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Interplay between sepsis and chronic health

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Abstract

Severe sepsis is associated with high short-term mortality. Several studies suggest that severe sepsis also worsens health status and increases disability among survivors. As the incidence of severe sepsis increases, and advances in critical care reduce the short-term mortality, the number of individuals who are at risk for poor long-term outcomes will increase. Recent studies suggest that the relationship between sepsis and chronic health may be bidirectional, however the mechanisms underlying this relationship remain poorly understood. Here we review the epidemiologic studies examining the interplay between sepsis and chronic health and propose a conceptual model, which has implications for preclinical and human study design.

Challenges of sepsis and chronic health

Sepsis, or systemic inflammatory response to infection, is a leading cause of hospitalization, disability, and death worldwide [1–3]. Severe sepsis occurs when acute organ dysfunction accompanies sepsis. Sepsis has long been observed to occur more frequently in individuals with poor chronic health (see Glossary), and recent work suggests that a single episode of sepsis worsens chronic health [4]. Thus, there may be a bidirectional relationship between sepsis and chronic health. Understanding the mechanisms of this relationship is challenging for several reasons. First, developing animal models where sepsis is superimposed on chronic disease is not trivial. Second, it is difficult to draw inferences of causality in human studies, and there are a wide array of potential factors involved in both the host health status prior to the episode of sepsis and the subsequent immune response to eradicate the pathogen. Nonetheless, the interplay between sepsis and chronic health is a key problem with significant public health implications. As the incidence of sepsis increases and its short-term mortality decreases, there will be a rapid rise in the number of individuals living with

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potentially significant post-sepsis sequelae. Yet the incidence and mechanisms underlying these sequelae remain poorly understood [5].

We focus this review on our current understanding from epidemiologic studies of the interplay between sepsis and chronic health and use the existing evidence to probe potential conceptual models of this interplay. The conceptual models have implications for the design of future pre-clinical and human studies and to test interventions to prevent or mitigate long-term consequences of sepsis.

Health status before sepsis

Older individuals and those with poor health status, as evidenced by higher burden of clinically apparent and subclinical diseases, are at higher risk for developing an infection. For example, the risk of pneumonia hospitalization, the most common infectious cause of hospitalization in developed countries and the most common cause of severe sepsis, was 5-fold higher in individuals between 65–70 years of age compared to those less than 50 years [6]. Most chronic health conditions, including diabetes, heart failure, cardiovascular disease, reduced lung function due to obstructive or restrictive lung disease, cognitive impairments, and chronic kidney disease increase the risk of pneumonia hospitalization. Of these conditions, severe reduction in lung function and diabetes are most important. For example, compared to individuals with normal lung function, those with severe reduction in lung function had 6.6-fold higher risk of pneumonia hospitalization [6].

In addition to clinically apparent diseases, subclinical changes in chronic health also increase the risk of pneumonia hospitalization. For example, small differences in circulating interleukin (IL)-6, tumor necrosis factor (TNF), and C-reactive protein (CRP) levels measured during baseline health states are associated with the subsequent risk of pneumonia hospitalization [7, 8]. Of note, the scale of these differences during baseline health is narrower than the scale of change during acute events. For example, 2–3 pg/ml changes in circulating IL-6 have large effects on subsequent risk of pneumonia. Yet, log-fold changes in IL-6 levels occur during an acute episode of sepsis. Similarly, small changes in cognitive function, such as a 5-point annual reduction in the Teng's mini-mental status exam score (range 0–100), may increase the risk of pneumonia by 11% [4]. The associations between small subclinical changes in chronic health and increased risk of infection are independent of clinically apparent measures. Thus, patients hospitalized with sepsis may appear to have the same burden of clinically apparent chronic diseases, yet their pre-infection health status may be quite different due to differences in subclinical, and thus unmeasured, disease burden.

