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Review Article

Severe Trauma Complications Prediction by Biomarkers

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Abstract: Trauma and its severe complications are major health problems and leading causes of mortality and morbidity among young people in the world. The increasing ability to keep most trauma patients alive has resulted in an increased incidence of complications in this population. The pathophysiology of trauma complications is tremendously complex. Biomarkers have traditionally been considered as important area of medical research: the measurement of certain biomarkers has led to a better understanding of pathophysiology, while others have been used either to assess the effectiveness of specific treatments or for prognostic purposes. If with early diagnosis and early intervention, trauma complications can be prevented and cured. The aim of the review is to discuss new biomarkers which can be used in the prediction of severe trauma complications, mainly sepsis and Multiple Organ Dysfunction Syndrome (MODS). We also discuss to which degree currently available trauma complications biomarkers may help to overcome the present diagnostic uncertainty. We address how new insights into the pathogenesis of trauma complications may help in the development of specific biomarkers and how this may also impact the identification and development of new therapeutic targets. Research into biomarkers may help to predict the prognosis of patients with severe trauma.

Keywords: Trauma Complications, Biomarkers, Sepsis, Multiple Organ Dysfunction Syndrome, Acute Phase Proteins, Immunocyte, Organ Damage, Cytokine, Single Nucleotide Polymorphism

1. Introduction

Severe trauma and it's complications are major health problems and leading causes of mortality and morbidity among young people in the world. More than 30% trauma patients developed complications [1]. Trauma complications are caused by trauma and are associated with trauma and (or) trauma care. With the development of standardized treatment strategies, improved resuscitation, graded surgical protocols, and organ system support, the survival rate of major trauma has improved significantly. But victims of severe injuries who survive the initial hours have great risk in additional life-threatening complications, including sepsis, septic shock, multiple organ dysfunction syndrome (MODS) and so on. They always happen one week after trauma. If with early diagnosis and early intervention, trauma complications can be prevented and cured.

By definition, biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic process or pharmacologic responses to a therapeutic intervention [2]. It has been shown that various biomarkers are very useful in clinical practice in sepsis diagnosis and some of them are thought superior to clinical signs as far as diagnosis. The study of the biological markers of trauma complications began in the 60's of the last century [3]. From the 80's of the last century, due to the rapid development of molecular biology and its penetration in clinical medicine, researchers paid more attention to trauma biomarkers. So far, there are hundreds of trauma biomarkers, summed up, mainly in the following aspects.

2. Acute Phase Proteins, APPs

In response to infections, trauma, acute arthritis, systemic autoimmune disorders and neoplasms [4], local inflammatory

cells (such as neutrophil granulocytes and macrophages) secrete a number of cytokines into the bloodstream, most notable of which are the interleukins IL-1, IL-6 and IL-8, and TNF-α. Following stimulation hepatocytes produce a number of proteins and release them into circulations. These proteins are thus referred to as acute phase proteins. The APPs include C-reactive protein (C-CRP), Procalcitonin (PCT), serum amyloid A (SAA), fibrinogen, etc. Many of these APPs are heavily glycosylated, they are very stable. That is why some APPs are ideal biomarkers of inflammation [5].

2.1. PCT

The best known biomarkers of sepsis are PCT and C-CRP. The secretion of PCT is a part of the inflammatory response that relatively specific to systemic bacterial infections. Bacterial infections cause a much higher rise in PCT level compared with viral and intracellular bacterial infections. A newly research indicated that PCT is a marker for clinical suspicion of systemic candidiasis. However, low PCT levels (<0.99 ng/mL) must combine the use of other specific markers of candidaemia to confirm the diagnosis, due to the great uniformity of PCT levels in systemic candidiasis and SIRS groups [6]. Uzzan et al [7] concluded that PCT is a good diagnostic marker for both sepsis and septic shock. PCT should be included in diagnostic guidelines for sepsis and in clinical practice in ICU. Tang et al [8] concluded that the PCT is not a reliably marker in differentiating sepsis from noninfectious causes of SIRS in critically ill. But Mohsen et al indicated that PCT is also a useful, sensitive and independent marker compared to CRP in early diagnosis of neonatal sepsis [9].

2.2. C-CRP

CRP is a protein produced in response to inflammation and infection and it is widely used in clinical tests to diagnose sepsis patients. Neunhoeffer et al found that within the postoperative period, CRP was a most reliable marker for the discrimination between sepsis and SIRS [10]. A research indicated that the combination of CRP, PCT, and neutrophil CD64 measure remained a significant predictor of sepsis with an excellent AUC (0.90). In a targeted ICU population at increased risk of sepsis, CRP, PCT, and neutrophil CD64 combined improve the diagnostic accuracy of sepsis [11]. Although its low specificity may be its primary drawback as a biomarker of sepsis in adults, it is commonly used to screen for early onset sepsis in neonatology [12].

