

Epidemiology and Outcomes of Acute Respiratory Failure in the United States, 2001 to 2009: A National Survey

Mihaela S. Stefan, MD^{1,2,3,4*}, Meng-Shiou Shieh, PhD¹, Penelope S. Pekow, PhD^{1,5}, Michael B. Rothberg, MD, MPH^{1,2,3}, Jay S. Steingrub, MD^{1,3,6}, Tara Lagu, MD, MPH^{1,2,3}, Peter K. Lindenauer, MD, MSc^{1,2,3}

¹Center for Quality of Care Research, Baystate Medical Center, Springfield, Massachusetts; ²Division of General Medicine, Baystate Medical Center, Springfield, Massachusetts; ³Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts; ⁴Program in Clinical and Translational Research, Sackler School of Graduate Biomedical Sciences, Tufts University, Boston, Massachusetts; ⁵School of Public Health and Health Sciences, University of Massachusetts–Amherst, Amherst, Massachusetts; ⁶Division of Critical Care Medicine, Department of Medicine, Baystate Medical Center, Springfield, Massachusetts.

BACKGROUND: The objective of this study was to evaluate trends in hospitalization, cost, and short-term outcomes in acute respiratory failure (ARF) between 2001 and 2009 in the United States.

METHODS: Using the Nationwide Inpatient Sample we identified cases of ARF based on International Classification for Diseases, Ninth Revision, Clinical Modification codes. We calculated weighted frequencies of ARF hospitalizations by year and estimated population-adjusted incidence and mortality rates. We used logistic regression to examine hospital mortality rates over time while adjusting for changes in demographic characteristics and comorbidities of patients.

RESULTS: The number of hospitalizations with a diagnosis of ARF rose from 1,007,549 in 2001 to 1,917,910 in 2009, with an associated increase in total hospital costs from

\$30.1 billion to \$54.3 billion. During the same period we observed a decrease in hospital mortality from 27.6% in 2001 to 20.6% in 2009, a slight decline in average length of stay from 7.8 days to 7.1 days, and no significant change in the mean cost per case (\$15,900). Rates of mechanical ventilation (noninvasive [NIV] or invasive mechanical ventilation [IMV]) remained stable over the 9-year period, and the use of NIV increased from 4% in 2001 to 10% in 2009.

CONCLUSIONS: Over the period of 2001 to 2009, there was a steady increase in the number of hospitalizations with a discharge diagnosis of ARF, with a decrease in inpatient mortality. There was a significant shift during this time toward the use of NIV, with a decrease in the rates of IMV use. *Journal of Hospital Medicine* 2013;8:76–82. © 2012 Society of Hospital Medicine

Acute respiratory failure (ARF), a common and serious complication in hospitalized patients, may be caused by several conditions including pneumonia, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), and congestive heart failure (CHF). Although ARF is conventionally defined by an arterial oxygen tension of <60 mm Hg, an arterial carbon dioxide tension of >45 mm Hg, or both, these thresholds serve as a guide to be used in combination with history and clinical assessment of the patient.^{1,2} Supplemental oxygen and treatment of the underlying cause is the mainstay of therapy for ARF, but in severe cases patients are treated with invasive mechanical ventilation (IMV) or noninvasive ventilation (NIV). ARF is the most frequent reason for admission to the intensive care unit (ICU)^{3,4} and has an in-hospital mortality rate of 33% to 37% among

those who require IMV.^{5,6} The majority of epidemiologic studies of ARF have been limited to patients requiring mechanical ventilation or those admitted to the ICU, and information about the characteristics and outcomes of patients across the full spectrum of severity is much more limited.^{5,7–11} General improvements in the management of underlying conditions, implementation of more effective ventilation strategies,^{12,13} and increasing use of NIV^{14,15} may have led to better outcomes for patients with ARF, yet empirical evidence of a change in the adjusted mortality rate over time is lacking.

The objective of this study was to provide a broad characterization of the epidemiology of ARF among adults hospitalized in the United States using a large nationally representative database. We sought to evaluate whether incidence, mortality, cost, or ventilation practice associated with ARF in the United States changed over the period of 2001 to 2009.

