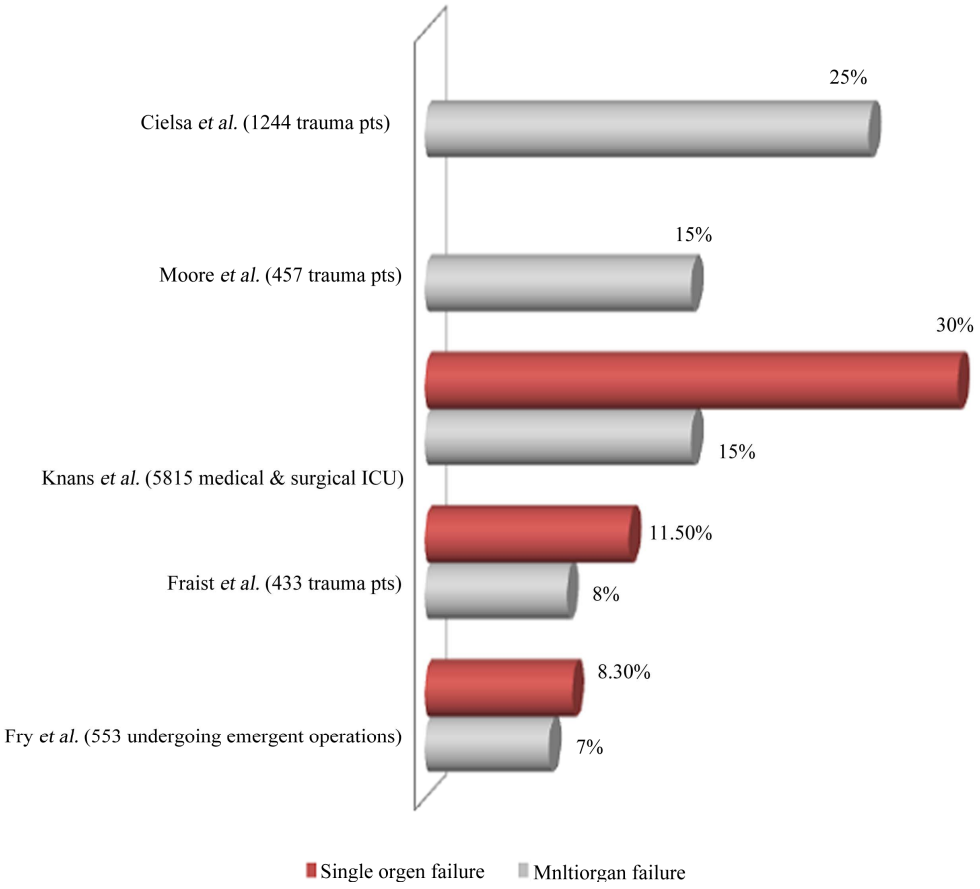

Figure 2. Incidence of organ(s) failure from western populations.

Table 1. Different scoring systems for multiorgan failure.