2.3. Lipopolysaccharide Binding Protein (LBP)

LBP is a soluble acute-phase protein. It binds to bacterial lipopolysaccharide (LPS) and present LPS to immune cell surface pattern recognition receptors CD14 and TLR4 to elicit immune responses. The LBP-LPS complex binds to CD14 and to TLR4 to initiate signal transduction, which leads to the activation of the MAPK and NF-κB pathways. The serum concentration of LBP is 5 to 10 μg/ml in human. It increases during acute-phase reaction, reaching a peak levels over 200 μg/ml [13]. According to many published data, LBP may be a useful marker of infection and sepsis [14]. However, this could not be confirmed in a more recent study [15]. That analysis found that pericardial fluid LBP levels do not correlate with septic states. No relationship was observed in either septic or non-septic groups.

3. Immunocyte

During sepsis, the immune system will be impaired not only on the function of immune cells but also the impaired antigen-specific antibody responses. For a long time it was the prevailing opinion that an initial inflammatory immune response is followed by a compensatory anti-inflammatory response to reconstitute immune homeostasis [16-18]. Studies show that immunocyte for detection of biomarkers has important clinical significance in the diagnosis of trauma early warning and prognostic evaluation of sepsis and MODS [19].

3.1. Neutrophil

In response to experimental inflammatory stimuli, neutrophils exhibit a pattern of responses that serve to direct the cells toward a focus of injury or infection [20]. In addition, the neutrophil can extrude its DNA to create neutrophil extracellular traps (NETs) that serve to enmesh bacteria and to activate local coagulation mechanisms. Neutrophil gelatinase-associated lipocalin (NGAL) is a good diagnostic and prognostic marker for sepsis and acute kidney injury. A recent study shows that urinary NGAL is a noninvasive biomarker with high negative predictive value at the time of late-onset sepsis evaluation in neonates and could be a useful in sepsis evaluations [21]. Hong et al indicated that plasma NGAL is a useful marker in sepsis severity assessment and prediction in ICU [22].

When activated, neutrophilic granulocytes express Fcγ receptor (FcγR) [cluster of differentiation 64 (CD64) antigen]. Demonstrated using flow cytometry, neutrophil CD64 can be used as a diagnostic marker of sepsis and infection. CD64 index on neutrophils may be used as a diagnostic tool to recognize sepsis induced by ventilator-associated pneumonia [23]. A recent study showed that CD64 expression on neutrophils showed high specificity, sensitivity and accuracy in the sepsis diagnosis but not for survival prediction [24]. Du et al also indicated that CD64 expression on neutrophils is a highly sensitive marker in early-onset sepsis in preterm neonates [25].

Neutrophil delta neutrophil index (DNI) is developed by Nahm et al [26] as a new indicator for immature neutrophils. Delta neutrophil index (DN) is the immature granulocyte fraction which is determined by subtracting the fraction of mature polymorphonuclear leukocytes in myeloperoxidase-reactive cells. In critically ill patients, the DNI is associated with septic shock, positive blood culture results, disseminated intravascular coagulation, and mortality [27]. Lewis et al found the percentage of neutrophils increasing was associated with sepsis and SIRS [28].

3.2. Lymphocyte

Lymphocyte plays a key role in the regulation of inflammatory response, and their loss due to continuous sepsis-induced apoptosis may lead to the immune system suppression and non-resolution of inflammation [29]. The neutrophil-to-lymphocyte ratio (NLR), as a readily accessible biomarker, can be calculated based on a complete blood count [30]. Liu et al indicated that increased NLR levels were independently associated with unfavorable clinical prognosis in patients with sepsis [31]. There is no consensus about the relationship between NLR levels and clinical prognosis in patients with sepsis until now. Researchers in a recent study showed a reversed NLR evolution according to the timing of death [32], whereas some other studies suggested that NLR was not associated with mortality in sepsis patients [33].

Stieglitz et al found that cecal ligation and puncture (CLP) is a clinically relevant mouse model for sepsis, the proliferation of CD4+ and CD8+ T cells were suppressed in septic mice [34]. Depletion of immune cells development of suppressive myeloid cells (MDSC) and increased numbers of regulatory T cells (Treg) are suppressed immune status in sepsis. In patients who died of sepsis marked signs of immune suppression were observed such as decreased cytokine production and expansion of Treg and MDSC [35]. Other studies showed that the decline of T-cell-mediated immunity during sepsis is associated with reduced CD8+ T memory cell counts [36-39].