METHODS

Data Source

We utilized data from the Nationwide Inpatient Sample (NIS) of the Health Care Cost and Utilization Project,¹⁶ which is a 20% stratified probability sample of all US acute-care hospitals each year. These data are drawn from a sampling frame that contains close to

*Address for correspondence and reprint requests: Mihaela S. Stefan, MD, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199; Telephone: 413-794-8121; Fax: 413 794 4054. E-mail: mihaela.stefan@bhs.org

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95% of all discharges in the United States, with the hospital discharge record as the unit of analysis. The NIS has been used to study trends in many different diagnoses.^{17–19} The database contains demographic information, payer information, principal and secondary diagnoses, cost, discharge disposition, and death during hospitalization. It also contains information on hospital characteristics including ownership, size, teaching status, and geographic region.

Definitions

We included patients ≥ 18 years old discharged between 2001 and 2009 with a primary or secondary diagnosis of ARF. We identified cases of ARF using diagnostic codes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) previously used in studies of acute organ dysfunction in sepsis (518.81, 518.82, 518.84, 518.4, 799.1, 786.09).^{17,20,21} To define ARDS we relied on ICD-9-CM codes (518.4, 518.82, 518.5, 786.09) used in prior studies that showed good sensitivity and specificity.^{22,23} The use of ventilatory support was identified using the ICD-9-CM procedure codes²⁴ (93.90, 93.70, 93.71, 93.76). Comorbidities were classified using the Agency for Healthcare Research and Quality's (Rockville, MD) Healthcare Cost and Utilization Project's (HCUP) Comorbidity Software version 3.10–3.5.²⁵

Outcomes

The primary outcomes included the annual number of hospitalizations, population incidence, hospital mortality, and costs of care. Secondary outcomes included length of stay, most common diagnoses associated with ARF, disposition at discharge, and use and type of ventilatory support.

Analysis

We estimated the number of hospitalizations with a diagnosis of ARF/year, and we calculated the weighted frequencies following HCUP-NIS recommendations using SAS/STAT survey procedures. Using population estimates for the years 2001 to 2009 from the US Census Bureau, we employed direct standardization to calculate age-, gender-, and race-adjusted population incidence and mortality rates of ARF per 100,000 population. Hospital mortality was defined as the ratio of ARF hospitalizations ending in death divided by total number of ARF hospitalizations. Mechanical ventilation rates and rates of selected comorbidities were similarly defined.

We employed indirect standardization to adjust hospital mortality rates for age, sex, race/ethnicity, comorbidities, and hospital characteristics using logistic regression models from 2001 to predict hospital mortality for 2002 to 2009. We used linear regression models to test whether the slope of year was significant for trends in outcomes overtime. Costs were calculated using hospital-specific cost-to-charge ratios

when available and a weighted group average at the state level for remaining hospitals. We converted all costs to 2009 US dollars using the Consumer Price Index. Costs and lengths of stay were not normally distributed, so we calculated weighted geometric means (the average of all logarithmic values), then converted back to a base-10 number. Using a Taylor series expansion, we then calculated standard errors. All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

The Baystate Medical Center institutional review board determined that the project did not constitute human subjects research.

RESULTS

Hospitalization Trends

The number of hospitalizations with an ARF diagnosis code increased at an average annual rate of 11.3% from 1,007,549 (standard deviation [SD] = 19,268) in 2001 to 1,917,910 (SD = 47,558) in 2009. More than two-thirds of ARF admissions were associated with medical, rather than surgical, conditions (69.5% in 2001 and 71.2% in 2009). The median age, racial make-up, and gender did not change significantly. Over the study period we observed an increase in ARF-related hospitalizations in large, urban, teaching hospitals and in hospitals located in the Midwest (Table 1).

After adjusting for age and sex, the population incidence of ARF increased from 502 (standard error [SE] = 10) cases per 100,000 in 2001 to 784 (SE = 19) cases per 100,000 in 2009 (a 56% increase, $P < 0.0001$). Hispanics had the lowest rates of ARF, with both black and white groups having similar rates (Table 2).