	N. of Organs	Comments
1) Fry *et al.* 1980 [15]	4 (Pulmonary, hepatic, GIT, and renal)	One or more organs failed in 15% of patients. The incidence of SOF and MOF were 8.3% and 6.9% and Mortality rates were 30% for SOF, 60% for 2 organ, 85% for 3-system organ, and 100% for 4-OF.
2) Stevens 1983 [17]	7	Numeric Sepsis severity scoring system
3) Goris *et al.* 1985 [18]	7	Organ dysfunction/failure had 3 categories: (0 = normal,1 = organ dysfunction, 2 = OF)
4) Knaus *et al.* 1985 [13]	5 (CVS, respiratory, renal, hematologic, and neurological)	One or more OFs occurred in 49% of patients: SOF occurred in ≈1/3 of patients at some time during their ICU stay. MOF occurred in 15%. SOF lasting more than 3 days had mortality of 40%. Mortality was 60% for 2-OF and 100% for 3-OF.
5) Marshall *et al.* 1995 (MODS) [10]	6 (Pulmonary, renal, hepatic, cardiac, hematological and neurological system)	Data collected from systematic review and clinical database
Marshall and SOFA scores	Both scores are very sensitive but not specific: More sensitive score causes high incidence of MODS, while a more specific score causes high mortality.	
6) Vincent *et al.* 1996 (SOFA) [19]	6 (Graded from 0 to 4 according to the degree of dysfunction failure)	The score individualizes the degree of dysfunction of each organ obtained daily(not to predict outcome but to describe a sequence of complications).
7) Le Gall *et al.* 1996 (LODS) [20]	6	Physiological variables of 6 organ systems by using logistic regression: GCS, PaO_2:FiO_2 ratio, heart rate, BP, serum urea, creatinine, urine output, white blood cell, bilirubin, platelet count, and prothrombin.
8) Moore *et al.* 1996 (Denver) [12]	4 (Pulmonary, renal, hepatic and cardiac)	One or more organ systems failed in 25% of patients and 2 or more organ systems failed in 15% of patients. Mortality was 11% in patients with 1 organ system failure, 24% with 2 organ systems, 60% in patients with 3 failures, and 62% in patients with 4 OFs.
Denver MODS score	To define and monitor the severity of MODS in trauma with ISS > 15 who survived >48 hrs and who are 16 yrs or older. Must be collected daily (day 2 to discharge). It rates 4 organ systems; pulmonary, renal, hepatic and cardiac. It is more specific and less sensitive in trauma population.	
Criteria of OF [7]	Cardiac: Heart rate ≤ 54 beats/min, Mean arterial pressure ≤ 49 mm Hg ventricular tachycardia, fibrillation, or both, Serum pH ≤ 7.24 with a $PaCO_2$ ≤ 49 mm Hg. Pulmonary : Respiratory rate ≤ 5 breaths/min or≥49 breaths/min, $PaCO_2$ ≥ 50 mm Hg AaDO2 ≥ 350 mm Hg, Dependent on ventilator on the fourth day of organ failure. Renal: Urine ≤ 479 mL/24 h or ≤149 mL/8 h, BUN ≥ 100 mg/dL, Creatinine ≥ 3.5 mg/dL; Hepatic: Bilirubin ≥ 3 mg/dL Serum glutamic oxaloacetic transaminase greater than two times normal Protime INR >1.5.	

GIT = gastrointestinal tract; SOF = single organ failure; MOF = multiorgan failure; CVS = cardiovascular system; ICU = intensive care unit; GCS = Glasgow coma scale; ≈ = approximately; OF = organ failure

scores performing slightly better due to greater specificity. Moreover, Denver MOF score performs better as a continuous scale to monitor individual patient's response to treatment. The analysis of individual organ dysfunction scores suggests that concepts of the two scores can be combined to develop more valid score [21].

However, what is validity and accuracy if the clinical scoring system is integrated into the biomarkers of organ dysfunction? This bio-clinical scoring has not tested yet.

7. MODS at Cellular Level

Numerous studies revealed that cells of the immune system (Polymorphic mononuclear [PMN], lymphocytes, monocytes/macrophages, dendritic cells and endothelial cells) and the release of pro- and anti-inflammatory cytokines, chemokines, adhesion molecules, complement, protease, eicosanoids, reactive oxygen species (ROS) and nitric oxide (NO) play a significant role in the pathogenesis of MOF. As these cells and molecules are released for primarily host defense, their release can be harmful to the host depending on the type and degree of injury, post-trauma surgery, intervention for diagnosis and therapy for trauma [22].

What is Systemic inflammatory response syndrome (SIRS)

Two or more of the following criteria are met:

—Temperature < 36.8˚C or temperature > 38.8˚C. – Heart rate > 90/min.

—Respiratory rate > 20 breaths/min or PCO_2 < 32 mm Hg.

—WBC < 4000/mL or WBC>12,000 mL or > 10% immature forms [1].

The role of Polymorphic mononuclear (PMN) priming

It is amplification of the PMN response to a certain

stimulus following prior exposure to a different stimulus. Clinically, priming is manifested by SIRS, characterized by alterations in body temperature, white blood cell count, respiratory dysfunction, and a hyperdynamic state. Primed PMNs cause a significant neutrophillia at 3 h postinjury. This neutrophillia represents the "vulnerable window" and a second hit during this period may precipitate MOF. In MOF there is a rapid neutropenia between 6 and 12 h postinjury (end organ sequestration). While in non-MOF, neutrophil priming and neutrophillia are not followed by neutropenia, and resolve over the next 36 h without end organ damage [1].

7. MODS at the Molecular Levels

Molecular events underlie the pathogenesis of MODS is not well-established, therefore, the temporal course of pathophysiological changes leading to the development of MODS are of great clinical and research interest. Keeping in mind "There is no gold standard diagnostic tool for MODS", however, several studies have utilized one or two biomarkers for detection of single rather than multiple organ dysfunctions. General markers of inflammation including cytokines are correlated with posttraumatic complications with a low sensitivity and specificity and are, therefore, of little utilization as prognostic markers [23]. To date, all therapeutic strategies focused on a single mediator or receptor has failed to improve the clinical outcome associated with MODS [2]. However, a recent small study showed that cytokine expression during shock may enable earlier identification of patients who are at risk for development of MODS [24].

