MAYO CLINIC

ORIGINAL ARTICLE

The Incremental Burden of Acute Respiratory Distress Syndrome: Long-term Follow-up of a Population-Based Nested Case-Control Study

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Abstract

Objective: To evaluate the long-term survival of patients at similar risk for hospital-acquired acute respiratory distress syndrome (ARDS) who did and did not develop ARDS.

Methods: We conducted long-term follow-up of a population-based nested case-control study in a consecutive cohort of adult Olmsted County, Minnesota, patients admitted from January 1, 2001, through December 31, 2010. Patients in whom ARDS developed during their hospital stay (cases) were matched to similar-risk patients without ARDS (controls) by 6 characteristics: age, sex, sepsis, high-risk surgery, ratio of oxygen saturation to fraction of inspired oxygen, and ARDS risk according to the Lung Injury Prediction Score. Hospital mortality, discharge disposition, and long-term survival were compared.

Results: Patients who developed hospital-acquired ARDS (n=400) had higher hospital mortality than at-risk controls (n=400) (35% vs 5%; $P<.001$). Among hospital survivors (252 matched pairs), ARDS cases were more likely to be discharged to rehabilitation (13% vs 4%) and long-term care (30% vs 15%) facilities, whereas more controls were discharged home (71% vs 41%). After discharge, differences in survival persisted beyond 90 days (adjusted hazard ratio [HR], 1.76; 95% CI, 1.2-2.5; $P=.002$) and 6 months (adjusted HR, 1.73; 95% CI, 1.2-2.6; $P<.001$).

Conclusion: These results suggest that in a population-based matched case-control study of patients with similar characteristics at the time of hospital admission, those who developed hospital-acquired ARDS had worse long-term survival.

 ■ Mayo Clin Proc. 2018;■■(■):1-8

First described in 1967 by Ashbaugh et al,[1] acute respiratory distress syndrome (ARDS) is still associated with substantial morbidity and mortality and tremendous costs.[2,3] Despite advances in ARDS treatment and supportive measures,[4,5] and studies showing a linear decrease in mortality in the past few decades,[3,6] the syndrome and its complications still impose a worldwide burden of disease,[7] and its prognosis remains disappointingly poor over more than a decade.[6,8] Usually, ARDS complicates critical illness and has been associated with intrapulmonary (pneumonia, aspiration, lung contusion, toxic inhalation) and extrapulmonary (sepsis, shock, trauma, multiple transfusions, pancreatitis, high-risk surgery) risk factors.[9]

Recent studies have identified multiple sequelae in ARDS survivors, including reduction in quality of life, decline in functional status, neurocognitive impairment, psychiatric morbidities (such as anxiety, depression, and posttraumatic stress disorder), and joblessness.[10-17] A few contemporary studies have evaluated the long-term survival of patients with ARDS, but most of these studies lack a control group of at-risk patients for comparison.[15,18-21] A single study[22] has evaluated the long-term survival of patients with ARDS compared with a control group; however, this study was published before the substantial changes in the quality of critical care delivery that occurred during the past decade.[5,23-26]

However, it is often difficult to distinguish the long-term effects of ARDS complications per se vs those of underlying conditions; that is, "Do the patients die from ARDS or with ARDS?"[27] The incremental burden directly attributable to ARDS remains uncertain and is difficult to assess unless there is a

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representative population and a control group of hospitalized at-risk patients without ARDS. Olmsted County, Minnesota, a region that is geographically isolated from other urban areas, provides the opportunity to study the burden of ARDS in the community through population-based studies with a robust follow-up of patients. The Lung Injury Prediction Score (LIPS), developed to predict patients at risk for ARDS,[28,29] allows us to select patients who are at similar risk for ARDS who did not develop this complication and who can serve as an appropriate control group.

A recent National Institutes of Health workshop[6] established future directions in ARDS research, pointing out the need for assessment of long-term outcomes and development of strategies to perform ARDS prevention trials. Neither of these goals can be achieved without a robust assessment of attributable burden of ARDS on long-term survival.

To evaluate the incremental burden of ARDS, we performed a long-term follow-up study to compare survival in patients who developed ARDS during hospitalization (cases) and a matched similar-risk group of patients who did not develop ARDS (controls) from a previously described nested case-control population-based study.[30] Some of the results of this study have been previously reported in the form of an abstract.[31]

MATERIALS AND METHODS

This is a secondary analysis of a population-based nested case-control study spanning 10 years in which short- and long-term outcomes of ARDS cases were compared with those of matched controls via previously published study methods.[9,30] The study was approved by the Mayo Clinic Institutional Review Board, and waiver of consent was granted for all prospective enrollments. For the retrospective arm of the study, medical records were reviewed for patients who gave research authorization only.

Study Population

Eligible patients included adult residents of Olmsted County admitted to a tertiary care center from January 1, 2001, through December 31, 2010.

Ascertainment of the matched case-control pairs was performed in a previously published study.[26] Briefly, ARDS cases were ascertained from patients who did not have ARDS on hospital admission but subsequently developed ARDS during the hospital course (hospital-acquired ARDS). A previously validated electronic surveillance tool identified all mechanically ventilated patients with possible ARDS.[32] Inclusion criteria were prompted by an electronic alert designed to recognize the following combination: (1) a qualifying arterial blood gas value, the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen concentration <200, and (2) a qualifying chest radiograph (free-text Boolean query containing the trigger words *bilateral* AND *infiltrate* OR *edema*). The medical records of those patients were subsequently reviewed by 2 trained study investigators (M.B. and A.A.) for accuracy and timing of ARDS development according to the American-European Consensus Conference on ARDS criteria.[33] An independent third investigator (R.K. or O.G.) resolved existing disagreements. This method has been shown to have good interobserver agreement (κ=0.83).[34] Screening to ascertain the cohort was conducted retrospectively from January 1, 2001, through October 31, 2008, and prospectively from November 1, 2008, through December 31, 2010.

Controls were identified from the remaining cohort of consecutive adult Olmsted County residents admitted to the hospital from January 1, 2003, through December 31, 2010, and did not have ARDS but had at least 1 risk factor for it. Cases were matched 1:1 to controls on the basis of 6 characteristics: age, sex, high-risk surgery, sepsis, oxygen saturation to fraction of inspired oxygen ratio, and ARDS risk according to the LIPS.[28] The selection of matching variables was performed a priori considering clinical and statistical factors.

Patients who were admitted for comfort care only, died within 24 hours of admission, were readmitted to the hospital during the study period, or declined the use of their medical records for research were excluded.

Outcome Measures

Using a previously validated database,[32] we obtained each patient's date of death or last