Health status after sepsis

Severe sepsis worsens cognitive and physical impairments, and increases burden of chronic diseases, such as chronic kidney disease and cardiovascular disease. These changes may persist for several years after the episode of severe sepsis [9–13]. While early studies often examined outcomes without accounting for poor pre-infection health status, recent studies have confirmed that the higher burden of chronic diseases after sepsis persists even after accounting for poor pre-infection health status [4, 9, 10]. However, the magnitude of effect

of severe sepsis on long-term outcomes is lower than previously estimated. Thus, a bidirectional relationship may exist between chronic diseases and sepsis, where poor chronic health may increase risk of infection, and once infection occurs, it may accelerate underlying chronic diseases.

The long-term sequelae after sepsis could follow different trajectories (Figure 1). For instance, these sequelae could occur due to ‘acceleration of pre-existing health status’ or ‘*de novo* appearance of a new health condition’ either during the acute phase of sepsis and persist during recovery or *de novo* appearance of a new health condition during recovery. The trajectories of these conditions during recovery may vary and follow a rapidly progressive, slow deteriorating, or relapsing course. Although some chronic diseases may be recognized for the first time after sepsis, subclinical changes may be underway prior to the occurrence of sepsis. For example, sepsis may accelerate clinical presentation of dementia, but pathophysiologic changes of dementia may have been underway for several decades preceding the acute episode of sepsis.

Factors affecting long-term sequelae

The effects of sepsis on chronic health may be due to factors prior to the hospitalization for sepsis, and during the acute and recovery or post-acute phases (Table 1). Factors that play a role prior to sepsis include host genetic factors, frailty, and chronic diseases. The factors relating to the acute phase may be related to non-infectious precipitating events (e.g. trauma or major surgery, which acutely increase the risk of infection), directly related to sepsis itself (e.g. release of inflammatory cytokines or epigenetic modifications), and other acute factors (e.g. accompanying organ dysfunction, immobilization during hospitalization, or discontinuation of medications due to transitions in care).

The factors that affect long-term outcomes within the different phases may occur within multiple domains, including biological, physiologic, behavioral, and social domains, and these factors may interact among each other (Table 1). The relative contribution of a factor within each domain and across different phases may vary for each health condition.

The effect of sepsis severity for different sequelae has been challenging to estimate in epidemiologic studies due to competing risk of death. Death competes with non-fatal events and it is difficult to estimate the likelihood of an event when sepsis patients die without experiencing the outcome of interest. For example, the risk of dementia was similar among those with and without severe sepsis [4]. However, the risk of dementia among severe sepsis patients may be underestimated because their short-term mortality was high.

Biological and physiologic factors

Several biological and physiologic factors are likely to play a role in the interplay between sepsis and chronic health. Frailty, burden of chronic diseases, disability, and immune dysfunction may play an important role in each phase of sepsis. The bidirectional relationship observed for clinical factors may also occur in the biological and physiologic domains. For instance, small perturbations in circulating IL-6 levels may increase the risk of sepsis, circulating levels of IL-6 may be log-fold higher during an episode of sepsis[14],

with higher levels worsening acute organ function, and IL-6 levels may fail to resolve and worsen long-term cardiovascular outcomes [15].

Frailty is a syndrome of decreased reserve and resistance to stressors, including sepsis, and results from cumulative declines across multiple physiologic systems [16]. It is often defined as a clinical syndrome in which three or more of the following criteria are present, including unintentional weight loss, self-reported exhaustion, weakness (as evidenced by reduced grip strength), slow walking speed, and low physical activity [16–22]. Frailty and disability may increase the risk of sepsis, and once sepsis occurs, they may worsen during recovery. Thus, sepsis may accelerate biological and physiologic mechanisms that worsen chronic health.

The host response to sepsis, while important to eradicate the infection, may lead to collateral tissue damage to cause acute organ dysfunction and worsen chronic health. Recent work suggests that the relationship between biological mechanisms to preserve organ function during sepsis and its effects on chronic health is complex [23]. First, a certain degree of tissue damage may be unavoidable during the host response to infection. The capacity of the host to prevent damage to the tissues due to the immune response to infection is called tolerance [23]. Tolerance may vary in different tissues based on their propensity to incur damage and ability to repair. Proteins may have opposite effects on the ability of the host to resist the infection and on tolerance. For instance, the Asp299Gly polymorphism within the toll-like receptor-4 (TLR4) protein reduces circulating inflammatory markers, and may increase susceptibility to infection, yet reduce downstream consequences of atherosclerosis [24, 25].

