

Commentary

Contributions to the epidemiology of acute respiratory failure

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Abstract

Recently, incidence ranges for acute respiratory failure (ARF), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in adults were reported and found to be 77.6–88.6, 17.9–34.0, and 12.6–28.0 cases/100 000 population per year, respectively. Mortality rates of approximately 40% were reported for patients with acute respiratory failure, and similar or slightly lower rates for those with ALI and ARDS. Some experts believe that there is a trend toward lower mortality rates in ALI and ARDS, but this suggestion has not been scientifically validated. Additional organ failures, but not oxygenation indices, appear to be crucial with regard to predicting outcome. Finally, it has remained uncertain whether there exists seasonal variability with respect to the frequency of various forms of respiratory failure.

Keywords acute lung injury, acute respiratory distress syndrome, acute respiratory failure, epidemiology, mortality

Introduction

For the intensivist with an interest in epidemiology, the recent report from Flaatten and coworkers [1], published in this issue of *Critical Care*, may serve as a focal point that highlights several interesting features of that special field. These include but are not limited to incidence figures and mortality rates for acute respiratory failure (ARF), the contribution of additional single organ failures or multiple organ dysfunction syndrome to mortality, the difficulties of comparing results of epidemiological studies, and chances missed to address urgent questions. In this commentary I highlight these and thereby, hopefully, enhance our understanding of the often complex associations that epidemiologists and readers of epidemiological articles will encounter from time to time.

First, however, I summarize the main findings of the report under discussion. In a 30-month prospective cohort study, of 832 adult patients treated in a Norwegian intensive care unit (ICU) 63% had severe ARF according to the Sequential Organ Failure Assessment (SOFA; i.e. a ratio of arterial oxygen tension [PaO_2] to fractional inspired oxygen [FiO_2]

≤ 200 mmHg [≤ 26.6 kPa] with respiratory support). If no additional organ failures occurred then the ICU mortality rate for ARF was 3.2%, and hospital and 90-day mortality rates were 14.7% and 21.8%, respectively. However, if severe ARF was accompanied by other organ failures then mortality increased with each additional organ failure, and was as high as 75% when five or six organs were in failure.

Incidence figures and mortality rates for acute respiratory failure

Incidence figures for various forms of ARF have come under intense scrutiny in recent years because they may allow assessment of the magnitude of public health consequences, permit observation of temporal, geographic and demographic variations, and inform decisions on distribution of hospital resources. A consensus definition for ARF is not yet available. However, two European studies, one in 72 ICUs in Berlin, Germany [2] and the other in 132 ICUs in Sweden, Denmark and Iceland [3], were conducted that used the same definition (intubation and mechanical ventilation for ≥ 24 hours); both employed a multicentre approach and included large patient cohorts, and both studies were

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ARF = acute respiratory failure; ICU = intensive care unit; FiO_2 = fractional inspired oxygen; PaO_2 = arterial oxygen tension; SOFA = Sequential Organ Failure Assessment.

conducted over 2 months. They found very similar incidences of ARF, namely 88.6 [2] and 77.6 [3] cases per 100 000 population per year. Regarding acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), several studies that were conducted all around the world and used the definitions provided by the American–European Consensus Conference on ARDS [4] found incidence ranges of 17.9–34.0 and 12.6–28.0 cases per 100 000 population per year, respectively [3,5,6].

Because incidence figures for a whole country or larger region may not correlate with the number or percentage of patients actually found in a given ICU, studies that examine the prevalence of various forms of ARF are helpful in estimating resource allocation and utilization. Some complex calculations may be required to determine whether more ARF patients were treated in one ICU than in another. In this context, it is difficult to compare the data provided by Flaatten and coworkers [1] (63% of their cohort of 832 adult ICU patients had severe ARF, according to their SOFA grade of 3–4) with, for example, the 1.7% ALI patients and 6.9% ARDS patients that were recently identified by Roupie and coworkers [7] in their 14-day prospective cohort study conducted in 36 French ICUs.

Finally, until now, no epidemiological study has assessed incidence according to the SOFA criteria for respiratory failure. However, interesting prevalence data are available from a study conducted by Pettilä and colleagues [8]. In 520 Finnish ICU patients, evaluated over a 1-year period, 169 (32.5%) fulfilled SOFA criteria for ARF (3 of a maximum 4 points) and/or had additional renal, haematological, hepatic, circulatory, and neurological organ failures. Nearly double the percentage (63%) of ARF patients fulfilling the same criteria were identified by Flaatten and coworkers [1]. This difference is difficult to explain. I speculate that it is based on a different patient case mix.

Currently, with no consensus definition for ARF available, the best estimates of ARF mortality rates stem from the Berlin [2] and Scandinavian [3] studies, namely 42.7% (ICU mortality) and 41% (90-day mortality), respectively. The hospital mortality rate for ARF (defined according to SOFA definitions) in the study conducted by Flaatten and coworkers [1] for the overall population was 32.9%. In the Finnish study by Pettilä and coworkers [8], an overall hospital mortality rate for ARF of 46% was reported. In summary, the reported mortality rates for ARF are of the same order of magnitude, although significant differences in study design and definitions applied are obvious.