The most common etiologies of ARF among medical patients were pneumonia, CHF, ARDS, COPD exacerbation, and sepsis. Over the 9-year study, the proportion of cases secondary to pneumonia and sepsis rose significantly: from 39% to 46% and 13% to 21%, respectively (Figure 1).

Mortality and Other Outcomes

The number of in-hospital deaths related to ARF increased from 277,407 deaths in 2001 to 381,155 in 2009 (a 37% increase, $P < 0.001$). Standardized to the population, deaths increased from 140 in 2001 to 154 cases per 100,000 in 2009 (a 10% increase, $P = 0.027$). Despite slightly increasing mortality rates at a population level, adjusted in-hospital mortality improved from 27.6% in 2001 to 20.6% in 2009 ($P < 0.001$). Mortality declined for both IMV and NIV patients from 35.3% in 2001 to 30.2% in 2009 and from 23.5% to 19%, respectively, but increased for those who required both NIV and IMV (from 26.9% in 2001 to 28% in 2009).

Adjusted hospital length of stay decreased from 7.8 days per patient in 2001 to 7.1 days in 2009 ($P < 0.001$), with a concomitant increase in discharges to nursing facilities, from 24% in 2001 to 29% in 2009.

TABLE 1. Hospitalizations With Acute Respiratory Failure in the United States, 2001 to 2009, by Patient and Hospital Characteristics

	2001	2003	2005	2007	2009
Patient characteristics					
All, N (SD)	1,007,549 (19,268)	1,184,928 (25,542)	1,288,594 (30,493)	1,480,270 (32,002)	1,917,910 (47,558)
Age, mean (SE), y	66.6 (0.2)	66.0 (0.2)	66.1 (0.2)	65.8 (0.2)	65.8 (0.2)
Age group, %					
18–44	11.5	12.0	11.5	11.6	10.9
45–64*	26.7	28.9	29.6	30.7	31.7
65–84*	50.2	47.8	47.0	45.7	45.3
85+	11.5	11.4	11.9	12.0	12.1
Male*	48.1	48.2	48.6	49.3	49.2
Race					
White	75.8	71.9	76.5	71.8	73.4
Black	12.7	13.6	11.2	14.2	12.5
Hispanic	7.2	9.8	7.7	8.5	7.8
Other	4.2	4.7	4.7	5.5	6.3
Primary ARF	20.7	20.9	25.9	26.1	19.9
Secondary ARF	79.3	79.1	74.1	73.9	80.1
Medical*	69.5	69.1	69.9	70.2	71.2
Surgical*	30.5	30.8	30.1	29.8	28.8
Hospital characteristics, %					
Number of beds					
Small	10.0	10.1	10.5	10.8	11.3
Medium†	25.2	25.3	24.6	24.0	22.7
Large	64.7	64.6	64.9	65.2	66.0
Region					
South*	18.5	18.5	17.6	17.0	16.3
Midwest	21.4	22.0	23.6	23.2	23.5
Northeast	42.6	41.7	41.4	42.2	42.1
West*	17.5	17.8	17.3	17.6	18.1
Hospital type					
Rural	13.6	13.0	11.8	11.0	10.8
Urban nonteaching	45.5	44.5	50.1	45.3	45.7
Urban teaching	40.9	42.5	38.1	43.7	43.6
Patient outcomes					
Ventilation strategy					
IMV*	48.5	48.4	47.5	46.5	42.1
NIV*	3.8	5.3	6.9	9.4	10.1
IMV or NIV	50.9	51.7	52.1	52.9	49.7
Disposition					
Home/home healthcare*	42.1	43.8	42.8	43.4	45.7
Transfer to acute care	5.2	4.7	4.6	4.6	4.4
Nursing facility*	24.4	24.9	27.4	28.6	29.0
Other	0.7	0.8	0.9	0.9	1.0
Adjusted mortality, % (SE)*‡	27.6 (0.3)	26.4 (0.4)	24.9 (0.4)	22.7 (0.4)	20.6 (0.3)
Adjusted mean, LOS/case, d (SE)*‡§	7.8 (0.1)	7.9 (0.1)	7.7 (0.1)	7.5 (0.1)	7.1 (0.1)
Adjusted mean cost/case, 2009 US\$, (SE)‡§	15,818 (251)	16,981 (419)	17,236 (411)	16,941 (436)	15,987 (402)