Social and environmental factors

Social and environmental factors influence both the development of severe sepsis and its outcomes. Many of the organisms that trigger sepsis are not part of the patients' baseline microbiota, and thus exposure to them must, by definition, be from 'the environment' and influenced by the rate at which that environment presents potential pathogens. More interestingly, there appear to be social gradients in the risk of incurring severe sepsis with respect to at least race and marital status [26, 27]. The relative importance of various microdynamics for these causes is not well known and may involve a combination of differences in exposure to infection and health behaviors. In this vein, sepsis researchers can interact with ongoing research on the physiological consequences of social networks, particularly with regard to inflammation [28].

At the same time, the consequences of severe sepsis can be understood from the patient perspective with regard to social and physical environment. Here it is useful to follow the approach outlined by the World Health Organization (WHO) and draw a distinction between body functions and structure, as related to activities and participation. The former can be understood as the capabilities of a body in a standardized environment; the latter refers to what the body can do '*in vivo*' in the world. Thus the extent to which a limitation in leg movement results in restrictions in mobility hinges not only on the leg itself, but the physical demands of the built environment in which that leg (and body) must walk. Two areas of focus within the broad 'social and environmental context' are the specific health system and family environments. They provide critical access to resources to both promote physical

restoration of function, and to the equipment and/or learning necessary to adapt to remaining differences in physical function during and after recovery. This is an emerging area of research in which promising pilot work has been done [29].

Understanding such multi-level interactions for sepsis is assuredly complex, but is critical. This approach builds on general conceptual work done years ago. Wilson and Cleary [30], and, relatedly, Verbrugge and Jette developed an approach that emphasized the distinct objects of study at each level of analysis [31]. They argued for the importance of explicitly studying why changes at one level (e.g. in a specific organ function) may or may not lead to changes in another level (e.g. mobility impairment or quality of life). Rather than assume away such multi-level models, they and others have argued for explicitly studying them and the effect modifiers that operate between levels and induce contingencies [32].

Conceptual model

Based on the findings discussed above and prior studies [33], we propose a conceptual model where the relationship between sepsis and chronic health is bidirectional. Poor chronic health, as evidenced by higher burden of clinically apparent and subclinical chronic diseases, increases risk of sepsis. Once sepsis occurs, survivors incur long-term sequelae due to further worsening of health status. Various biological, behavioral, and social factors before, during, and after sepsis are important determinants of long-term sequelae.

Sepsis is a heterogeneous condition. The effects of sepsis on chronic health may be due to factors that are generic to several conditions that share pathophysiologic mechanisms with sepsis and occur in older, frail adults (Table 1). For example, high pre-illness burden of frailty, reduced physical activity, and interruption of medications may occur in other conditions that require hospitalization, such as hip fracture and stroke, as well as in sepsis. Sepsis and trauma may share common biological mechanisms due to activation of the immune response or failure to resolve it [34, 35].

This conceptual model underscores the importance of considering multifaceted strategies to reduce long-term sequelae, and borrowing from strategies that have proven to be successful in other conditions. For instance, interventions targeted to patients and their caregivers to take an active role with support from a ‘transition coach’ to improve transition of care from hospital to the community setting may reduce re-hospitalization in a broad range of conditions[36], including sepsis.

Implications for study design

The conceptual model outlined above has important implications for designing pre-clinical and human studies to understand mechanisms and test therapeutic interventions. Pre-clinical studies are often conducted in young mice. This approach may ignore key biological mechanisms that play a role in humans, such as frailty and the presence of subclinical or clinically apparent chronic diseases prior to sepsis. Older mice (18–24 months) or animal models of chronic diseases, such as the high fat-fed apoE mouse with atherosclerosis, may be more useful [37].

