Review Article

Prognostic value of circulating lymphocyte B and plasma immunoglobulin M on septic shock and sepsis: a systematic review and meta-analysis

Lin Tian, Jie Zhu, Jun Jin, Chakkwan Tong, Weixian Zeng, Sujun Deng, Shan Zou

Adult Intensive Care Unit, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Abstract: Objective: Normal B lymphocyte function and antibody secretion during inflammation can provide critical protection for the host. We aimed to synthesize existing evidence to explore whether circulating B cells and plasma immunoglobulin M (IgM) levels were associated with survival during sepsis. Methods: PubMed, Embase, ISI Web of Knowledge, Cochrane Central Register of Controlled Trials were systematically searched. Studies with data on circulating B cells and plasma IgM levels within the initial 24 hours after sepsis onset were selected. Results: A total of 11 studies were qualified for inclusion in this systematic review and meta-analysis with a total of 829 patients with sepsis and/or septic shock. Number of circulating B cells was similar between septic patients and health controls (SMD = -1.81, 95% CI: -4.15, 0.54; P = 0.13, I^2 = 99%), while it was significantly reduced in sepsis survivors versus sepsis non-survivors (SMD = -0.60, 95% CI: -0.87, -0.32; P < 0.0001, I^2 = 0%). Concentration of plasma IgM level was significantly decreased in septic patients as compared with healthy controls. Also, the plasma IgM level was significantly lower in sepsis survivors versus sepsis non-survivors. Conclusions: A poor prognostic survival outcome was observed for patients with decreased circulating B cells as well as IgM levels within the initial 24 h after sepsis onset.

Keywords: B cell, IgM, sepsis, survival

Introduction

Sepsis, as a series of pathological, physiological and biochemical abnormalities induced by infection, is a major problem in the field of critical medicine. Most patients died of multi-organ dysfunction in the end [1-3]. With the wide application of supportive technologies such as new antibiotics, ventilators and continuous renal replacement therapy, great improvement in the treatment of sepsis has been obtained. However, the mortality rate of sepsis is still high (25%-30%) and the mortality rate of septic shock is as high as 50% [4-7]. In 2016, the forty-fifth annual meeting of the American Society of Critical Care Medicine issued a new definition of Sepsis-3. The meeting defined sepsis as a fatal organ dysfunction caused by an imbalance in the host response to infection [8]. The diagnostic criteria were sequential organ failure assessment (SOFA) score (≥ 2), i.e. sepsis = infection + SOFA (≥ 2). Meantime, septic shock

belongs to a subtype of sepsis, and is redefined as circulatory failure and cellular metabolic abnormalities caused by infection [9]. The diagnostic criteria were that, on the basis of sepsis and adequate fluid resuscitation, the use of vasopressors could maintain mean arterial pressure above 65 mmHg, while at the same time blood lactate is more than 2 mmol/L [8, 9]. Therefore, sepsis is a fatal organ dysfunction caused by infection, accompanied by the induction, synthesis and release of a variety of cytokines and inflammatory mediators. The pathogenesis of sepsis is very complex. It is the result of the interaction of multiple factors from molecular level to organ level. It involves a series of problems such as infection, inflammation, immunity, coagulation and tissue damage. Finally, it is closely related to the pathophysiological changes of multiple systems and organs.

In recent years, although molecular pathogenesis based on targeted therapy has been exten-

sively studied. The survival rates of severe sepsis and septic shock have not improved significantly. Host cell-mediated immunity is essential for understanding the pathological process of sepsis and its complications. Studies have shown that innate immune cells such as neutrophils, macrophages, dendritic cells, T lymphocytes, regulatory T cells, natural killer T cells play an important role in maintaining the balance of the body's internal environment and regulating immune response during sepsis. Therefore, understanding the biological characteristics and pathophysiological functions of different cells may be helpful to understand the immunomodulatory mechanism of sepsis [10, 11].

Current evidence has indicated that the detection of peripheral blood lymphocyte subsets in patients with sepsis is closely related to the prognosis, and to a certain extent, it can significantly reflect the current immune status and prognosis of patients with sepsis [3, 4]. The function of lymphatic B cells and the associated antibodies play a protective key role in the process of inflammation. Immunoglobulin M (IgM) is also the earliest antibody in the first humoral immune response, and is the "pioneer team" of anti-infection. Detection of IgM in serum indicates a recent infection, which can be used for early diagnosis of infection. Recent studies have indicated that the apoptosis of spleen immunoreactive cells is associated with a decrease in the survival rate of septic patients. Of note is the observation that current evidences on circulating B cells and plasma IgM levels on sepsis prognosis are in debate [12, 13]. Thereby, the purpose of this systematic review and meta-analysis is to comprehensively study the relationship between circulating B cells and plasma IgM levels and sepsis survival rate on the basis of available evidence.