There are only few registries and prospective studies that reported the prevalence of MODS worldwide [11,25]. Furthermore, there is no consensus to support the sensitivity and specificity, predictive values of one or more serum markers in the diagnosis or prediction of organ dysfunction before the overt clinical failure. Therapeutic strategies to combat the post injury MODS have focused on control of the post injury inflammatory response [25].

Early detection of MODS need extensive prospective studies as this will be reflected on the morbidity and mortality in all ICUs. For that purpose, ICUs should have prospective data collection on MODS in its database registry. Subsequently, registries will pave ways for the appropriate evaluation and management.

8. Animal Models

Trauma, shock or sepsis, researchers studied the basic mechanisms that drive the pathogenesis of end-organ injury and MODS at the cellular, tissue and whole organism levels. Previous studies demonstrated that endorgan injury and subsequent MODS result from a cause-effect relationship between three pathophysiologic events, which likely interact in a time-dependent, tissue-specific fashion. First, a persistent and progressive splanchnic vasoconstriction and hypoperfusion leading to relative ischemia/hypoxia [26,27]; Second, a gut-derived systemic inflamematory response generated by the ischemic gut [28]; and third, inevitable fluid shifts at both the cellular level due to ionic-disequilibrium and at the capillary level due to alteration of the trans-capillary Starling forces that govern fluid exchange [29,30].

9. Gut Hypothesis

Preclinical experimental studies showed that shock or trauma cause gut barrier failure and bacteria translocating to distant organs. Also, the subsequent gut released proinflammatory and tissue injurious factors could result in acute lung injury, bone marrow failure, myocardial dysfunction, neutrophil activation, red blood cells injury and endothelial cell activation and injury. Interestingly, these factors are carried in the mesenteric lymphatics, but not in the portal blood flow and are sufficient to cause MODS [31].

10. The Trigger and Targeted Organ

It has been shown that certain organs are more vulnerable and presage the chain or occurrence of MOD. There is no solid data showing whether the dysfunction will affect single organ or multiple organs. Post-traumatic lung dysfunction precedes cardiac dysfunction by 0.6 days, hepatic dysfunction by 4.8 days and renal dysfunction by 5.5 days on average [1,4,5]. This early involvement of the lungs supports the contention of the time dependency and tissue (organ) specificity of SIRS. The mechanism of post-traumatic lung injury and dysfunction occur at least in part through mesenteric lymph-induced activation of neutrophils and activation/injury of endothelial cells. Subsequent infiltration of the tissue with activated neutronphils is time dependent and organ specific [28]. In the shock lung, resuscitation from hemorrhagic shock secondary to trauma increases the myeloperoxidase (MPO) level, an index of neutrophil tissue infiltration, in a near-linear fashion during the first 4 h following resuscitation. However, lung MPO level returned to baseline at 24 h following resuscitation from hemorrhagic shock [28]. This data suggest that a vulnerable window for neutron- phil-mediated lung damage exists during the first 4 h following resuscitation from hemorrhagic shock in rats [28]. Thus, demonstration of a time-dependency and organ-specificity of the proposed composite biomarkers in a fashion similar to SIRS, adds more specificity and sensitivity to the composite biomarkers, which helps the development of specific intervention before the initiation of the pathogenesis of multi-system organ failure. **Figure 3** shows the inflammatory response after trauma in hrs and days [2,32-35].

