



Feature—Classic Papers

The Acute Physiology and Chronic Health Evaluation II article¹ of Knaus et al with expert commentary by Dr Derek Angus

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Abstract This paper presents the form and validation results of APACHE II, a severity of disease classification system. APACHE II uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. An increasing score (range 0 to 71) was closely correlated with the subsequent risk of hospital death for 5815 intensive care admissions from 13 hospitals. This relationship was also found for many common diseases. When APACHE II scores are combined with an accurate description of disease, they can prognostically stratify acutely ill patients and assist investigators comparing the success of new or differing forms of therapy. This scoring index can be used to evaluate the use of hospital resources and compare the efficacy of intensive care in different hospitals or over time.

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At the heart of optimal clinical medicine is the ability to prognosticate. Understanding a patient's likely outcome and how that outcome might change depending on alternative interventions is essential if care is to be optimized. Perhaps nowhere is this issue both more important and more difficult than intensive care. The intensive care unit (ICU) is home to a wide array of expensive technologies that can both help and harm the critically ill patient; ICU patients often have multiple complex conditions that make prognostication difficult, and decisions must be made rapidly and courageously as time is of the essence.

It is not surprising, therefore, that intensive care has seen the development of extremely sophisticated tools to aid clinicians in predicting outcome. A common theme to risk

prediction scores (or scoring systems) is their heavy reliance on acute derangement in physiology as predictors of subsequent survival. Acute Physiology and Chronic Health Evaluation (APACHE) II uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. An increasing score (range, 0-71) was closely correlated with the subsequent risk of hospital death for 5815 intensive care admissions from 13 hospitals. When APACHE II scores are combined with an accurate description of disease, they can prognostically stratify acutely ill patients and assist investigators comparing the success of new or differing forms of therapy. This scoring index can be used to evaluate the use of hospital resources and compare the efficacy of intensive care in different hospitals or over time.

Dr Knaus's APACHE II is one of the most widely quoted articles in all of medicine, let alone intensive care, and, more

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than 21 years after its publication, is still used to stratify patients in clinical trials throughout the world.

1. Dr Angus's commentary

It is hard to imagine critical care without APACHE II. Although all the articles in this series are “classics,” one can make a reasonable case that the APACHE II article is the single most important article in the history of critical care. Not only is it the most cited article in our field, it represents a revolutionary concept. Specifically, it demonstrates that acute physiologic derangement, age, and underlying comorbidity can be expressed together in a numeric score that predicts outcome, regardless of the reason for ICU admission. Thus, APACHE II allowed us to compare apples with oranges. Single-handedly, this idea has provided the foundation for an immense body of literature in critical care comparing patients across diseases, ICUs, and interventions. Although risk prognostication is still underdeveloped as a tool for live decision making, that too will likely change with advances in electronic medical records. As with other “sea-changes,” one struggles to even think about what life must have been like before APACHE II. The other testament to APACHE II is its sheer longevity. Although the mortality risk prediction now no longer calibrates very well with actual mortality, because of advances in care, the raw score remains a robust and common measure of severity of illness around the world. To paraphrase Newton, if we see further because we stand upon the shoulders of giants, then Knaus et al are surely some of our most prominent giants.



William A. Knaus

2. Dr Knaus answering Dr Al-Khafaji's questions

2.1. What was your position and where were you prior to conducting the study?

I was the codirector of the ICU at The George Washington University Hospital (GWUH), a position I had held since 1978. I also had completed my internal medicine residency and critical care fellowship at GWUH.

2.2. How long did it take you to think about the study?

We began work on APACHE in 1977 during my critical care fellowship. At that time, the concept of case mix adjustment was very new. Diagnosis related groups had been introduced, but there was little discussion of systematically measuring severity of illness. We realized, of course, that although diagnosis was important for an ICU patient, the acuity of their illness was the major factor—influencing prognosis and resource use. We wanted to develop a reliable and systematic way to measure severity so that outcomes from critical care could be more accurately assessed. We knew that this would be a complicated and multidisciplinary project, so I and my clinical colleagues, Jack Zimmerman and Elizabeth Draper, spent a great deal of time thinking about how the system might be designed and the professional skills required. We also started soliciting collaborators at the annual Critical Care Meeting in San Antonio, Tex, in 1978, and we introduced our first approach, APACHE I, in *Critical Care Medicine* [1]. APACHE I was based on 582 admissions from 2 hospitals, and it required data from 33 potential laboratory measures. We knew that a severity system that people could use when there were no electronic interfaces for laboratory or other clinical data needed to be streamlined. We also wanted to validate the relationship among APACHE scores and outcomes with a larger number of hospitals and patients. This prompted the design of APACHE II. APACHE II was based on data from 5815 patients treated at 13 institutions. APACHE II also reduced the amount of data required to 17 elements. So, by the time APACHE II was published in 1985, we had spent almost a decade thinking about and working on this challenge.

