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ORIGINAL ARTICLE

Causes of death in intensive care patients with a low APACHE II score

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ABSTRACT

Background: Little is known about the actual causes of death of patients with a low APACHE II score, but iatrogenic reasons may play a role. The aim of this study was to evaluate the demographics, course of disease, and causes of death in this specific group of ICU patients.
Methods: For this retrospective observational study, adult patients (>18 years) admitted to the ICU were included.
Results: During the 47-month study period, 9279 patients were admitted to our ICU, of which 3753 patients had an APACHE II score ≤15. Of the latter group of patients, 131 (3.5%) died during their hospital stay. Their median (IQR) APACHE II was 12 (11-14) and their main reason for ICU admission was respiratory insufficiency (47%). Both in patients with and without limited therapy, haemodynamic insufficiency was the main cause of death (50 and 69%, respectively). Three patients died directly related to medical interventions.
Conclusion: Most patients with an APACHE II score lower than 15 who died were admitted to the ICU because of respiratory insufficiency. The main cause of death was haemodynamic insufficiency following limited therapy because of an unfavourable prognosis. In less than one out of 1000 cases of this low-risk group of patients death was related to iatrogenic injury.

KEYWORDS

APACHE, causes of death, iatrogenic disease, intensive care, mortality

INTRODUCTION

The Acute Physiology and Chronic Health Evaluation II (APACHE II) system is a severity of disease classification system for adult patients admitted to the intensive care unit (ICU). The APACHE score, based on several patient characteristics (including age and comorbid conditions) and 12 physiological parameters obtained during the first 24 hours following ICU admission, represents the severity of illness and is closely correlated with hospital mortality.[1] However, the APACHE II score should not be used for individual treatment decisions.[2] There is a good correlation between the APACHE II score and risk of death in large groups of patients, but the individual mortality risk predicted by the score varies considerably with the underlying diagnosis.[3] Although the APACHE II score has a moderate predictive accuracy,[1,4,5] it appears superior compared with other scoring systems.[6-9] The APACHE II score has proven its value for monitoring quality of care and for conducting clinical studies as it enables comparison of outcomes among groups of critically ill patients.[1,10]

According to the original database, hospital mortality of patients with an APACHE II score of 15 is up to 21%.[1] Other factors, not included in the APACHE II scoring system, seem to play a role in the mortality outcome for this low-risk group of patients. Although the role of the APACHE II score in prediction of death has been studied widely, we are not aware of any studies that examined the causes of death in patients with a low APACHE II score. Our hypothesis is that iatrogenic causes could be a potentially relevant factor and that a more detailed analysis of this group of patients may function as a valuable quality control measure. The aim of the present study is to describe the demographic characteristics, courses of their disease, and cause of death in this specific group of patients with a predicted low mortality rate.

MATERIALS AND METHODS

Patient population

We retrospectively evaluated the medical records of all patients admitted to the adult ICU of Radboud University Nijmegen Medical Centre between January 2004 and December 2008 with an APACHE II score ≤15 who died during their hospitalisation up to 30 days after being discharged from the ICU. For all patients, the APACHE II score was manually recalculated from the worst physiological and laboratory parameters in the first 24 hours after ICU admission. Patients who were admitted to the ICU more than once within 30 days were evaluated based upon their APACHE II score during their first ICU stay.

Data collection

Medical records were examined by one of three investigators for each patient. Pre-admission data were documented in a case record form to minimise inter-observer variability. Collected data included patient demographics such as age, sex, height and weight. The recalculated APACHE II score was documented, along with the date of admission, diagnosis at admission, reason for ICU admission, type of admission (elective versus emergency) and comorbidities.
Comorbidities were defined in relation to a specific index condition according to the seminal definition of Feinstein.[11] The question which condition should be designated as the index and which as the comorbid condition is not always self-evident and was therefore defined as the disease that prompted the need for critical care. Indexes were classified according to organ system as were any distinct additional entities. Once included in the study, the remainder of the case record form was designed to register a patient's course of disease (improving, stable or worsening), including possible risk factors related to death and complications.