Methods

The methods of literature search, inclusion and exclusion criteria, outcome measures, and methods of statistical analysis were following the *Cochrane Handbook for Systematic Reviews of Interventions*, and defined in a protocol according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement* [14, 15]. Patient consent

and ethical approval and were not mandatory, as all data available were based on previously published studies.

Data sources and searches

The primary data sources of Pubmed, Embase, Web of science, EBSCO, and the Cochrane library were searched until September 2018. Only those with English abstracts were considered in order to confirm the quality of included studies. We combined the database-specific search terms of circulating B cells/plasma IgM and septic shock/sepsis respectively as well as truncated search terms utilizing the wildcard ("*") character for prospective and retrospective observational studies on the prognosis of severe sepsis or septic shock patients. Additionally, the "related articles" function was also used to broaden the search, and the reference lists of retrieved studies and relevant reviews, primary studies, and abstracts from meetings were also hand-searched until no further article was identified (the process was performed repeatedly). All enrolled studies were imported into the bibliographic citation management software of EndNote (Version X6, Thomson Corporation, Toronto, Canada). Authors of relevant abstracts were contacted to obtain any unpublished data (if available). When the results of a single study were reported in more than one publication, only the most recent and complete data were included.

Study selection

Prospective and retrospective observational studies on the predictive prognostic value of circulating B cells/plasma IgM on the sepsis or septic shock patients were selected. Studies with unclear comparator groups were excluded. All of the studies included in the meta-analysis met the following criteria:

(1) Patients have to be more than 18-year-old, have suspected or confirmed infection, as indicated by the blood culture. At least two of the systemic inflammation response syndrome criteria were met (heart rate > 90 beats/min, respiratory rate > 20 breaths/min, temperature > 38 or < 36°C, white blood count > 12,000 or < 4000 cells/mm^3). (2) Patients have a pulmonary artery wedge pressure/central venous pressure > 12 mmHg, should be maintained with norepinephrine. Mean arterial pressure
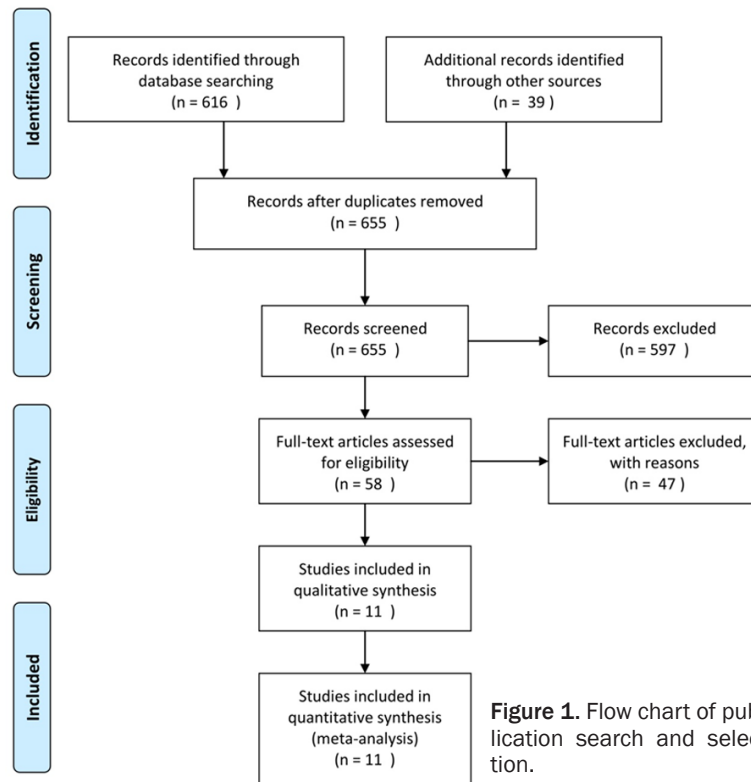
Figure 1. Flow chart of publication search and selection.

comes included changes in hemodynamic variables, the level of proinflammatory factors in the serum, myocardial injury markers, organ function variables, duration in the ICU and in hospital, as well as adverse events caused by drug treatment up to 28 days after enrolment.

Data extraction and synthesis

The literature was independently screened and cross-checked by two researchers. In case of disagreement, the literature was discussed and resolved and submitted to a third researcher for decision if necessary. Data were extracted and entered by one researcher and checked by another according to a pre-designed data extraction table.

greater than 65 mmHg, heart rate greater than 95/min after 6 h early goal-directed therapy. (3) Patients without acute left heart failure or acute myocardial infarction, cardiac function classification New York Heart Association (NYHA) grade III and above; without long-term use of beta-blockers, severe asthma, chronic obstructive pulmonary disease, grade II and above atrioventricular block, not pregnant women. (4) The number of circulating B cells and/or the level of plasma IgM were evaluated.