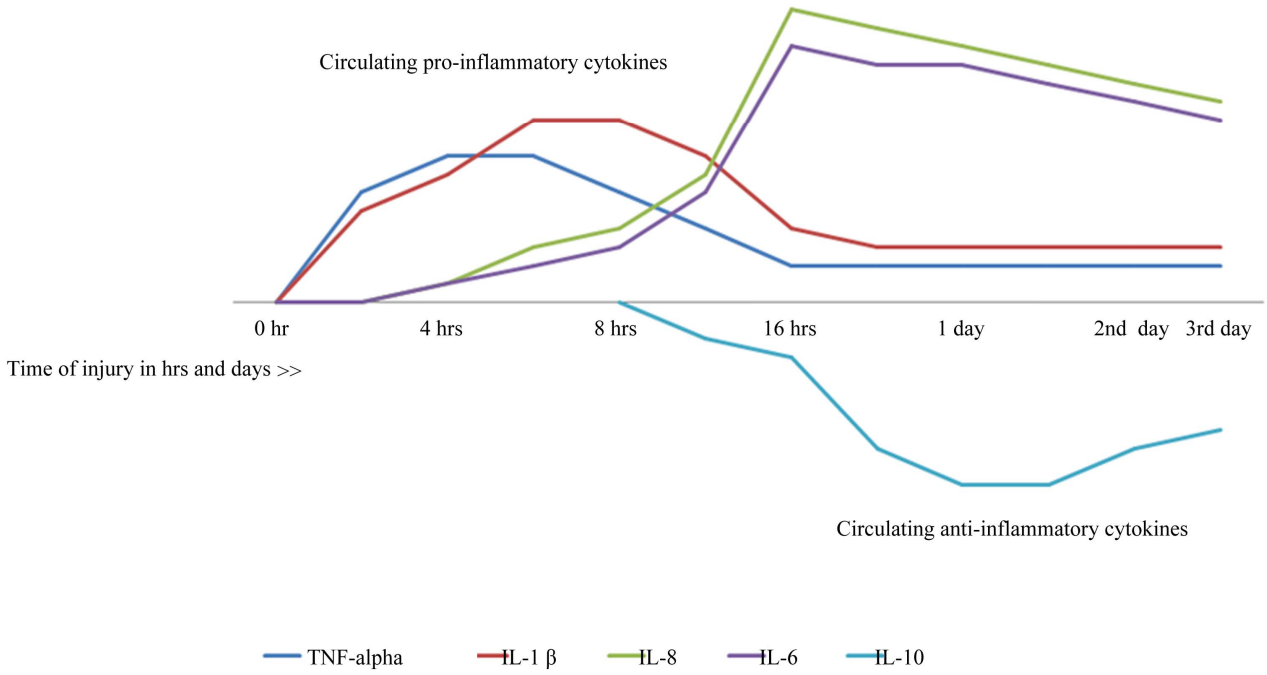

Figure 3. Cytokines response after trauma in hrs and days.

11. Role of Biomarkers

Different biomarkers [35-47] play various ways on the occurrence of organ dysfunction. Detailed information for the clinical utility of biomarkers is given in brief in **Table 2**. Certain markers have been studied frequently and prove important clinical impact on certain organs {*i.e.*, lung (pentraxin-3 and IL-8 & 18), heart (NT-pro BNP, Adrenomedullin and pentraxin), kidney (NGAL) and liver (glutamate/glutamine and cytokeratin-18)} in addition to Vascular cell adhesion molecule (VCAM-1) and Endothelial cell-specific molecule 1 (ESM-1) [48]. Biomarkers for early detection of sepsis (*i.e.*, procalcitonin) is also important. Several studies tackling proinflammtory (*i.e.*, IL-8 &18) and anti-inflammatory *(i.e.*, IL-6 &10) cytokines have shown that there is no single cytokine turned out to be legible enough to predict the outcome [35].

The cytokine response is an important factor in the development of SIRS as a response to trauma. Pro-and anti-inflammatory cytokines are released excessively during the initial phase of trauma. The role of the anti-inflammatory cytokines is to down-regulate the production of pro-inflammatory cytokines. Normally, the bala nce of pro- and anti-inflammatory cytokines is in equilibrium, however, when this natural balance is unbalanced with the release of predominantly pro-inflammatory cytokines, this leads to SIRS, while predominance of anti-inflammatory cytokines causes immunosuppression, which lead to infection, sepsis and subsequently result in MOF [22]. ***The role of acute phase proteins***: Levels of CRP rapidly increase within 2 hours of acute insult, reaching a peak at 48 hours. With resolution of the acute phase response, CRP declines with a relatively short half-life of 18 hours. PCT is proposed to be a better and more specific marker for inflammation than CRP, as the kinetics of PCT more closely resembles the kinetics of inflammation [37,38]. Serum levels of PCT more rapidly increase after the onset of inflammation and decline faster as inflammation diminishes.

12. Recommendation and Conclusion

Bring up new bio-clinical scoring to a stage where it is ready for field trials will pave the way for implementing new risk-stratification strategy in the intensive care to reduce the morbidity and mortality and save resources.

