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Effects of statins on the development of sepsis and organ dysfunction in hospitalized older patients in China

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ABSTRACT

This study aimed to evaluate the protective role of statins on the development of sepsis and infection-related organ dysfunction and mortality in a hospitalized older Chinese population with bacterial infections. In this retrospective cohort study, 257 older patients with bacterial infection were divided into two groups: a statin group, those who had received statin therapy for ≥1 month before admission and continued receiving statin during hospitalization; and a non-statin group, those who had never received statin or used statin for <1 month prior to admission. A multivariate logistic regression analysis was performed to identify risk and protective factors for severe sepsis. A significantly lower incidence of organ dysfunction was found in the statin group, as compared with the non-statin group (13.3% vs 31.1%, respectively; $p = 0.002$), corresponding to adjusted rates ratio of 0.32 (95% confidence interval [CI], 0.13–0.75; $p = 0.009$). No significant difference was found between statin and non-statin groups in 30-day sepsis-related mortality (4.4% vs 10.2%, respectively; $p = 0.109$), incidence of intensive care unit admission (13.3% vs 16.8%, respectively; $p = 0.469$), or length of hospital stay (20.5 vs 25.9 days, respectively; $p = 0.61$). Statins significantly reduced the development of sepsis and infection-related organ dysfunction in hospitalized older Chinese patients but did not reduce 30-day mortality, ICU admission incidence, or length of hospital stay.

Introduction

Sepsis occurs in approximately 2% of general hospitalized populations in developed countries, including 6%–30% of all patients admitted to intensive care units (ICU).[1,2] About one-half to three-quarters of patients with sepsis experience organ failure.[3] In the United States, approximately 751,000 patients developed severe sepsis in 1995; currently, among the more than 1,000,000 hospitalized patients in the United States diagnosed with sepsis annually, the incidence is projected to increase by 1.5% annually, with only 50%–70% of

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patients surviving.[1,4] However, a 20-year study showed that sepsis is increasing at a rate of 8.7% per year, which is greater than the population growth rate.[5] The incidence of sepsis is also high in China; older patients with comorbidities who are admitted with bacterial infections have a higher risk.[6]

Although the pathophysiology of sepsis has not been fully elucidated, general consensus indicates that sepsis arises from immunodysregulation and uncontrolled systemic inflammatory responses.[7] The inflammatory cascade is multilevel and involves the production of pro-inflammatory cytokines, adhesion molecules, and reactive oxygen species.[8] Given this pathophysiology, clinical trials have investigated adjuvant mediator therapy to identify drugs that block specific inflammatory mediators.[9–11] Toward that end, statins are well known as lipid-lowering agents and have also demonstrated anti-inflammatory and immunomodulatory properties.[12] Almog et al.[13] demonstrated that prior statin therapy might reduce rates of severe sepsis and ICU admissions. This findings have prompted researchers worldwide to study the pleiotrophic effects of statins on sepsis, with largely unconfirmed results.[12,14–16] A recent meta-analysis of randomized controlled trials (RCTs) suggested that statins should not be recommended to manage severe sepsis in critically ill patients.[17] In addition, a recent systematic review reported that statins do not decrease the incidence of sepsis, progression to severe sepsis, or associated mortality rates.[18] Nevertheless, patients receiving statins prior to hospital admission due to infection, bacteremia, sepsis, and infection-related organ dysfunction continue to demonstrate reduced risks of sepsis progression/severity, rates of hospital-acquired bacteremia, and hospital mortality.[13,16] Most previous studies were conducted in Western populations except for a retrospective study conducted by Yang et al.[19] who studied an Asian population in Taiwan, indicating that statins neither benefited Asian patients with sepsis nor improved short-term survival.

Although RCTs have examined the potential value of statins in sepsis through meta-analysis and systematic review,[17,18] to our knowledge Asian patients or exclusively older patients with bacterial infections have not been studied, and conclusions have not shown a beneficial role of statins in bacterial infections. Therefore, the present study aimed to investigate the protective role of statins on the development of bacterial infections and infection-related organ dysfunction and mortality in older Chinese patients hospitalized due to bacterial infections.

Material and methods

Study design and patients

A retrospective cohort study enrolling older Chinese patients hospitalized due to bacterial infection was conducted between March 2011 and March 2012 in the Geriatric Medicine Department at First Affiliated Hospital, School of Medicine of Zhejiang University, Zhejiang Province, China. This study was approved by the Clinical Research Ethics Committee of First Affiliated Hospital. As patient data were de-identified and patients remained anonymous during the retrospective review, signed informed consent was waived.

For data collection purposes, only the first admission from a series of multiple admissions involving the same patients during the study period was included. For this study, inclusion criteria were: patients aged ≥65 years old with sepsis whose records included complete clinical and laboratory data.

Patients were divided into two groups based on those who had prior statin use and no statin use. The statin group were those who had used a statin for at least one month prior to the first hospital admission and continued statin treatment during hospitalization. Based on a prior study that indicated that the therapeutic effects of statins are demonstrated after one month of continuous use, the non-statin group was characterized by patients who either had never taken statins or had taken a statin for <1 month prior to admission.[13] Although other characteristics between the two groups were different, all patients received treatment for bacterial infection, and the study endpoint was development of sepsis. Patients in the statin group were treated with several different statin drugs and dosages including atorvastatin, 20 mg daily; simvastatin, 40 mg daily; fluvastatin, 40 mg daily; pravastatin, 20 mg daily; and rosuvastatin, 10 mg daily. Data from both groups were reviewed 30 days after admission.

Sepsis and severe sepsis with organ failure were defined by the most recent criteria from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) written by Singer et al.[20] Patients were assessed using Acute Physiology and Chronic Health Evaluation II (APACHE II) criteria, and their APACHE II scores were determined upon admission. Sepsis management was based on SCCM practice parameters for the hemodynamic support of sepsis in adult patients.

Data were obtained from electronic medical records from time of admission and in the following 30 days, with the exception of those with nosocomial infections whose data were collected at the time their sepsis diagnosis was confirmed. Patient characteristics were collected from data on a single admission, including demographics, pre-existing medical conditions, concurrent medications, infection type and site, APACHE II scores, laboratory data, microbiological culture results, ICU admission, length of hospital stay, and sepsis-related mortality. Laboratory values (e.g., albumin, triglycerides, C-reactive protein [CRP]) selected for analysis were a single measure in any 24-h period that most accurately represented patient status (i.e., highest or lowest value depending on specific test). The primary endpoints were the development of sepsis as indicated by the incidence of multiple organ dysfunction syndrome (ICD Code 995.92) and 30-day sepsis-related mortality. Secondary outcomes included incidence of ICU admission and length of hospital stay.

Statistical analysis

Continuous data are presented as median and interquartile range and were compared between groups using the Mann–Whitney *U* test. Categorical data are presented as number and percentage (%) and were assessed using χ^2 test or Fisher's exact test. Logistic regression analysis was conducted to screen for variables independently associated with severe sepsis (defined as sepsis with organ dysfunction). Age, gender, and variables with a p of <0.05 in univariate analysis were included in a model for the multivariate analysis.