NOTE: Abbreviations: ARF, acute respiratory failure; IMV, invasive mechanical ventilation; LOS, length of stay; NIV, noninvasive ventilation; SD, standard deviation; SE standard error. †P value for trend <0.01, including all years 2001–2009. *P value for trend <0.0001, including all years 2001–2009. ‡Adjusted for sex, age, race, hospital characteristics, and comorbidities. §Geometric mean reported, standard errors from Taylor series expansion.

There was no linear trend in adjusted cost per case, with \$15,818 in 2001 and \$15,987 in 2009 (in 2009 US dollars) (Table 1).

Ventilation Practices

Overall, 50.9% patients received ventilatory support (NIV or IMV or both) in 2001 and 49.7% in 2009

($P = 0.25$). The use of NIV increased from 3.8% to 10.1% ($P < 0.001$), a 169% increase, whereas the utilization of IMV decreased from 48.5% in 2001 to 42.1% in 2009 (P for trend < 0.0001), a 13% decrease. Uses of both NIV and IMV during hospitalization were seen in 1.4% of cases in 2001 and 2.5% of cases in 2009.

TABLE 2. Cases of Acute Respiratory Failure per 100,000 Population

	2001	2003	2005	2007	2009
All*	502 (10)	569 (12)	595 (14)	627 (14)	784 (19)
Age group					
18–44*	107 (3)	130 (4)	137 (4)	153 (5)	189 (6)
45–64*	422 (9)	500 (12)	521 (13)	580 (14)	739 (19)
65–84*	1697 (35)	1863 (42)	1950 (50)	2066 (46)	2578 (69)
85+	3449 (86)	3792 (106)	3981 (120)	3429 (97)	4163 (123)
Sex					
Male*	491 (10)	553 (13)	582 (14)	629 (14)	782 (20)
Female*	512 (10)	583 (12)	607 (15)	625 (13)	786 (19)
Race/ethnicity					
White*	398 (11)	427 (12)	466 (16)	450 (13)	699 (21)
Black*	423 (27)	513 (33)	432 (26)	574 (38)	738 (37)
Hispanic*	247 (24)	381 (42)	307 (27)	353 (34)	478 (42)
Other*	268 (20)	342 (29)	347 (26)	424 (29)	713 (77)
In-hospital mortality	140 (3)	148 (3)	146 (3)	140 (3)	154 (4)

NOTE: Data are presented as number per 100,000 population (standard error), standardized to 2000 US Census population. *P value for trend < 0.0001, including all years 2001 to 2009.

2009 Data Analysis

In 2009 the 1,917,910 hospitalizations with ARF resulted in 381,155 (SD = 8965) deaths and a total inpatient cost of \$54 billion. The most common etiologies in patients over 65 years old were pneumonia, CHF, COPD, ARDS, and sepsis. In patients younger than 45 years the most frequent diagnoses were pneumonia, ARDS, sepsis, asthma, drug ingestion, and trauma. Stratified analysis by gender and by age groups showed that mortality rates among men were higher than for women and were highest in patients older than 85 years (Table 3).

When we examined ventilation practices among medical patients we found that patients older than 85 years, when compared to patients younger than 45 years, were less likely to be treated with IMV (25% vs 55%) and more likely to be treated with NIV (12.7% vs 7%). At the same time, the average cost per case was lowest among patients 85 years and older, and hospital costs per case fell sharply after age 70 years. Costs were considerably higher for those who did not survive during hospitalization, particularly for patients younger than 45 years (Figure 2).