Methodology quality assessment and outcome measures

Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of cohort and case-control studies. The scale consists of three parts: population selection, comparability between groups, and results measurement. It has 8 items and a total of 9 points. A score of more than 7 points should be classified as high quality research [16]. Our main outcome measures were the number of circulating B cells and the concentration of plasma IgM in both survivors and non-survivors of sepsis. Also, the number of circulating B cells between sepsis patients and non septic patients was evaluated. Other secondary out-

Meta-analysis was conducted by Review Manager 5.3 software (Cochrane collaboration, Copenhagen, Denmark) [17]. Standard Mean difference (SMD) was used as a summary statistics for the pooled outcomes. Heterogeneity among the results was analyzed by Q test, the test level was alpha = 0.1, and I^2 was used to measure the heterogeneity. If there were no statistical and clinical heterogeneity between the results of each study (P > 0.1, I^2 < 50%), the fixed-effect model was used for meta-analysis; if there were moderate or higher statistical heterogeneity among the results but no clinical heterogeneity (P < 0.1, I^2 < 50%), subgroup analysis or sensitivity analysis could be performed, if there were no obvious heterogeneity sources. A random effect model was used for Meta analysis [18]. Sensitivity analysis was performed by eliminating the impact of individual studies on the overall analysis results.

Results

Literature retrievals

Figure 1, a total of 655 papers were found, 597 were excluded from duplicate and unrelated papers, 58 were preliminarily screened, 47 were excluded from retrospective case analysis

Table 1. Characteristics of the included studies

Authors	Study purposes	Study design/Enrolled patients	Interventions	Main Outcomes
Wang et al[19]/China (2017)	The predicting value of peripheral blood CD20+CD24hiCD38hi Bregs on the prognosis of elderly patients with sepsis	• Prospective study • 58 Septic patients aged > 65 years old, compliance with diagnostic criteria for Sepsis-3, admitted to emergency and emergency ICU	• According to 28-day outcome, patients were divided into death group and survival group. • Clinic data and Bregs were compared, Bregs level and other indicators was analyzed.	• Bregs was significantly decreased at 1, 3 and 7 days in death group. • Peripheral blood Bregs could predict the clinical outcome of elderly patients with sepsis.
Suzuki et al[20]/Japan (2016)	Changes in humoral immunity caused by defective B cell function during severe sepsis	• Prospective study • 33 severe sepsis patients and 44 healthy subjects	• Participants were divided into two age groups: adults (18-64 years) and elderly (65 years). • B-cell subtypes, serum IgM, and CpG-B ODN-induced IgM concentration were measured.	• CD21-/low exhausted B cells in acute sepsis patients was higher than that observed in healthy donors. • CD21-/low exhausted B cells may be a critical immunological change in sepsis together with IgM insufficient.
Bermejo-Martín et al[21]/Spain (2014)	Endogenous IgM on the prognosis of patients with severe sepsis	• Prospective multicentre cohort study • 172 adult patients admitted to the ICU with severe sepsis/septic shock	• Patients were classified based on deciles of IgM concentrations. • Categorical variables were created and tested for their association with survival during hospitalization in the ICU.	• 35 mg/dL for IgM was associated with shorter survival times. • Combined presence of low levels of the endogenous IgG1, IgM and IgA in plasma is associated with reduced survival in patients with severe sepsis/septic shock.
Park et al[22]/South Korea (2014)	Leukocyte subpopulation on the discrimination of severity and outcome prediction in sepsis	• Retrospective study • 181 samples with sepsis who were admitted to the surgical ICU and 60 normal healthy volunteers	• The enrolled patients were classified into three groups: uncomplicated sepsis, severe sepsis, and septic shock. • Proportions and absolute numbers of each cell type in the four groups were obtained using the CytoDiff FCM system and compared.	• Only B lymphocytes showed independent ability to discriminate patients with complicated sepsis from uncomplicated sepsis. • B lymphocytes possessed a significant adverse prognostic impact on overall survival.
Giamarellos-Bourboulis et al[23]/Greece (2013)	Kinetics of IgM during the different stages of sepsis	• Prospective multicentre cohort study • 332 critically ill were enrolled	• Sampling on worsen was done for 83 patients, stimulation of IgM production was performed for 55 patients. • IgM was monitored daily for 30 patients with septic shock for 7 days. PBMCs were isolated from 55 patients and stimulated for IgM production.	• Serum IgM was decreased in septic shock compared to patients with SIRS and patients with severe sepsis. • Specific changes of circulating IgM occur when sepsis progress into septic shock.