Further trials will be based on that to establish preventive measures and goal-targeted therapy in the ICUs. Understanding the different pathphysiology of early MODS will discriminate the signs of intense inflammatory response from early signs of sepsis. This will reduce the inappropriate use of antibiotics or to correctly start antibiotics at the early stages of sepsis and subsequently reduce hospital stay and mortality. As there are no guidelines or consensus for management of high-risk patients, further studies utilizing the integrated bio-clinical hypothesis will be of great interest. Further prospective studies are needed to answer our question and convert MODS from inevitable to preventable disorder.

Table 2. Biomarkers play a role in MODS.

Biomarker	Clinical utility
1) Neutrophil gelatinase-associated lipocalin (NGAL)	NGAL is ideal biomarker for acute kodney injury (AKI); its concentration rapidly decreases with attenuation of renal injury; and it is readily and easily measured in plasma and urine. NGAL typically detected AKI 36 to 48 h earlier than creatinine.
2) Serum glutamate/glutamine	Glutamine itself may act as a key precursor for nucleic acids in glutamine consuming cells, but in many circumstances acts to provide glutamate, however, glutamate also serves as a precursor for the formation of glutamine.. Glutamate could be a marker of liver dysfunction during sepsis.
3) Cytokeratin-18 (CK-18)	CK-18 presents in most simple epithelial and parenchymal cells. Fragments of CK-18 are more specific for apoptotic cell death. The measurement of caspase-cleaved and uncleaved CK-18 appears to be an early predictor for survival in severe septic patients with hepatic dysfunction
4) Procalcitonin (PCT)	PCT supports early diagnosis and clinical decision making which could direct an effective therapy at the right time and avoid unnecessary spending for critically ill patients. Unlike CRP, PCT values typically declined rapidly after trauma. The rapid decline of the trauma-induced response of PCT towards its normal range compared with the long-lasting increase of CRP promises an earlier diagnostic use of PCT as a marker of sepsis and infection than of CRP. The PCT half life of about 22 hours
5) Adrenomedullin (AM)	AM production and secretion is augmented by several pro-inflammatory and pro-atherogenic factors. Circulating adrenomedullin levels are elevated in acute cardiac injury. plasma levels are markedly increased in early septic shock. Plasma AM and IL-8 levels correlated positively with (APACHE) II score, peak MODS score during the first month and prognosis in patients with septic shock, as did plasma IL-6 levels in patients with traumatic shock. Adrenomedullin has a circulating half life of 22 ± 1.6 min
6) Pentraxin-3 (PTX3)	PTX3 is a rapid marker for primary local activation of innate immunity and inflammation It is associated with acute lung and heart injury. PTX3 behaves as an acute phase response protein, as the blood levels of PTX3, low in normal conditions (<2 ng/mL in humans), increase rapidly (peaking at 6 - 8 h after induction) and dramatically (200 - 800 ng/mL) during endotoxic shock, sepsis and correlating with the severity of the disease.
7) NT-pro-BNP	NT-proBNP, is supposed to be a better marker of myocardial dysfunction and prognosis in patients with severe sepsis and septic shock. Its levels correlate with the severity of organ dysfunction as assessed by the SOFA score in septic patients. The half-life of human NT-proBNP is considered to be 60 - 120 min (depending on renal function).
8) VCAM-1	Vascular cell adhesion protein 1 is also known as vascular cell adhesion molecule 1 .VCAM-1 protein mediates the adhesion of lymphocytes, monocytes, eosinophils, and basophils to vascular endothelium. It also functions in leukocyte-endothelial cell signal transduction.
9) Cytokines (interleukine; IL)	MODS is associated with higher levels of systemic proinflammatory cytokines(IL6, IL8 and IL10). Patients who develop late MODS show a second peak of IL6 at day 7, while in early MODS, IL6 returns to baseline levels by day 4. IL8 can activate PMNs via two different receptors. IL-8 is a chemokine and its production following trauma leads to leucocyte recruitment and activation at the site of injury. In contrast to NT-proBNP and PCT,initial IL-6 are highly predictor of mortality after myocardial infarction with shock. Increased IL-6 is associated with narrowed macro-and microcirculation,a center pathomechanism for development of MODS. After trauma, the levels of IL-8 correlate with the subsequent development of ARDS and MODS.
10) Endothelial cell-specific molecule 1 (ESM-1)	Inflammatory cytokines such as TNF-α strongly stimulate human endothelial cell to increase the secretion, synthesis and expression of endocan. Studies agreed on the endocan's prognostic value and how it could be of huge help to predict the outcome of sepsis. As its increase at ICU admission is indicative of poor prognosis.

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