DISCUSSION

In this large population-based study, we found that the number of hospitalizations associated with a diagnosis of ARF almost doubled over a 9-year period. In 2009 there were nearly 2 million hospitalizations with ARF in the United States, resulting in approximately 380,000 deaths and inpatient costs of over \$54 billion. The population-adjusted ARF hospitalization rates increased in all age groups, and patients 85 years and older had the highest age-specific hospitalization rate. Although overall rates of mechanical ventilation (NIV or IMV) remained stable over the 9-year period, there was an important shift away from IMV (which decreased from 48% in 2001 to 42% in 2009) toward

NIV (which increased from 4% in 2001 to 10% in 2009). Overall, there was a significant increase in the number of total deaths despite a decline in adjusted in-hospital mortality rates. In-hospital mortality rates decreased for all cases of ARF regardless of ventilation choice.

The findings of this study mirror results of others that have shown that although the incidence of critical care illnesses like sepsis^{17,20,21,26} and acute renal failure²⁷ has increased over the last decade, in-hospital mortality rates have decreased.^{20,21,28} Our results also compliment the results of a recent study that looked at hospitalizations for noncardiogenic ARF, which observed a 3.7-fold increase in the number of cases and a steady decline in case fatality.¹¹

Most prior studies addressing the incidence of ARF have included only patients receiving mechanical ventilation. In 1994, the estimated number of cases of ARF requiring IMV was 329,766,⁹ which increased to 790,257 in 2005.¹⁰ In our study we found that in 2009, the number of patients with ARF hospitalizations with IMV increased to 806,538. The increase in the overall number of cases with ARF was mainly driven by a surge in cases of sepsis and pneumonia. Our findings are consistent with national trends over time in noncardiogenic ARF¹¹ and in conditions that predispose patients to ARF such as sepsis^{17,20,28} and acute renal failure.²⁷ As the number of claims for ARF doubled and the number of deaths increased, we found that adjusted hospital mortality improved from 27.6% in 2001 to 20.6% in 2009. This decline in hospital mortality was observed among all patients groups, regardless of ventilation choice. The decline in overall case fatality is consistent with prior findings in noncardiogenic ARF,¹¹ sepsis,^{17,28} and CHF.²⁹

There are a number of potential explanations for the reduction in mortality observed over the study period, including improvements in hospital management of the underlying conditions leading to ARF, an increase in the proportion of patients being treated

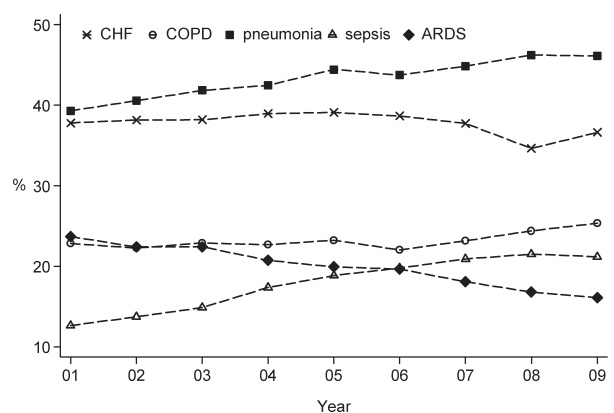


FIG. 1. Proportion of patients with acute respiratory failure with the 5 most common medical conditions from 2001 to 2009. Abbreviations: ARDS, adult respiratory distress syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

TABLE 3. Characteristics of Hospitalizations by Etiology (Medical, Surgical, Comorbidities, Procedures) in 2009