B cells and plasma IgM on the prognosis in sepsis

Monserrat et al[24]/Spain (2013)	Abnormal distribution and activation of circulating B lymphocytes in patients with septic shock	• Prospective study • 52 septic shock patients were included. 36 healthy volunteers	• Patients and volunteers were matched. • B-cell phenotypes were assessed by quantitative flow cytometry upon admission to the ICU and 3, 7, 14 and 28 d later.	• Different patterns of abnormalities in circulating B lymphocytes were presented on the survival outcomes. • A reduction in circulating B cells persisted during 28 d of ICU follow-up.
Tamayo et al[25]/Spain (2012)	Relationship between endogenously produced immunoglobulins and the clinical outcome in septic shock	• Retrospective study • 42 patients with septic shock and in 36 patients with SIRS	• Levels of immunoglobulins were measured in plasma in patients of septic shock and SIRS. • Association of immunoglobulin levels with severity and outcome was evaluated.	• Levels of IgM was inversely associated to the death at 28 d. • Immunoglobulins isotypes and subclasses seem to play a beneficial role in septic shock.
Venet et al[26]/France (2010)	Alteration develops of circulating lymphocyte number after diagnosis of shock	• Prospective study • 21 septic shock patients with no comorbidities	• Serial blood samples were obtained from 21 patients at the time of diagnosis and every 6 h during the first 48 h afterward. • FCM phenotyping of circulating leukocyte subpopulations and qRT-PCR of T-bet, GATA-3, FOXP3, and RORγ mRNA were performed.	• The numbers of every lymphocyte subpopulations including B cells were diminished. • Sepsis-induced loss of lymphocytes involving every lymphocyte subsets, which will remain stable during the first 48 h afterward.
Hawkins et al[27]/Australia (2006)	Long-term consequences of sepsis for immune function	• Retrospective study • 21 patients with bacteraemia	• 21 patients with bacteraemia were evaluated. • Full blood count and lymphocyte subsets were measured.	• In a cohort of patients with Gram(+) and Gram(-) bacterae-mia, persistent B- and T-cell lymphopenia were observed. • A state of longer lasting immunodeficiency may be induced by sepsis.
Ditschkowski et al[28]/Germany (1999)	NK cells and HLA-DR molecules on B cells in the development of severe sepsis after injury	• Prospective study • 46 severely injured (Injury Severity Score >16) patients	• 13 patients of severe sepsis was compared with 33 patients without sepsis. • HLA-DR expression on B cells and counts of B and NK cells measured by FCM.	• HLA-DR expression on circulating B cells was significantly reduced in severe sepsis patients. • Reduced counts of HLA-DR molecules on B lymphocytes is associated severe sepsis development.
Strutz et al[29]/Germany (1999)	Prognostic value of determining anti-EndoCab IgG and IgM in medical patients with sepsis syndrome	• Retrospective study • 29 patients with sepsis syndrome without septic shock and 21 ICU patients without infections	• 29 patients were studied and furtherly divided into survivor and non-survivor groups. • Blood samples were obtained and sepsis scores were determined daily.	• Significantly lower initial EndoCab IgM in sepsis patients than controls. • Septic patients with decreased levels of anti-EndoCab may have an increased mortality risk.

Abbreviations: Breg, regulatory B cell; ICU, intensive care unit; IgM, immunoglobulin M; ODN, oligodeoxynucleotide; PBMC, peripheral blood mononuclear cells; SIRS, systemic inflammatory response syndrome; qRT-PCR, quantitative real-time polymerase chain reaction; FCM, flow cytometry; NK, natural killer; HLA-DR, human leukocyte antigen DR; EndoCab, endotoxin core antibodies.

and non-contrast group after reading the title and abstract, and incomplete data, other interventions and low quality were excluded after reading the full text. Finally, a total of 11 studies were qualified for inclusion in this systematic review and meta-analysis with a total of 829 patients with sepsis and/or septic shock [19-29].

Characteristics of the included studies

Table 1 listed the baseline clinicopathological characteristics of the included studies of circulating B cells and plasma IgM level in sepsis and septic shock. The 11 studies were published between 1999 and 2017, and sample sizes ranged from 21 to 181. Authors, country, the year of publication, study purposes and designs, enrolled patients and healthy controls, interventions of research measures and main outcomes were extracted. The numbers of peripheral circulating B cells were investigated in 7 studies [19, 20, 22, 24, 26-28]. Whereas plasma IgM level was measured in 4 studies [21, 23, 25, 29]. Meantime, 7 were prospective cohort studies [19-21, 23, 24, 26, 28] while the other rest [22, 25, 27, 29] were retrospective researches. Prospective multicentre cohort studies were performed by Bermejo-Martín et al [21] from Spain and Giamarellos-Bourboulis et al [23] from Greece. The NOS scale was employed to assess the quality of the included studies, and all the 11 studies were moderate to high quality.

Specifically, Wang et al investigated peripheral blood $CD20^+CD24^{hi}CD38^{hi}$ regulatory B cells in elderly patients > 65 years old [19]. Changes of $CD21^{-/low}$ exhausted B cells in acute sepsis patients were observed in Suzuki et al's study [20]. Endogenous IgG1, IgM and IgA in plasma on the prognosis of patients with severe sepsis was studied by Bermejo-Martín et al [21]. Giamarellos-Bourboulis et al highlighted the kinetics of IgM during the different stages of sepsis [23]. HLA-DR molecule expression on B cells and the initial endotoxin core antibodies of IgM were analyzed respectively [28, 29].