Surprisingly, in the 24 patients with isolated pulmonary failure in the Finnish study [8] the hospital mortality rate was only 17%. Similarly, in the study by Flaatten and colleagues [1] ICU mortality and hospital discharge mortality rates in patients with ARF as the only organ failure were 3.2% and

14.7%, respectively. The question arises as to why isolated respiratory failure leads to such relatively low mortality rates. Possible explanations are as follows. First, standard ventilatory treatment strategies are effective in treating patients with isolated respiratory failure, and other organ systems that are healthy may be better able to tolerate the well known adverse effects of mechanical ventilation. Second, the lung has a marked ability to recover its function. Finally, it is a well known fact that mortality in the ICU strongly depends on the presence or absence of multiple organ dysfunction [9]. Common sense suggests that the general rule of ‘many organ dysfunctions = bad prognosis’ may be equally valid when rephrased – ‘few organ dysfunctions = good prognosis’.

Of note, Flaatten and coworkers [1] reported different mortality rates at different time points. Mortality was lowest on ICU discharge, it rose on hospital discharge and it reached its peak when evaluated 90 days after diagnosis of ARF. This trend was also observed when patients were subgrouped according to the number of additional organ failures complicating ARF. These findings underscore the necessity to continue mortality assessment in clinical studies far beyond the time of discharge from the ICU. Many examples can be found in the published literature of studies that suggest that the risk for dying in the aftermath of ICU treatment for ARF is not comparable with that in the general population. In a recent study conducted in 347 patients requiring 14 days or more of mechanical ventilation [10], of the 208 patients who died 72% did so in the ICU and 28% between the first and 57th month after ICU discharge. Data from a long-term follow-up study suggested that mortality associated with ARDS continues for years after hospital discharge. In this context it has been calculated that clinical trials that use hospital mortality as an end-point will capture only 80% of all deaths, and those that use 100-day mortality will capture 89% [11]. The logical conclusion that should be drawn from these findings is that the period of observation following hospital discharge should be extended substantially. Organizational problems, bureaucratic barriers, and financial restraints, however, may limit researchers’ ability to follow up patients several years after survival from an episode of ARF.

For many years experts have discussed the issue of whether mortality rates in ARDS patients are declining. Since the 1992 American–European Consensus Conference on ARDS, most clinical series have continued to report a mortality rate of 40–60% in patients with ARDS [12]. There have been several recent lines of investigation that suggest that mortality from ARDS at some centres [13–15] may be falling. However, the broad applicability of these finding is unclear [16].

Multiple organ dysfunctions and severity of acute respiratory failure

Abnormal organ function may involve the liver, kidneys, cardiovascular system, brain, blood, and/or the immune

system. These organ dysfunctions may be related to the underlying illness or to the treatment, or they may occur through the same inflammatory process that injured the respiratory tract. Apart from the severity of the acute illness, dysfunctions of vital organs – especially when associated with severe sepsis or septic shock – and pre-existing diseases significantly contribute to the observed high mortality rates in patients with ARF [7,17–19].

The role of the severity of ARF itself is under discussion. It may depend on the indicator used to assess this severity. The prognostic value of the $\text{PaO}_2/\text{FiO}_2$ ratio, which is used, for example, in SOFA, has been subjected to particular scrutiny. Most authors have not found this variable to be of prognostic significance [19–21]. In accordance with the latter findings is that ALI and ARDS, although they are distinguished by different $\text{PaO}_2/\text{FiO}_2$ cutoff points, have similar outcomes [3,6]. In this context it is worth mentioning that, in the recent ARDS Network Trial on low versus traditional tidal volumes [22], better oxygenation was observed in patients treated with large tidal volumes during the acute phase of ALI/ARDS. However, mortality in the latter group was significantly higher than in those patients treated with low tidal volumes and a worse $\text{PaO}_2/\text{FiO}_2$. This does not mean that sufficient oxygenation is an inferior goal of treatment in ARF patients. Data reported by Hopkins and associates [23] showed that, in ARDS, there were significant correlations between the amount of time that arterial oxygen saturation was below 90%, below 85% and below 80% during the acute phase of the illness and various cognitive skills assessed 1 year later. This added to earlier work that had demonstrated the relation between hypoxic brain injury, hippocampal atrophy and memory deficit [24].

Chances missed

Until now it has remained uncertain whether there exist statistically significant differences in the monthly incidences of adult ARF and ALI. Although common sense dictates that there are more ARF cases in the winter months, this assumption has not been scientifically confirmed. The key underlying problem is that all epidemiological studies on incidence of ARF were conducted during relatively short time periods. Therefore, one would have wished that Flaatten and coworkers [1] had not missed their chance to report on seasonal variance of occurrence of ARF throughout their 30-month study period. With respect to ARDS, it was recently shown that no such monthly variation exists [25]. Because the patient population was rather small ($n=66$) in that study, confirmation in a larger patient cohort is needed.

Conclusion

The study by Flaatten and coworkers [1] substantially contributes to our knowledge of ARF epidemiology. It highlights the crucial role of additional organ failures in the setting of ARF. The data suggest that rather low mortality rates can be expected when the patient suffers from isolated

respiratory failure but that these increase exponentially when additional organ dysfunctions occur. Furthermore, it has again been shown that there exists ongoing mortality in ARF patients following their discharge from the ICU. Consequently, researchers should seek to assess mortality at ICU discharge, hospital discharge, after 90 days, and ideally after 6–12 months. One would also hope that the issue of seasonal variability with respect to the frequency of various forms of ARF will be addressed by systematic studies in the near future.

Competing interests

None declared.

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