Disease	Total	Age <45 Years	45–65 Years	65–84 Years	85+ Years	Male	Female
Medical							
Total, N (%)	1,364,624 (71.2)	144,715 (10.6)	416,922 (30.6)	615,009 (45.1)	187,977 (13.8)	647,894 (47.5)	716,635 (52.5)
Pneumonia, %*†	46.1	41.7	42.8	46.9	54.3	48.8	43.7
CHF, %*†	36.6	10.4	27.3	43.6	54.8	35.0	38.1
ARDS, %*†	16.1	22.9	16.2	14.5	15.9	15.5	16.7
Sepsis, %*†	21.2	18.1	21.3	21.3	23.1	22.8	19.8
COPD, %*	25.4	4.2	25.6	32.3	18.3	25.0	25.7
AMI, %*†	9.0	2.6	7.1	10.5	13.3	9.3	8.8
Asthma, %*†	9.2	18.1	11.6	6.7	5.4	6.2	12.0
Stroke, %*	4.8	2.3	4.1	5.5	6.0	5.0	4.7
Trauma or burns, %*†	3.4	5.4	2.9	3.0	4.1	4.3	2.5
Cardiorespiratory arrest, %*†	4.1	3.9	4.4	4.1	3.8	4.6	3.7
Drug, %*	3.7	16.6	5.1	0.8	0.3	3.8	3.6
IMV, %*†	37.7	54.6	43.7	33.5	24.8	41.1	34.5
NIV, %*†	11.9	7.1	11.5	13.0	12.7	11.4	12.3
In-hospital mortality (CI)‡	22 (21.3–22.7)	12.9 (11.9–13.9)	18.5 (17.6–19.4)	23.9 (23.0–24.9)	31.8 (30.6–33.1)	24.2 (23.3–25.1)	20.9 (20.1–21.7)
Surgical							
Total, N (%)	552,971 (28.8)	64,983 (11.8)	190,225 (34.4)	254,336 (46)	43,426 (7.9)	295,660 (53.5)	257,287 (46.5)
Pneumonia, %*†	34.9	33.0	34.0	35.0	40.5	37.1	32.2
CHF, %*	27.2	8.9	21.7	33.3	42.6	26.7	27.7
ARDS, %*	45.5	51.5	45.2	44.7	42.7	45.0	46.1
Sepsis, %*	25.1	22.8	25.4	25.2	26.1	25.4	24.7
COPD, %*	8.2	1.1	7.4	10.8	7.5	8.3	8.1
AMI, %*†	16.9	4.9	17.0	19.8	17.9	19.1	14.4
Asthma, %*†	6.1	7.6	7.2	5.4	3.6	4.1	8.5
Stroke, %*	8.9	6.6	9.2	9.4	7.2	8.9	8.8
Trauma or burns, %*†	12.2	26.5	9.6	9.2	20.3	13.8	10.4
Cardiorespiratory arrest, %*†	5.5	4.4	6.0	5.4	5.2	6.1	4.7
Drug, %*†	0.5	1.3	0.7	0.2	0.2	0.4	0.6
IMV, %*†	52.9	57.1	54.3	51.3	50.0	54.5	51.0
NIV, %*	5.8	3.5	5.5	6.4	6.4	5.6	6.0
In-hospital mortality, % (CI)‡	18.6 (17.8–19.5)	10.7 (9.3–12.0)	15.5 (14.2–16.8)	20.8 (19.8–21.9)	29.4 (27.8–31.1)	19.0 (18.2–19.8)	18.3 (17.3–19.2)

NOTE: One patient can have more than 1 diagnosis.
 Abbreviations: AMI, acute myocardial infarction; ARDS, adult respiratory distress syndrome; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation. * $P < 0.0001$ for age group. † $P < 0.0001$ for gender. ‡The P values are not from Rao-Scott χ^2 test.

with NIV,³⁰ and advances in the care of critically ill patients such as the use of low-tidal volume ventilation.^{31,32} Another contributor may be an increase in the proportion of discharges to nursing facilities, although this change in discharge disposition cannot fully explain our findings. For example, from 2007 to 2009, mortality decreased by 2 percentage points, and nursing home discharges increased by only 0.4 per-

centage points. Growth and aging of the US population only partially explain the increase we observed in the incidence of ARF, as age- and sex-adjusted population rates increased by 56% from 2001 to 2009. In addition, the NIS captures data on hospital discharges and not individual patients; thus, a patient may have had multiple admissions. Over the last decade adoption of a more intensive practice style has been associated with improved in-hospital mortality,^{33,34} and although these patients may be living longer they may have multiple readmissions.^{35,36}