Pooled outcomes

Figure 2A, the number of circulating B cells was similar between septic patients and controls (SMD = -1.81, 95% CI: -4.15, 0.54; P = 0.13, I^2 = 99%), while it was significantly reduced in sepsis survivors versus sepsis non-survivors (SMD = -0.60, 95% CI: -0.87, -0.32; P < 0.0001, I^2 = 0%) (**Figure 2B**).
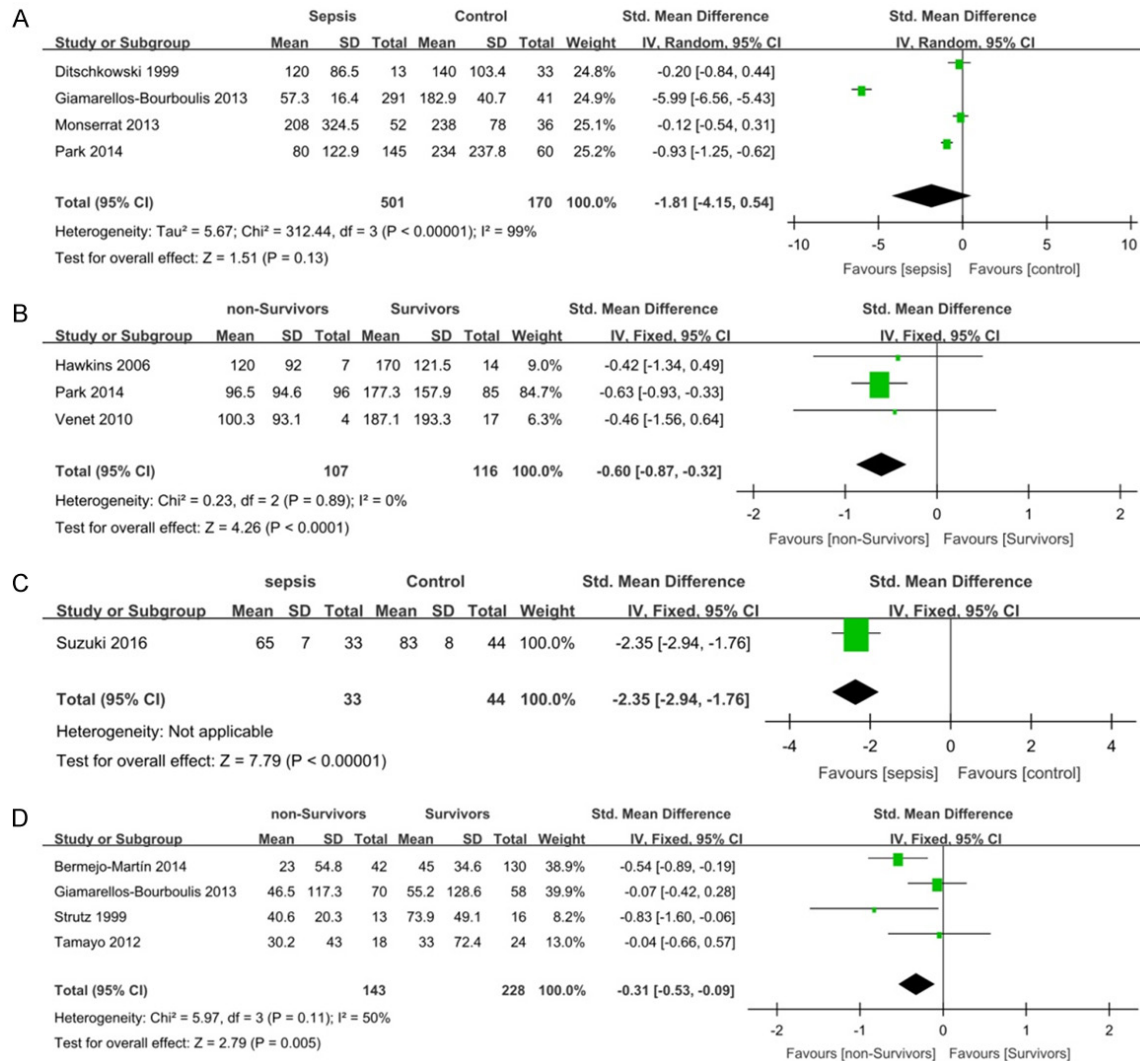
Figure 2C, similarly, concentration of plasma IgM level was significantly decreased in septic patients (SMD = -2.35, 95% CI: -2.94, -1.76; P < 0.00001, I^2 = 0%) as compared with healthy controls. Also, the plasma IgM level was significantly lower in sepsis survivors versus sepsis non-survivors (SMD = -0.31, 95% CI: -0.53, -0.09; P = 0.005, I^2 = 50%), **Figure 2D**.