4. Organ Damage Biomarkers

Organ damage is a common complication of trauma, in the severely injured who survived the early posttraumatic phase, multiple-organ failure is the main cause of morbidity and mortality. Currently widely used scoring methods are multiple organ dysfunction score [40] and sequential organ failure assessment score (Sequential Organ Failure Assessment, SOFA). The diagnosis of organ dysfunction is the use of some conventional biochemical indicators, such as serum creatinine (renal function), blood bilirubin (liver function), etc., combining the changes of the value of the indicators to quantify the score. The treatment effect and the prognosis will be better if the organ damage is found earlier. Therefore, research on early biomarkers of organ damage in recent years was paid much attention [41].

4.1. Acute Lung Injury (ALI) / Acute Respiratory Distress Sydrome (ARDS)

During sepsis, ALI and ARDS happen especially when patients get MODS. There are alao many cytokines or immune chemicals which can be used as biomarker for ALI and ARDS. As a transmembrane pattern-recognition receptor of the immunoglobulin superfamily, receptor for advanced glycation end products (RAGE) is constitutively expressed at low levels in all cells but abundantly in the lung. During the early stage of ARDS, the expression of RAGE significantly elevated [42]. Plasma levels of SP-A and SP-B are also increased ARDS patients [43]. Plasma KL-6 is increased in ARDS patients, it is correlated with ALI and mortality [44]. High-throughput technologies are recently used in the biomarkers screening. Genome-wide association studie (GWAS) was used in ARDS biomarkers screening, 14 new candidate genes (IL1R2, IL1beta, PAI1, IL6, SOCS3 and etc.) were discovered associated with ARDS [45].

4.2. Traumatic Brain Injury (TBI)

TBI is a leading cause of death after severe trauma. The findings of many studies suggest that Substance P could play a key role in TBI. A study showed that non surviving TBI patients showed higher serum Substance P levels than survivors, and that serum SP levels were associated with TBI severity and with early mortality [46]. CD40L and its soluble counterpart (sCD40L) are proteins with proinflamatory and procoagulant effects when binding to their cell surface receptor CD40. A study found that nonsurviving TBI patients had higher serum sCD40L levels than surviving ones, and an association between serum sCD40L levels and TBI severity and mortality [47].

4.3. Acute Kidney Injury (AKI)

Many studies have found some biomarkers for the diagnosis or even prognosis of sepsis-induced Acute Kidney Injury (AKI). Alpha-1-microglobulin (a1m) is a protein that is synthesized in liver. Terzi et al. assessed the utility of urine concentrations of a1m as biomarker of early sepsis-induced AKI diagnosis in critically ill patients managed in an ICU. They revealed elevated levels of a1m in all septic patients and a progressive increase of a1m in patients who finally developed sepsis-induced AKI [48]. As a fragment of CD14, presepsin is a 13kDa protein with truncated N-terminal, the receptor for LPS/LBP complexes. Nakamura et al. demonstrated that blood presepsin level can be a reliable indicator of sepsis in non-AKI patients and less severe AKI patients [49]. Tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and Matrix metalloproteinase-9 (MMP-9) ratio are also diagnostic biomarkers of sepsis-associated AKI [50].

5. Cytokines

Cytokines are many kinds of small proteins (5-20 kDa) which are important in cell signaling, proliferation, cell death and so on, including autocrines, interferons, interleukins, lymphokines, tumor necrosis factor but generally not hormones or growth factors [51-52]. A large numbers of cytokines were detected in the circulation of patients with severe sepsis and trauma. Dozens of relatively small cohort studies have shown plasma cytokine concentrations are correlated with outcome in sepsis and trauma [53].

5.1. Tumor Necrosis Factor (TNF)

TNF is one of the best defined pro-inflammatory cytokines. It's not only a potent stimulator of the activation of many cell types such as macrophages/monocytes and NK cells but can

also induce cell survival or cell death by apoptosis. Several studies have are conflict regarding levels of cytokines in circulation and severity of sepsis in critically ill patients. A study indicated that low TNF-α concentration in patients with severe acute pancreatitis predicts development of MODS [54]. Contrarily, some authors found that high serum TNF-α levels correlate positively with the severity of disease and even death [55]. Florence Riche et al. found that in patients with high serum TNF levels were associated with increased survival in abdominal septic shock [56].