Observational studies are underway to understand the interplay between severe sepsis and chronic health conditions. These studies have sought to determine the relative contribution of pre-infection factors, and factors during the acute and recovery phases. The long-term risk of a health condition could be compared either in a matched cohort analysis where severe sepsis patients could be matched to those that did not develop severe sepsis but had the same propensity to develop severe sepsis. For example, the incidence of dementia in older adults after severe sepsis in unselected US population is 23 cases/1,000 person-years [38]. Once pneumonia occurs, these patients have a higher risk of dementia (92 cases/1,000 person-years), but propensity-matched pneumonia patients had an intermediate risk of dementia (65 cases/1,000 person-years), suggesting that both pre-infection risk factors and factors during the acute and recovery phases are important. Individual factors during the acute phase, such as a specific pathway, could be important, but therapeutic interventions targeting only this pathway may have a small effect on long-term cognition.

The conceptual model also highlights the importance of being quite clear about what one is studying. In certain models, one might attempt to isolate sequelae of severe sepsis that are unique to severe sepsis, as distinct from other forms of critical illness, for example. Such a study design might seek to isolate the mechanisms by which acute respiratory distress syndrome (ARDS) after severe sepsis is different from ARDS after trauma. Such very specific targeted studies help understand key aspects of severe sepsis and may help target specific therapies. In contrast, other study designs will help further delineate those aspects of severe sepsis that lead to common critical illness experiences, for example the experience of ventilator-induced lung injury and the mechanisms of this, regardless of the means a patient develops ARDS requiring mechanical ventilation. While such studies do not isolate severe sepsis-specific pathways, they do explain key components of the total morbidity of severe sepsis, and any study portfolio failing to include them is unlikely to account for the majority of problems faced by severe sepsis patients.

Interventions

There is increasing interest to change the target of sepsis interventions from examining mortality to preventing or mitigating morbidity. For instance, trials could be designed to improve long-term cognition and physical function. Multifaceted interventions that target multiple domains may be more likely to improve outcomes rather than interventions targeting a single mechanism, if there are no major adverse interactions among the interventions. The timing of initiation and duration of the intervention are important considerations. Based on mechanisms that are targeted, it may be necessary to initiate these interventions early but continue it during recovery over weeks or months.

Concluding remarks

With the growth of intensive care facilities both across the US and worldwide, and with the falling short-term mortality due to better standards of care, there is a growing population of patients who are cared for aggressively and who are now more likely to survive. Early epidemiologic studies highlighted that sepsis survivors often had a wide range of unwanted and protracted sequelae. However, with the realization that these same patients were often of

poor health prior to sepsis, investigators became interested in strategies to adjust or control for pre-sepsis morbidity. This work confirmed that sepsis often occurred in individuals who already had significant health problems and that, after sepsis, further sequelae were often simply part of the underlying health trajectory. However, sepsis also appeared to contribute independently to acceleration in the rate of underlying disease progression and the occurrence of new conditions.

Sepsis is a complex disease process with a plethora of potential mechanisms to explain how different aspects of sepsis, and the short-term care of sepsis patients, may drive late sequelae. Some of these pathways may be unique to sepsis while others may be shared with other acute illnesses. Further observational studies require sophisticated designs to isolate potentially causal pathways. In addition, the ultimate step will be to conduct experiments where patients are randomly assigned to alternative care strategies designed specifically to alter these pathways with the hope of improving long-term outcomes of sepsis.