Discussions

Sepsis is a systemic inflammatory reaction and host autoimmune injury caused by various microorganisms and immune substances. It is a common complication after severe trauma, injury and major surgery, and is the main cause of death in critically ill patients. The main pathophysiological mechanism of sepsis is the loss of the host's ability to destroy invasive pathogens due to impaired immune function, which increases the susceptibility to secondary infections. Basic and clinical studies over the past decade have shown that sepsis not only causes severe infections, but also impairs adaptive immune system disorders and the body's antibacterial capacity. More and more studies have shown that immune dysfunction plays a key role in the pathogenesis of organ failure caused by sepsis [30-32]. The present systematic review and meta-analysis implied that the number of circulating B cells in non-septic survivors decreased significantly within 24 hours prior to sepsis compared with septic survivors. Furthermore, based on published results on the function of IgM plasma levels in the prognosis of sepsis, significant heterogeneities were existed. However, in our meta-analysis, we found a significant reduction in IgM plasma levels in non-septic survivors during the first 24 hours. This supports the hypothesis that circulating B cells provide important protective mediators in the early stages of sepsis by producing IgM.

B cells function in the initial stage of sepsis has been clearly described in the experimental study. However, their clinical relevance has not been fully studied. It is well known that B lymphocyte activation can be divided into thymus-dependent antigen activation and thymus-independent antigen activation. Thymus-dependent

Figure 2. Forest plots depicting the pooled outcomes of (A) Numbers of circulating B cells in septic patients and controls, (B) Numbers of circulating B cells in sepsis survivors vs. sepsis non-survivors, (C) Concentration of plasma IgM levels in septic patients and controls, and (D) Concentration of plasma IgM levels in sepsis survivors vs. sepsis non-survivors

antigens are antigens that require antigen presenting cells (APC) and helper T (Th) cells to activate B cells to elicit immune responses, including soluble proteins or intact cells, viruses, parasites, etc. Thymus independent antigen is a class of antigens which can activate B cells directly without the action of APC cells and Th cells. It mainly includes capsular polysaccharides, lipopolysaccharides and polymeric flagellin (polymer after bacterial flagella lysis). One of the iconic functions of B cells is the production of antibodies. Usually, specific antibodies are produced by B cells in adaptive immune responses after clonal amplification, including complex interactions between macrophages,

dendritic cells, T cells and B cells. However, in the early stages of sepsis, B cells may be activated by stimulation of the invading pathogen itself, leading to the first immune response of innate B cells. In the present review, in sepsis survivors, the number of circulating B cells increased significantly during the first 24 hours of sepsis compared with non-sepsis survivors, which may have protective effects on circulating B cells. Patients with sepsis had fewer circulations of B cells than those in the control group 24 hours after the onset of sepsis.

In addition, IgM accounted for 5%-10% of total serum immunoglobulin, and the serum concen-

tration was about 1 mg/ml. The monomeric IgM is expressed on the cell surface by membrane-bound (mIgM), forming B cell antigen receptor (BCR). IgM is also the earliest antibody in the first humoral immune response, is the body's anti-infection "front line"; serum detection of IgM suggests a recent infection, can be used for early diagnosis of infection. IgM on membrane surface is the main component of B cell antigen receptor. Activation of innate-like B cells leads to the production and release of natural antibody IgM, which is important for controlling gram-negative bacteremia. Thus, the concentrations of circulating B cells are paralleled to plasma IgM, which is observed in the included studies that the reduced B cells are accompanied by IgM decrease.

Sepsis is thought to consist of two stages: the proinflammatory stage and the anti-inflammatory phase. Generally, the pro-inflammatory phase is predominant, in which the innate immune system releases cytokines to mobilize the host's ability to resist infection and recruits members of the adaptive immune system to produce a strong immune response. The anti-inflammatory stage, called compensatory anti-inflammatory response syndrome, is often defined as the body's inability to respond to certain antigens or infectious attacks. Although these stages are considered to be pathological processes at different stages, most experimental therapies are primarily targeted at the proinflammatory stage. These initial treatments are based solely on the premise that when stimulated by sepsis or infections, high concentrations of pro-inflammatory agents can cause significant organ damage in experiments or in clinical settings, leading to critical illness. However, treatment focused on the proinflammatory phase does not specifically address sepsis-induced immunosuppressive effects. Currently, in contrast to conventional therapies for inflammatory response, the use of cytokines and co-inhibitory molecule antagonists to improve the immune response of critically ill patients has become a new treatment for sepsis.