5.2. Interleukin-6 (IL-6)

Although several kind of cytokines are reported to be closely related with sepsis, only IL-6 has approached routine clinical use. IL-6 is a cytokine that acts as both a pro-inflammatory and an anti-inflammatory cytokine. It is an important cytokine functions in adaptive immunity an in the initiation of innate immunity too [57]. It's attractiveness as a biomarker lies in the fact that it elevated very early, and reaches a peak concentration within two hours under experimental conditions [58]. So IL-6 is a potentially good biomarker of sepsis. Oberholzer et al. showed that in a prospective randomized double-blind placebo controlled trial that baseline IL-6 concentrations were much higher in patients with septic shock and patients with bad prognosis [59].

6. Gene Polymorphisms

Unlike protein biomarkers that may be transiently expressed during disease process, gene polymorphisms (e.g., Single Nuleotide Polymorphism, SNPs) do not vary in response to underlying illnesses, so they may be better predictive indicators of sepsis [60-61].

6.1. Gene Polymorphisms of Innate Immune Receptors

Sepsis is a major complication of trauma which is a systemic inflammatory response of the body to bacterial. LPS binds to monocyte phagocyte receptor-CD14 molecule to induce the immune response in Gram-negative infection. LBP is responsible for the binding of LPS to CD14 is liver-derived LBP present in the plasma [62-63]. SNP within the promoter region at positions -159 (C159T) and -260 (C260T) of the CD14 gene have been identified to be associated with sepsis after trauma [64]. Rs2232618 (Phe436Leu) is a nonsynonymous variation on the LBP gene. It is closely associated with higher susceptibility to sepsis and MODS in two major trauma patients. The molecular mechanism was that rs2232618 (436Leu) can enhance LBP protein activities, showing an increases in LPS binding to macrophages, LPS-induced macrophage activation, and LBP-CD14 interaction [60].

6.2. Gene Polymorphisms of Cytokines

Sepsis is accompanied by an uncontrollable cytokine response ("cytokine storm"). Therefore, a number of variations in cytokine genes have been reported in gene association studies with the complications of trauma. TNF-α is an important gene in sepsis, it's promoter SNP-rs1800629 A allele had a 4.28-fold higher risk for septic compared with severe sepsis. Individuals with the TNF-α 308 rs1800629 A had a higher prevalence of septic shock [65]. Baqhel et al indicated that TNF-α-308 G/A polymorphism is closely associated with the development of postoperative sepsis and with increased expression of cytokines TNF-α, IL-6/8 [66]. Another study showed that plasma TNF-α level was higher in patients with sepsis and septic shock. It can be used in the guide the therapy of sepsis patients [67]. Another important pro-inflammatory cytokine is IL-1α/β. An IL-1α polymorphisms was located in intron 6 ("variable number tandem repeats", 46 bp), but this SNP didn't show an association with sepsis [68]. However, our study found that polymorphisms in the IL-1β gene was associated with bad outcome in severe trauma patients [69].

6.3. Gene Polymorphisms of Pattern-Recognition Receptors (PRRs)

PRRs are receptors which can recognize microbe-specific molecules such as bacterial carbohydrates, nucleic acids, bacterial peptides and so on. Our studies identified a SNP in TLR2 gene-19216T/C was associated with the expression of cytokine and related with an increased risk of sepsis and MODS after major trauma [70]. TLR4 11367G/C and −2242T/C were two functional SNPs that are related to sepsis morbidity too [71]. The myeloid differentiation 2 (MD-2) is interacted with TLR4 on the cell surface and confers a responsiveness to LPS, thus plays a key role in LPS signaling. −1625C/G, a SNP in MD-2 promoter influenced MD-2 promoter activity and expression of MD-2 in vitro, also showed clinical influence in sepsis after major trauma [72].

7. Conclusions and Recommendations

Although there are so many biomarkers for trauma complications and almost all of them are quite promising in sepsis diagnosis and prognosis, but more evidence is needed so as to be valuable for clinical use. Taking into account the complexity of the pathogenesis and of posttraumatic complications, scientists try to use multi-biomarkers to predict their incidence and prognosis which can better comprehend the pathophysiology of multiple interactions in sepsis and MODS after trauma. As dramatic increase in our understanding of this area, more advanced biomarkers may be found helping in the clinical diagnosis and therapeutics.

Abbreviations

Multiple organ dysfunction syndrome (MODS); Acute Phase Proteins (APPs); Single nucleotide polymorphism Acute phase protein (SNP); C-reactive protein (CRP); Procalcitonin (PCT); Lipopolysaccharide binding protein (LBP); Acute Respiratory Distress Sydrome (ARDS); Traumatic brain injury (TBI); Acute Kidney Injury (AKI);

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