GLOSSARY

Chronic health	health status over a long time. Individuals often have poor chronic health due to high burden of chronic diseases or presence of disabilities
Cognitive function	the intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves perception, thinking, reasoning, and remembering
Dementia	the clinical syndrome characterized by acquired loss of cognitive and emotional abilities severe enough to interfere with daily functioning and the quality of life
Frailty	there is no single well-accepted definition of frailty, however it is often considered as a state of reduced physiological reserve associated with increased susceptibility to disability. Biologically, it is a state of age-related physiologic vulnerability resulting from impaired homeostatic reserve and reduced capacity of the organism to withstand stress
Subclinical disease	an illness that may not be easily detected by standard clinical evaluation
Teng's mini-mental status exam	a neuropsychological test to determine cognitive function. The Teng's mini-mental status exam is often used to assess cognition in well-functioning and community-dwelling individuals, and to screen for dementia

References

1. Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003; 31:1250–1256. [PubMed: 12682500]
2. Angus DC, van der Poll T. Severe Sepsis and Septic Shock. N Engl J Med. 2013; 369:840–851. [PubMed: 23984731]
3. Riedemann NC, et al. Novel strategies for the treatment of sepsis. Nat Med. 2003; 9:517–524. [PubMed: 12724763]

4. Shah FA, et al. Bidirectional Relationship between Cognitive Function and Pneumonia. *Am J Respir Crit Care Med*. 2013; 188:586–592. [PubMed: 23848267]
5. Iwashyna TJ, et al. Population Burden of Long-Term Survivorship After Severe Sepsis in Older Americans. *J Am Geriatr Soc*. 2012; 60:1070–1077. [PubMed: 22642542]
6. Yende S, et al. Epidemiology and long-term clinical and biologic risk factors for pneumonia in community-dwelling older Americans: analysis of three cohorts. *Chest*. 2013; 144:1008–1017. [PubMed: 23744106]
7. Yende S, et al. Pre-Infection Systemic Inflammatory Markers and Risk of Hospitalization due to Pneumonia. *Am J Respir Crit Care Med*. 2005; 172:1440–1446. [PubMed: 16166617]
8. Yende S, et al. Epidemiology and long-term clinical and biologic risk factors for pneumonia in community-dwelling older Americans: analysis of three cohorts. *Chest*. 2013; 144:1008–1017. [PubMed: 23744106]
9. Wunsch H, et al. Three-year outcomes for medicare beneficiaries who survive intensive care. *JAMA*. 2010; 303:849–856. [PubMed: 20197531]
10. Iwashyna TJ, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010; 304:1787–1794. [PubMed: 20978258]
11. Pandharipande PP, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013; 369:1306–1316. [PubMed: 24088092]
12. Herridge MS, et al. One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2003; 348:683–693. [PubMed: 12594312]
13. Corrales-Medina VF, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Med*. 2011; 8:e1001048. [PubMed: 21738449]
14. Kellum JA, et al. Understanding the Inflammatory Cytokine Response in Pneumonia and Sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med*. 2007; 167:1655–1663. [PubMed: 17698689]
15. Yende S, et al. Inflammatory Markers at Hospital Discharge Predict Subsequent Mortality after Pneumonia and Sepsis. *Am J Respir Crit Care Med*. 2008; 177:1242–1247. [PubMed: 18369199]
16. Fried LP, et al. From bedside to bench: research agenda for frailty. *Sci Aging Knowledge Environ*. 2005; 2005:e24.
17. Walston J, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc*. 2006; 54:991–1001. [PubMed: 16776798]
18. Leng SX, et al. White Blood Cell Counts, Insulin like Growth Factor-1 Levels, and Frailty in Community-Dwelling Older Women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2009; 64A:499–502.
19. Rockwood K, et al. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J*. 2005; 173:489–495. [PubMed: 16129869]
20. Rockwood K, et al. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci*. 2007; 62:738–743. [PubMed: 17634321]
21. Fallah N, et al. Transitions in frailty status in older adults in relation to mobility: a multistate modeling approach employing a deficit count. *J Am Geriatr Soc*. 2011; 59:524–529. [PubMed: 21391943]
22. Cigolle CT, et al. Comparing Models of Frailty: The Health and Retirement Study. *J Am Geriatr Soc*. 2009; 57:830–839. [PubMed: 19453306]
23. Medzhitov R, et al. Disease Tolerance as a Defense Strategy. *Science*. 2012; 335:936–941. [PubMed: 22363001]
24. Kiechl S, et al. Toll-like receptor 4 polymorphisms and atherogenesis. *N Engl J Med*. 2002; 347:185–192. [PubMed: 12124407]
25. Lorenz E, et al. Relevance of mutations in the TLR4 receptor in patients with gram-negative septic shock. *Arch Intern Med*. 2002; 162:1028–1032. [PubMed: 11996613]