Patients admitted to the ICU may be subject to many complications related to advanced monitoring and therapy. All relevant complications were assessed including possible medical omissions during a patient's ICU admission. Medical omissions were defined as the failure to do something required by the patient's condition in the acute situation, which may have contributed to the patient's death. Iatrogenic complications were defined as adverse effects that were not associated with the index condition or any of the patient's recorded comorbid conditions. These were likely related to medical treatment and resulted in either significant morbidity or mortality. Significant morbidity was defined as the need for reoperation, transfusion, systemic inflammatory response syndrome (SIRS), sepsis, acute respiratory distress syndrome, respiratory or haemodynamic insufficiency, continuous veno-venous haemofiltration or extra corporeal membrane oxygenation.
Data documentation was completed with registration of the number of admissions to the ICU, duration of the ICU stay in days, hospital mortality and cause of mortality. If available, the autopsy report was examined to obtain a better insight into the course of disease and cause of death. If clinical data were incomplete, the patient was excluded from the study. To ensure a uniform assessment of the gathered data, patient data and conclusions were reviewed by all three primary investigators. A database containing the data of all patients was used for further calculations.

Statistics

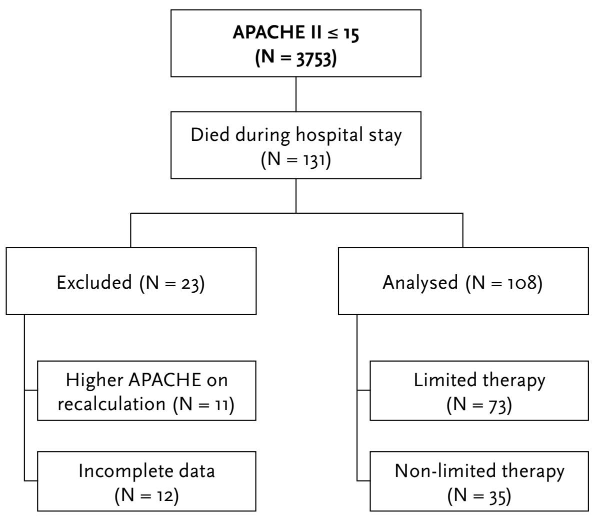
Calculations were computed using commercially available software (Excel, release 11.5.5, Microsoft Corporation). Data are expressed as number of patients (%), or median and interquartile range (IQR) or mean ± SD, depending on its distribution.

RESULTS

Demographic data

During the 47-month study period, 9279 patients were admitted to the ICU of the Radboud University Nijmegen Medical Centre, of which 3753 patients had an APACHE II score ≤15. Of 3753 patients, 131 (3.5%) died during their hospital stay. From this group of patients, 23 were excluded from further analysis, 11 because of an APACHE II score ≥20 after recalculation and 12 patients because of incomplete data. The remaining 108 patients who died were included in the study (*figure 1*). The median (IQR) APACHE II score of this group of patients was 12 (11-14). The demographic characteristics of the patients are illustrated in *table 1*.

Figure 1. *Flowchart of study population*



Reasons for ICU admission and length of stay

Indications for ICU admittance are depicted in *figure 2*. The most frequent indications for ICU admittance were respiratory insufficiency (47%), postoperative monitoring (27%) and haemodynamic instability (20%). The median (IQR) hospital length of stay was 13 (4-31) days, including 9 (3-7) days on the ICU.

Comorbidity and risk factors for complications or death

The three most frequently occurring comorbidities were circulatory (hypertension, ischaemic heart disease, atherosclerosis), respiratory (chronic obstructive pulmonary disease, pneumonia), and cancer, 68%, 22% and 22%, respectively (*table 2*). Besides these pre-ICU-admission risk factors, several risk factors occurred during the ICU stay. The most frequent risk factor was the use of vasoactive medication (74%). The other monitored risk factors during the ICU stay are listed in *table 2*.

In 77% of the cases, the cause of death was directly related to the ICU admission diagnosis. In 23% of the patients, death was due to development of a new diagnosis during ICU stay or unexpected complications. In this group relevant complications were bleeding, vascular insufficiency (ischaemia, necrosis), renal failure, brain damage and multi-organ dysfunction syndrome.