Current studies have confirmed that pathogens and trauma can activate systemic inflammatory responses leading to metabolic and physiological responses to sepsis, but the underlying mechanisms of immunity and inflammation need to be further clarified. It is generally accepted that systemic inflammatory response syndrome can cause extensive activation and dysfunction of innate immune system. The innate immune system includes humoral and cellular immunity. It is generally acknowledged that microorganisms cause innate immune system systemic responses, mostly mediated by the release of secretory proteins or cytokines. Host innate immune activation, however, produces internal risk signals not only after microbial invasion, but also during cell damage, tissue ischemia, hypoxia and necrosis. Inherent immunity is fully stimulated, and host reaction can lead to inflammatory response syndrome, shock and even multiple organ failure. Generally speaking, in the early stage of sepsis, the body releases a large number of pro-inflammatory factors, including TNF-alpha, TNF-gamma, IL-33 and IL-2. However, as the course of the disease prolongs, immunosuppressive reactions occur, including macrophage inactivation, decreased antigen presentation, and inhibition of lymphocyte proliferation, resulting in the release of a large number of anti-inflammatory cytokines, such as IL-10, IL-13 and IL-27. The present systematic review indicated that both B cells and its associated antibody production of IgM are important predictive prognostic factors in sepsis.

It is important to note that heterogeneity in the literature may cause some unavoidable bias. The problems affecting the stability of data include insufficient data, selection bias and confounding factors. Other constraints may be due to loss of information about the extent of fluid resuscitation at the time point of blood sampling. It is also important to note that sepsis may occur in different immunological patterns, such as significant changes in circulating B cells or IgM plasma levels, depending on the underlying lesion. However, due to the lack of data, we could not solve this hypothesis in subgroup analysis.

In conclusion, the results of this systematic review suggested that the reduction of circulating B cells and IgM plasma levels is negatively correlated with sepsis survival. However, further experimental and clinical studies are needed to further clarify on the biological mechanisms of both B cells and its associated IgM involved in sepsis initiation. Large future studies are still needed to further validate the reliability of circulating B cell and IgM plasma lev-

els as prognostic factors during the course of sepsis.

Disclosure of conflict of interest

None.

Abbreviations

Breg, regulatory B cell; ICU, intensive care unit; IgM, immunoglobulin M; ODN, oligodeoxynucleotide; PBMC, peripheral blood mononuclear cells; SIRS, systemic inflammatory response syndrome; qRT-PCR, quantitative real-time polymerase chain reaction; FCM, flow cytometry; NK, natural killer; HLA-DR, human leukocyte antigen DR; EndoCab, endotoxin core antibodies.

Address correspondence to: Lin Tian, Adult Intensive Care Unit, The University of Hong Kong-Shenzhen Hospital, 1# Haiyuan 1st Road, Futian District, Shenzhen 518053, China. Tel: 0755-86913333-3972; E-mail: tianlin118@sohu.com

References

[1] McKenna H, van der Horst GTJ, Reiss I, Martin D. Clinical chronobiology: a timely consideration in critical care medicine. Crit Care 2018; 22: 124.

[2] Graber ML, Patel M, Claypool S. Sepsis as a model for improving diagnosis. Diagnosis (Berl) 2018; 5: 3-10.

[3] Venet F, Rimmelé T, Monneret G. Management of sepsis-induced immunosuppression. Crit Care Clin 2018; 34: 97-106.

[4] Zaccone V, Tosoni A, Passaro G, Vallone CV, Impagnatiello M, Li Puma DD, De Cosmo S, Landolfi R, Mirijello A; Internal Medicine Sepsis Study Group. Sepsis in internal medicine wards: current knowledge, uncertainties and new approaches for management optimization. Ann Med 2017; 49: 582-592.

[5] Taeb AM, Hooper MH, Marik PE. Sepsis: current definition, pathophysiology, diagnosis, and management. Nutr Clin Pract 2017; 32: 296-308.

[6] Gül F, Arslantaş MK, Cinel İ, Kumar A. Changing definitions of sepsis. Turk J Anaesthesiol Reanim 2017; 45: 129-138.

[7] Perner A, Rhodes A, Venkatesh B, Angus DC, Martin-Loeches I, Preiser JC, Vincent JL, Marshall J, Reinhart K, Joannidis M, Opal SM. Sepsis: frontiers in supportive care, organisation and research. Intensive Care Med 2017; 43: 496-508.

[8] Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M; Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 775-787.

[9] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 801-810.

[10] Rodriguez-Rosales YA, Kox M, van Rijssen E, van Cranenbroek B, van Welie M, Pickkers P, Joosten I, Koenen H. Long-term effects of experimental human endotoxemia on immune cell function: similarities and differences with sepsis. Shock 2019; 51: 678-689.

[11] Torres LK, Choi AMK. Determination of early immune function in sepsis and its influence on organ dysfunction. Is a more pragmatic outcome on the horizon? Am J Respir Crit Care Med 2018; 198: 298-300.