26. Seymour CW, et al. Marital status and the epidemiology and outcomes of sepsis. *CHEST Journal*. 2010; 137:1289–1296.
27. Mayr FB, et al. Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis. *JAMA*. 2010; 303:2495–2503. [PubMed: 20571016]
28. Hawkley LC, et al. Effects of social isolation on glucocorticoid regulation in social mammals. *Horm Behav*. 2012; 62:314–323. [PubMed: 22663934]
29. Cox CE, et al. Development and preliminary evaluation of a telephone-based coping skills training intervention for survivors of acute lung injury and their informal caregivers. *Intensive Care Med*. 2012; 38:1289–1297. [PubMed: 22527082]
30. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA*. 1995; 273:59–65. [PubMed: 7996652]
31. Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med*. 1994; 38:1–14. [PubMed: 8146699]
32. Iwashyna TJ, Netzer G. The burdens of survivorship: an approach to thinking about long-term outcomes after critical illness. *Semin Respir Crit Care Med*. 2012; 33:327–338. [PubMed: 22875378]
33. Lunney JR, et al. Patterns of functional decline at the end of life. *JAMA*. 2003; 289:2387–2392. [PubMed: 12746362]
34. Cobb JP, et al. Application of genome-wide expression analysis to human health and disease. *Proc Natl Acad Sci U S A*. 2005; 102:4801–4806. [PubMed: 15781863]
35. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003; 348:138–150. [PubMed: 12519925]
36. Coleman EA, et al. The care transitions intervention: results of a randomized controlled trial. *Arch Intern Med*. 2006; 166:1822–1828. [PubMed: 17000937]
37. Nakashima Y, et al. ApoE-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree. *Arterioscler Thromb*. 1994; 14:133–140. [PubMed: 8274468]
38. Tate JA, et al. Infection Hospitalization Increases Risk of Dementia in the Elderly. *Crit Care Med*. 2013 (In press).

HIGHLIGHTS

- Severe sepsis worsens chronic health and causes physical and cognitive impairment.
- A bidirectional relationship exists between chronic diseases and sepsis.
- Various factors during different phases of sepsis affect this relationship.

Figure 1.

Conceptual model describing chronic health status before and during sepsis and the trajectories of health during recovery. *A* denotes health status trajectory prior to sepsis. *B* denotes the health status during the acute phase. Health status often worsens during this phase due to organ dysfunction. *C* denotes trajectories during recovery. These include no change in trajectory compared to *A* (*C1*), slow progressive worsening (*C2*), relapsing (*C3*), and rapidly progressive (*C4*) health status.

Table 1Factors that play a role in long-term sequelae of sepsis^a

Domains	Biological/physiologic	Behavioural	Social
Pre-Event	Frailty Disability (limitations to perform ADL and IADL) Immune abnormalities that predisposes to higher risk of infection	Depression/Anxiety	Social support Socioeconomic status
Acute could occur before sepsis (e.g. trauma), during sepsis itself, or may be generic to other acute conditions	Severity and number of organ dysfunction Interventions (e.g. medications, early rehabilitation) Reduced physical activity Magnitude of the host immune response (e.g. IL-6 and CRP) Epigenetic modifications Alteration in the host microbiome	Depression/Anxiety Delirium	
Recovery	Persistence of organ dysfunction Degree of immunosuppression Resolution of immune response (e.g. lipoxins and resolvins)	Psychological adaptation Compensation to perform activities	Environmental modifications Interruption of medications Social support

^a Abbreviations: ADL, activities of daily living; IADL, independent activities of daily living; IL-6, interleukin 6; CRP, C reactive protein.