Table 2. *Comorbidity and risk factors for complications or death*

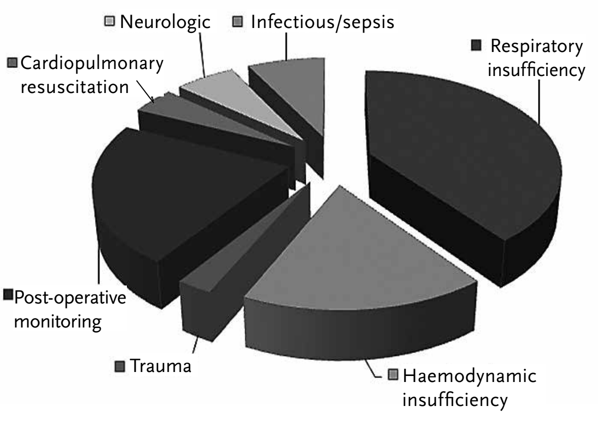
Variable	N (% of cases)
Chronic comorbidity	
Haemodynamic problems	73 (68%)
Cancer	24 (22%)
Respiratory problems	24 (22%)
Neurological status	21 (19%)
Infection	13 (12%)
Renal disease	12 (11%)
Immunosuppressive medication	7 (6.5%)
Diabetes mellitus	7 (6.5%)
Obesity	6 (5.5%)
Risk factors for complications	
Vasoactive medication	80 (74%)
Trauma	32 (30%)
Sepsis	16 (15%)
Cardiopulmonary resuscitation	10 (9%)
Mechanical ventilation	6 (5.5%)

Table 1. *Demographics characteristics of patients*

Variable	Value
Total number of patients	9279
Patient with APACHE ≤15	3753 (40.4%)
Number of patients who died	131 (1.4%)
Patients included	108
Sex	
Male	67 (62%)
Female	41 (38%)
Age (years)	61.6 ± 15.0
Height (cm)	171 ± 0.7
Weight (kg)	74.6 ± 1.9
BMI (kg/m^2)	25.4 ± 0.9
APACHE II	12 (11-14)
SAPS	43 (35-51)

Data are expressed as mean ± SD or median and interquartile range or as number (%).

Figure 2. *Reason for ICU admission*

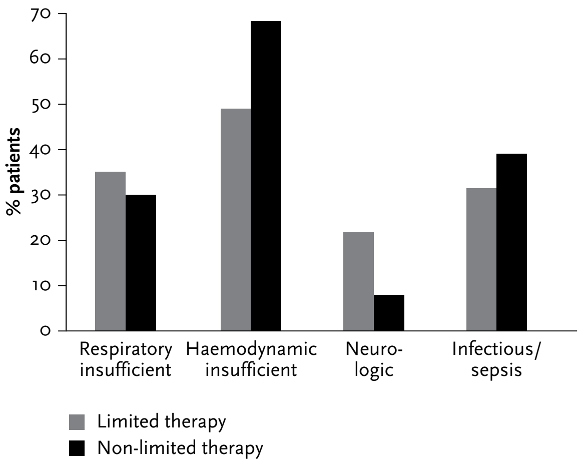


Mortality

Of the complete group of patients who died during hospital stay, 75% died in the ICU after 7 (IQR 3-15) days. The remainder of the patients died on the ward 8 (IQR 3-26) days after their ICU admission. Post-mortem examination was performed in 34% of the patients.

Seventy-three patients who died (68% of total) were judged to have an unfavourable prognosis and died following limitations of therapy (*figure 3*). It is true that the decision to limit therapy may eventually result in the death of a patient; however, this is not always the cause. To illustrate what percentage of patients die, e.g., of shock (e.g. following termination of vasopressor therapy), or because of respiratory insufficiency (e.g. following detubation), the consequence of limitation of therapy was taken as the ultimate cause of death in this group of patients. Shock related to low cardiac output or low blood pressure was labelled haemodynamic insufficiency, and this was the main cause of death in patients both with and without treatment limitations. Next were infectious causes and respiratory failure due to pneumonia, acute respiratory distress syndrome (ARDS), or exacerbation of their chronic

Figure 3. *Cause of death*



obstructive lung disease (COPD). These patients died with a clinical picture of hypoxia or hypercapnia.

In three patients an iatrogenic event was directly related to the death of the patient. One patient died of arterial pulmonary bleeding following Swan-Ganz catheter insertion on the Cardiac Care Unit. Another patient suffered from intestinal perforations due to abdominal surgery and died following abdominal septic shock. The third patient developed catheter-related bacteraemia with *Pseudomonas* spp. following renal replacement therapy and died of haemodynamic insufficiency. The courses of these patients are described as 'illustrative cases' and available in the online supplement.

DISCUSSION

To the best of our knowledge, this is the first study describing the course of disease and cause of death in ICU patients with a low risk of death as predicted by the APACHE II score. Major reasons to conduct this study were our interest in the fate of this category of patients and to examine our quality of care, as our hypothesis was that iatrogenic damage may be a potentially relevant factor in this low-risk group of patients. We found that most patients with an APACHE II score ≤15 who eventually died were admitted to the ICU because of respiratory insufficiency. In most patients, death was preceded by limitations of therapy because of a perceived unfavourable prognosis. Both patients with and without limited therapy ultimately died in the ICU because of haemodynamic insufficiency. Although medical records were analysed with special attention to complications of medical interventions and possible omissions related to the outcome of the patient, only three such cases were identified. To our knowledge, there are no reports that quantify the incidence of lethal complications of medical interventions. In our view, further insight into the reasons for death in patients with a low APACHE score could serve as an evaluation of the quality of care and more published data from other ICUs and countries is necessary to be able to benchmark different units.