We also observed that older patients were less likely to be treated with IMV, had a higher mortality rate, and less expensive care. These results are consistent with other studies and suggest that the intensity of treatment decreases with increasing age, and decisions to withhold or withdraw life-supporting treatments are more frequent in the elderly.^{26,37} Prior research has shown that severity of illness is more important than age on patients' prognosis,^{38,39} and aggressive treatment strategies are not less cost-effective when provided to older patients.⁴⁰

Another important finding of this study is the marked increase in the use of NIV paired with a

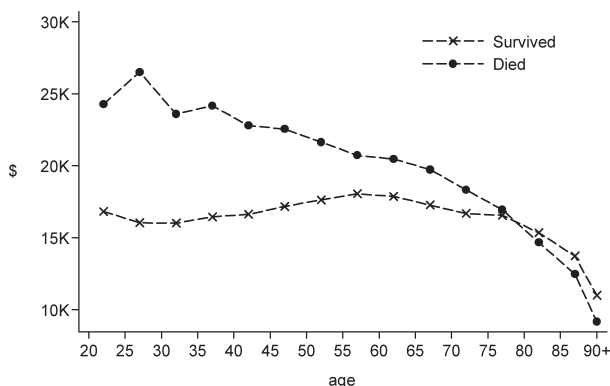


FIG. 2. Age-specific hospital cost per patient (geometric mean) stratified by surviving status.

modest reduction in the use of IMV in the treatment of patients with ARF. This finding adds to evidence from other studies, which have similarly reported a dramatic increase in the use of NIV and a decrease in the use of IMV in patients with COPD as well as in ARF of other etiologies.^{30,41}

Our work has several limitations. First, we identified ARF based on ICD-9-CM codes and therefore cannot exclude disease misclassification. We did not find any studies in the literature addressing the accuracy and the completeness of ARF coding. However, we employed the same codes used to define ARF as has been used to define organ dysfunction in studies of severe sepsis,^{17,20} and the ICD-9-CM codes that we used to identify cases of ARDS have been used in prior studies.^{11,22,23} Another limitation is that it is not clear to what extent the trends we observed may be due to changes over time in documentation and coding practices. Although this should be considered given the additional reimbursement associated with the diagnosis of ARF, our observation that rates of assisted ventilation have remained almost flat over the 9-year period of the study suggest that would not wholly account for the rise in ARF. Second, because we did not have access to physiological data such as results of blood gas testing, we could not determine whether the threshold for applying the diagnosis of ARF or for delivering ventilatory support has changed over time. Third, for the purpose of this study we employed a broad definition of ARF, not limiting cases to those requiring mechanical ventilation, and this led to a more heterogeneous cohort including less severe cases of ARF. However, this is not dissimilar to the heterogeneity in disease severity observed among patients who receive a diagnosis of heart failure or acute renal failure. Fourth, survivors of ARF remain at high risk of death in the months after hospitalization,⁴² but we assessed only in-hospital mortality. It is possible that although in-hospital mortality has improved, 30-day mortality remained stable. Finally, as the NIS contains only discharge-level data, we could not distinguish between patients admitted for ARF from those who developed ARF (potentially iatrogenic) after admission.

In summary, over the period of 2001 to 2009, there was a large increase in the number of patients given a diagnosis of ARF and a concomitant reduction in inpatient mortality. Although rates of mechanical ventilation remained relatively constant, there was a significant shift toward greater use of NIV at the expense of IMV.

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Dr. Stefan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: Mihaela S. Stefan, Penelope S. Pekow, Michael B. Rothberg, Jay Steingrub, Peter K. Lindenauer; analysis and interpretation: Meng-Shiou Shieh, Mihaela S. Stefan, Penelope S. Pekow, Michael B. Rothberg, Tara Lagu, Peter K. Lindenauer; drafting the manuscript for important intellectual content: Mihaela S. Stefan, Penelope S. Pekow, Michael B. Rothberg, Jay Steingrub, Tara Lagu, and Peter K. Lindenauer.

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