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Clinical factors influencing mortality risk in hospital-acquired sepsis

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SUMMARY

Background: Identification of factors that confer an increased risk of mortality in hospital-acquired sepsis (HAS) is necessary to help prevent, and improve the outcome of, this condition.
Aim: To evaluate the clinical characteristics and factors associated with mortality in patients with HAS.
Methods: Retrospective study of patients with HAS in a major Spanish Hospital from 2011 to 2015. Data from adults receiving any of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes associated with sepsis were collected. Those fulfilling the SEPSIS-2 definition with no evidence of infection during the first 48 h following hospitalization were included ($N = 196$). Multivariate analysis was employed to identify the risk factors of mortality.
Findings: HAS patients were found to have many of the risk factors associated with cardiovascular disease (male sex, ageing, antecedent of cardiac disease, arterial hypertension, dyslipidaemia, smoking habit) and cancer. Vascular disease or chronic kidney disease were associated with 28-day mortality. Time from hospital admission to sepsis diagnosis, and the presence of organ failure were risk factors for 28-day and hospital mortality. Experiencing more than one episode of sepsis increased the risk of hospital mortality. 'Sepsis code' for the early identification of sepsis was protective against hospital mortality.
Conclusion: This study identifies several major factors associated with mortality in patients suffering from HAS. Implementation of surveillance programmes for the early identification and treatment of sepsis translate into a clear benefit.

Introduction

A tentative extrapolation of data from high-income countries suggests that 31.5 million cases of sepsis occur globally each year. Of these cases, 19.4 million corresponded to severe sepsis, with potentially 5.3 million deaths annually [1]. The overall incidence of sepsis, as well as overall mortality, appear to be increasing in spite of advances in care and new antibiotics

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[2,3]. To improve the outcome of sepsis patients, more effort is required to identify those factors associated with mortality. Prevention and early intervention should be the cornerstones to obtain better results in this regard [4—6].

Traditionally, sepsis has been classified according to location of acquisition, i.e. community-acquired (acquired outside the hospital setting) and nosocomial (hospital-acquired). These forms of sepsis differ in the patients' characteristics, causative micro-organisms and outcomes [7]. Most studies of sepsis in hospitalized patients have not distinguished between community-acquired sepsis and hospital-acquired sepsis (HAS) [3,8]. Consequently, the specific clinical profile of patients in the latter group is poorly understood.

HAS is associated with considerable economic impact. The average cost of each case of HAS ($38,369) clearly exceeds that caused by healthcare-associated sepsis ($8796) or community-acquired severe sepsis ($7023) [9]. Moreover, HAS is associated with greater mortality, and is among the major preventable causes of admission to the intensive care unit (ICU) [9—11]. However, HAS occurring outside the setting of cases acquired on the ICU has been poorly studied [12,13].

To improve the outcome of HAS, it is necessary to identify those risk factors conferring an increased risk of mortality in patients suffering from this condition, in ICU and non-ICU settings. An understanding of who is at risk of adverse outcomes from HAS can certainly assist with initiation of early treatment, and might also assist with targeting of infection prevention and control measures [14]. The aim of this study was to identify risk factors for mortality in patients suffering from HAS in a major hospital in Spain.

Methods

Study design

This was a retrospective observational study evaluating the factors associated with mortality in patients suffering from HAS. Data were obtained from clinical records of a major university hospital in Spain (Hospital Clínico Universitario de Valladolid, HCUV). The study was approved by the Clinical Research and Ethics Committee of this hospital. Informed consent was waived due to the observational nature of the study.

Inclusion criteria

In a first step, we identified all the patients receiving any of the ICD-9-CM codes associated with sepsis (Supplementary Table I, Appendix A) in the hospital discharge database of our hospital during a five-year observation period (from 2011 to 2015, inclusive) ($N = 3902$ patients). A specialist doctor in infectious diseases reviewed each of these cases and excluded patients aged <18 years, those without clinical or analytical signs of infection, and those who were receiving antimicrobial treatment and/or had suspected sepsis on admission or within 48 h of admission [15]. In all, 196 patients with HAS were identified using the criteria of the SEPSIS-2 definition [16].

Data collection

A specific standard data sheet was employed to collect the clinical data, including medical history, haematological, biochemical, and microbiological investigations. Empirical antimicrobial treatment was considered appropriate when it accorded with the result of the antibiotic susceptibility test, and the micro-organism was susceptible to at least one of the administered antibiotics. Patients with human immunodeficiency virus infection and those undergoing radiotherapy or receiving immunosuppressive drugs, including chemotherapy or systemic steroids, in the last three months prior to the diagnosis of sepsis were considered to be immunosuppressed.

Statistical analysis

Differences in demographic and clinical characteristics between survivors and non-survivors were assessed using the χ^2-test for categorical variables and the Mann—Whitney *U*-test for continuous variables. Factors associated with mortality risk during the acute phase of the disease were evaluated using univariate and multivariate Cox regression analysis. Those variables yielding $P < 0.1$ in the univariate analysis were further introduced into the multivariate one using the Wald selection method. Those variables yielding significant results in the multivariate Cox regression analysis were analysed for their impact on survival mean time using the Kaplan—Meier test plus log-rank test. Time was censored at 28 days following sepsis diagnosis for Cox and Kaplan—Meier analysis. Factors associated with mortality risk including the post-acute phase of the disease (hospital mortality) were studied using univariate and multivariate logistic regression analysis. Again, those variables yielding $P < 0.1$ in the univariate analysis were further introduced into the multivariate one with the Wald selection method. The data were analysed using the statistical software IBM SPSS version 20.0 for Windows. Values with $P < 0.05$ were considered statistically significant.

Results

Patients' clinical characteristics

In all, 196 patients were identified with sepsis, severe sepsis, or septic shock due to hospital-acquired infection (Tables I and II). Patients were more frequently elderly and male. The most frequent antecedents were cardiac disease, arterial hypertension, dyslipidaemia, smoking habit, and cancer. Vascular disease and chronic kidney disease were more frequent in non-survivors. The largest proportion of patients with nosocomial sepsis came from the critical care units (medical, surgical, cardiac ICUs) (47.4%), followed by those admitted to a surgical (29.1%) or medical service (23.5%). Sepsis associated with organ failure was present in 146 patients (74.5%). Hospital mortality was 45.4%, but it was especially high in those patients with organ failure, who represented 85.4% of the group of non-survivors ($N = 76$). In 2013 a 'sepsis code' programme was implemented in our hospital. This was aimed to achieve an early diagnosis and treatment of this disease. Patients recruited prior to implementation of the sepsis code showed a significantly higher mortality compared with those recruited after (58.4% vs 43.0%, $P = 0.031$). One-quarter of the patients had more than one episode of sepsis during the hospitalization period. Of these, 61.2% ultimately did not survive. Median time from admission to diagnosis was 10 days. In those patients with available data for biomarkers,