The use of death among low-risk groups as a quality control is not a novel concept as shown in a study conducted by Hannan *et al.*[12] In this study they reviewed 8109 charts within a defined subset of in-hospital deaths in New York hospitals and found that patients who died in low-mortality risk groups (with a risk of death <0.5%) were 5.2 times more likely to be associated with quality of care problems than other patients who died. Other indications for 'care departed from professionally recognised standards' were: cardiopulmonary arrest (OR 3.4), renal failure (OR 3.2) and infection (OR 3.0).

However, our approach to use low Apache II scores for measuring quality of care in ICU patients is novel. The APACHE II score is extensively used in both research and the clinic, but so far no study has described the demographics and causes of death in patients predicted to have a small chance of dying. Two possibilities appear likely to explain the mortality in this group of patients. First, the APACHE score might lack specificity in certain groups of patients resulting in a false-negative prediction of a small chance of dying for a given patient. Second, the APACHE score was correct considering the condition of the patient during ICU admission, but a patient's condition can deteriorate during the ICU stay, resulting in his/her unfavourable outcome. In addition, as a recent study showed that the benefit of an ICU admission is substantially lower in patients with a lower severity of illness,[13] death due to iatrogenic reasons may play a role, especially in these patients with a low chance of dying.

Although in the majority of cases cause of death could be directly related to the conditions present during ICU admission, we observed a discrepancy between the primary reason for ICU admission, being respiratory insufficiency, and haemodynamic insufficiency as the most frequently observed cause of death. This is most likely related to the natural course of the disease. For example, in a pneumonia patient, the pulmonary problems may subside, while septic shock or multi-organ failure may become present in a later phase. Naturally, patient outcome not related to the reason for ICU admission is difficult to predict during the first 24 hours following ICU admission. While this was only the case in approximately a quarter of the patients, it does explain the limited predictive value of the APACHE score, especially in patients with a low score. Another example illustrating this issue concerns triage decisions. It was recently reported that of patients who were evaluated as 'too sick' or 'too old' to be admitted to an ICU, the 90-day survival rate on the general ward was approximately 20%.[13] It appears plausible that the survival percentage of the group of patients expected to have an unfavourable prognosis could have been higher if they had indeed been admitted to an ICU. Naturally, other factors that were not reported and that go beyond life expectancy, such as quality of life, may also have played a role in the decision not to admit a patient to the ICU. Nevertheless, findings such as these are of major importance to evaluate our processes of care. In the present study, most patients died following limitation of therapy. Although a decision to limit further therapy is carefully taken and always in consensus with the physicians involved, we must remain vigilant about its justice and correctness.

Several limitations of the study should be addressed. First, we acknowledge that the choice to use an APACHE ≤15 is completely arbitrary. Nevertheless, it appears unlikely that another cut-off value would alter the results to a significant extent. Second, inter-observer variability is a theoretical limitation. It is recognised that the APACHE score has a high inter-observer variation,[14] limiting the sensitivity and specificity of its predictive value. Importantly, we used data from the Netherlands Intensive Care Evaluation, for which training in data acquisition is mandatory and improvements of training have been determined.[15] In our study, the data were collected by three individual observers who were instructed on how to use the case record form. As we prospectively acknowledged that inter-observer variability might occur, patient data and conclusions were reviewed by all three primary investigators following data collection. Also, in patients for which an autopsy report was not available the cause of death was retrospectively retracted from the charts and reviewed by the investigators until consensus. In addition, it was not possible to analyse the consequences of nosocomial infections, drug interactions or side effects, nutritional disturbances, acid-base problems or psychological complications. Finally, this study is a single-centre study. Therefore, it may not allow generalisation to other centres due to institution-based differences in treatment, termination of treatment and admission policies.

In conclusion, most patients with a low APACHE II score who did not survive died following limitations of therapy. Haemodynamic insufficiency as a consequence of shock related to low cardiac output or low blood pressure was the main cause of death in this group. Without limitation of therapy haemodynamic insufficiency was also the main cause of death, followed by infection/sepsis and respiratory insufficiency. Only a small proportion of patients died directly related to iatrogenic events.

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