[12] Rauch PJ, Chudnovskiy A, Robbins CS, Weber GF, Etzrodt M, Hilgendorf I, Tiglao E, Figueiredo JL, Iwamoto Y, Theurl I, Gorbatov R, Waring MT, Chicoine AT, Mouded M, Pittet MJ, Nahrendorf M, Weissleder R, Swirski FK. Innate response activator B cells protect against microbial sepsis. Science 2012; 335: 597-601.

[13] Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD 2nd, Kreisel D, Krupnick AS, Srivastava A, Swanson PE, Green JM, Hotchkiss RS. Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA 2011; 306: 2594-2605.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-269.

[15] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. March 2011. Cochrane Collaboration, 2011. Available at: http://www.cochrane-handbook.org. Accessed March 29, 2019.

[16] Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Applied Engineering in Agriculture 2014; 18: 727-734.

[17] Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

[18] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[19] Wang C, Tang L, Xu H, Zhang X, Bai J. Evaluation value of the levels of peripheral blood CD20+ CD24hi CD38hi regulatory B cells on

the prognosis of elderly patients with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2017; 29: 673-678.

[20] Suzuki K, Inoue S, Kametani Y, Komori Y, Chiba S, Sato T, Inokuchi S, Ogura S. Reduced immunocompetent B cells and increased secondary infection in elderly patients with severe sepsis. Shock 2016; 46: 270-278.

[21] Bermejo-Martín JF, Rodriguez-Fernandez A, Herrán-Monge R, Andaluz-Ojeda D, Muriel-Bombín A, Merino P, García-García MM, Citores R, Gandía F, Almansa R, Blanco J; GRECIA Group (Grupo de Estudios y Análisis en Cuidados Intensivos). Immunoglobulins IgG1, IgM and IgA: a synergistic team influencing survival in sepsis. J Intern Med 2014; 276: 404-412.

[22] Park SH, Park BG, Park CJ, Kim S, Kim DH, Jang S, Hong SK, Chi HS. An extended leukocyte differential count (16 types of circulating leukocytes) using the CytoDiff flow cytometric system can provide information for the discrimination of sepsis severity and prediction of outcome in sepsis patients. Cytometry B Clin Cytom 2014; 86: 244-256.

[23] Giamarellos-Bourboulis EJ, Apostolidou E, Lada M, Perdios I, Gatselis NK, Tsangaris I, Georgitsi M, Bristianou M, Kanni T, Sereti K, Kyprianou MA, Kotanidou A, Armaganidis A; Hellenic Sepsis Study Group. Kinetics of circulating immunoglobulin M in sepsis: relationship with final outcome. Crit Care 2013; 17: R247.

[24] Monserrat J, de Pablo R, Diaz-Martín D, Rodríguez-Zapata M, de la Hera A, Prieto A, Alvarez-Mon M. Early alterations of B cells in patients with septic shock. Crit Care 2013; 17: R105.

[25] Tamayo E, Fernández A, Almansa R, Carrasco E, Goncalves L, Heredia M, Andaluz-Ojeda D, March G, Rico L, Gómez-Herreras JI, de Lejarazu RO, Bermejo-Martin JF. Beneficial role of endogenous immunoglobulin subclasses and isotypes in septic shock. J Crit Care 2012; 27: 616-622.

[26] Venet F, Davin F, Guignant C, Larue A, Cazalis MA, Darbon R, Allombert C, Mougin B, Malcus C, Poitevin-Later F, Lepape A, Monneret G. Early assessment of leukocyte alterations at diagnosis of septic shock. Shock 2010; 34: 358-363.

[27] Hawkins CA, Collignon P, Adams DN, Bowden FJ, Cook MC. Profound lymphopenia and bacteraemia. Intern Med J 2006; 36: 385-388.

[28] Ditschkowski M, Kreuzfelder E, Majetschak M, Obertacke U, Schade UF, GrosseWilde H. Reduced B cell HLA-DR expression and natural killer cell counts in patients prone to sepsis after injury. Eur J Surg 1999; 165: 1129-1133.

[29] Strutz F, Heller G, Krasemann K, Krone B, Müller GA. Relationship of antibodies to endotoxin core to mortality in medical patients with sepsis syndrome. Intensive Care Med 1999; 25: 435-444.

[30] Golucci APBS, Marson FAL, Ribeiro AF, Nogueira RJN. Lipid profile associated with the systemic inflammatory response syndrome and sepsis in critically ill patients. Nutrition 2018; 55-56: 7-14.

[31] Zheng G, Huang R, Qiu G, Ge M, Wang J, Shu Q, Xu J. Mesenchymal stromal cell-derived extracellular vesicles: regenerative and immunomodulatory effects and potential applications in sepsis. Cell Tissue Res 2018; 374: 1-15.

[32] Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: barriers and potential solutions. Crit Care 2018; 22: 232.