

Sepsis and cardiovascular events: The story so far

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Sepsis is a state of life-threatening organ dysfunction that results from a dysregulated host immune response to infection.¹ Sepsis is a common condition that leads to admission to the intensive care unit (ICU). Although advances have been made in the management of sepsis, mortality from sepsis remains high.² Among patients diagnosed with sepsis each year, up to 1 in 3 will succumb to the disease.²

Cardiac dysfunction is a well-recognised complication of sepsis and sepsis-related cardiomyopathy.³ However, in recent years, cardiovascular events (CVEs) such as myocardial infarction, acute coronary syndrome, congestive cardiac failure, cerebrovascular accident and cardiovascular-related deaths are becoming increasingly recognised as complications of sepsis. Although CVEs are a recognised complication of sepsis, most studies do not report risk factors associated with CVEs, posing a challenge to identify individuals at risk of developing sepsis-related CVEs.⁴⁻⁷ Thus, it is a challenging task to identify patients with sepsis who are at risk of developing CVEs.

In this issue of the *Annals*, Ho et al. had conducted a study to examine the incidence of CVEs in a medical ICU.⁸ The authors should be commended for this research as they examined several parameters in the search for risk factors related to CVEs. Although studies have been performed on CVEs in sepsis, these mostly compared incidence between patients with and without sepsis.⁴⁻⁷ This is evident in studies conducted by Ou, Angriman, Yende and Jafarzadeh,⁴⁻⁷ where the incidence of CVEs in patients with sepsis was compared with a matched non-sepsis population. These findings showed that the incidence of CVEs is higher in patients with sepsis when compared with a matched non-sepsis population. A few studies reported risk factors associated with CVEs. Wu et al. not only reported risk factors associated with CVEs in sepsis but also mortality.⁹ His team showed that patients with sepsis who developed CVEs had a 2-fold mortality at 180 days and 365 days after the onset of CVEs.

In their work, Ho et al. performed a single-centre study looking at factors that may be associated with CVEs in sepsis.⁸ This was done retrospectively by

collecting data from the electronic medical record system of patients admitted to a medical ICU of a tertiary university-affiliated hospital from July 2015 to October 2016. A detailed data collection was performed, which included patients' baseline demographics, medical history, comorbidities and hospital admission details, such as length of hospital and ICU stay, presence or absence of sepsis, laboratory results and treatment details. Patients' disease severity was assessed with Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score. Such details were not reported in earlier studies. From analysis of the data, Ho et al. found that 3 independent parameters were associated with an increased incidence of CVEs. These parameters were older patients, those with pre-existing ischaemic heart disease, and patients of certain ethnicities, particularly Malay and Indian. Age has been reported to affect the incidence of CVEs in 2 earlier studies. While Wu et al.⁹ reported a similar finding of CVEs being higher in older patients, Angriman's study reported that CVEs were more common in those below 40 years of age.⁵ Wu also found that CVEs were associated with pre-existing neurological disorder, which was not reported by Ho et al. The latter further noted factors associated with a lower risk of developing CVEs. These were a body mass index (BMI) lower than 18.5 and the presence of chronic lung disease. The association between chronic lung disease and a lower incidence of CVEs is interesting. Existing evidence shows that cardiovascular complications are well established in chronic obstructive pulmonary disease (COPD).¹⁰ However, in this study, chronic lung disease was taken as a collective rather than individual diseases like asthma, COPD, bronchiectasis, etc. Ho et al. also showed that patients with sepsis who develop CVEs had longer hospital and ICU length of stay. The occurrence of CVEs in sepsis however did not affect the in-hospital mortality.

All studies performed thus far have been retrospective, with differences in the conclusions due to the various methods and analyses of the data collected. Comparing

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the differences in these studies will provide a better understanding of the differing conclusions.

Firstly, the source of data collection varies between the different studies. Studies by Ou,⁴ Yende⁶ and Wu⁹ relied on information from insurance databases, while Angriman⁵ and Jafarzadeh⁷ used population-based databases. The authors were able to collect data on thousands of patients who had sepsis, CVEs, prior medical conditions, length of stay and mortality. On the other hand, Ho et al. collected data from ICU inpatient electronic records. In total, 879 patients were recruited, of whom 682 had a diagnosis of sepsis. Despite the small sample size compared with earlier studies, more information was actually gathered from the electronic medical records, including laboratory results, clinical parameters and patients' clinical progress. Such data are not available from insurance and population-based databases, thus electronic medical records are more reflective of the "real world".

Secondly, these studies have different end points. Ou, Angriman, Yende and Jafarzadeh compared the incidence of CVEs between patients with and without sepsis. In contrast, Wu and Ho et al. compared outcomes between presence and absence of CVEs in patients diagnosed with sepsis. Unlike the studies mentioned earlier, studies by Wu and Ho et al. do not have a matched group of patients without sepsis, but instead focused only on patients who were diagnosed with sepsis.

Finally, mortality was reported differently in the various studies. Yende and Ou included mortality in patients with all cause of sepsis, and not exclusive to those who developed CVEs. Wu reported that patients with sepsis who developed CVEs had a higher mortality compared to those without CVEs. On the other hand, Ho et al. found no difference in mortality when these 2 groups of patients were compared. However, it is important to note that Wu reported mortality at 180 and 365 days, while Ho et al. only looked at inpatient mortality. The latter clearly stated the number of patients requiring admission to a medical ICU but Wu did not mention ICU admission in his study.

As of now, current evidence suggests that CVEs are more common in patients with sepsis and possibly more likely to affect older patients. CVEs may be associated

with higher mortality risk beyond 1 year of diagnosis. However, these observations are inconclusive and need more supportive evidence due to inconsistencies in conducting the studies.

The work by Ho et al. can serve as a "real-world" pilot study for CVEs in sepsis. Hopefully, more clinical studies will be conducted, ideally prospective multicentre trials. Such studies will lead to a better understanding of the condition and help identify patients with sepsis who are at risk, for better management of CVEs. This will be a useful addition to existing management bundles that are currently utilised in the management of sepsis.¹¹

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