2.3. Why and how did you decide to perform the study?

I had a strong personal desire to achieve a better way of handling all the information that was available for the typical ICU patient. I wanted to improve our ability to be accountable for the substantial economic and human resources that intensive care demands; to describe patients in a way that would strengthen and support our deep respect for the individual and their right to choose; and to create outcome assessment system that could help improve future care.

All of these needs were brought dramatically home for me the first morning I was an attending faculty making ICU rounds. The patient was a young woman with severe sepsis after emergency surgery for an abdominal abscess. Admitted to the unit a few hours before, she was in severe circulatory collapse and there were dozens of pieces of article scattered throughout her room: the emergency room forms, the operating room log, the scattered recordings from consultants and nurses, and flow sheets. Realizing that, for the first time in my life, I was the individual ultimately responsible for her care, I really wanted to know exactly how ill she was and whether how treatments were effective in stabilizing and hopefully reducing her risk. I also knew that this kind of information, captured on all ICU patients, would make it possible to compare care, track outcomes, and better evaluate the quality and progress of intensive care throughout the world.

2.4. What were the challenges you faced during the study?

Soliciting collaborators and obtaining resources for a new idea is always challenging. We were very fortunate in receiving great collaborative support from the Critical Care Society and the 13 hospitals and their critical care units that formed the basis for APACHE II. They all collected high quality data without any direct financial support and were very committed to the success of the effort. We were also successful in obtaining federal funding initially from the forerunner of Centers for Medicare and Medicaid Services (Baltimore, MD), previously known as the Health Care Financing Administration, and then from the National Center for Health Services Research, now the Agency for Health Care Research and Quality (Rockville, MD). The Robert Wood Johnson Foundation was also very supportive over a sustained period of time. These ongoing collaborations and sustained financial support permitted us to bring high-quality analytic expertise, specifically Dr Douglas Wagner and then many others, to insure that APACHE used valid and contemporary analytic and computing approaches.

One interesting historical challenge was that, when we first began to work with what was then considered a very large patient data set, a few hundred patients, we had to run our analytic programs over weekends because of the demands on the university's computing capability. A Monday morning confronted with a programming error meant we had to wait another week to try again. Today, of course, data sets with hundreds of thousands of patients can be run on laptops in a manner of seconds.

2.5. How was the peer review process? Can you remember any discouraging comments?

I tried to find the original referee comments on APACHE II, but they have been long discarded. I do not remember the critiques being all that critical. It was only later when we were expanding and attempting to disseminate and support

the use of APACHE III did we receive very intense and at times highly critical comment on submitted manuscripts.

2.6. Was there any suspected or unsuspected setback?

No, in many ways, APACHE II represented the "honeymoon" period of our work. APACHE II was a severity measure based on physiology, validated well to patient outcomes, and simple to use. We had not used it to make comparisons among institutions or proposed it as a component of new practice, device, or drug evaluations. All of these later applications as well as subsequent attempts to improve on APACHE II with more accurate but also more complex models were when the going got a great deal tougher. In this regard, APACHE II was both our most widely known contribution and our greatest competition. Even today, in research efforts using APACHE to evaluate the efficacy of new drugs, we find that, despite its being badly outdated, people are still relying on APACHE II rather than the more accurate and updated versions such as APACHE III [2] or the very recently released APACHE IV [3].

There is confusion that these equations are not freely available, but if one goes to <http://www.cerner.com>, there are spread sheets for calculating both the hospital mortality and length of stay equations for these contemporary and more accurate tools.

2.7. Did you imagine that the article would have this great impact on practicing critical care physicians?

We certainly hope so. It was our intent and we are very gratified that it remains acknowledged over 2 decades later as an important contribution. I believe that the impact of the APACHE II was substantially enhanced by an article we published 2 years later in the *Annals of Internal Medicine* [4]. This article used APACHE II to compare mortality outcomes across the 13 original hospitals and made the provocative observation that the highest quality care was found in the unit that had the best coordination among nurses and physicians. The unit that lacked collaboration had the worst performance. There is now a substantial amount of evidence that collaboration matters. There also has been great work by the American Association of Critical Care Nurses (Alison Viejo, CA), the Society of Critical Care Medicine (Des Plaines, IL), and the Institute for Healthcare Improvement (Cambridge, MA) toward advancing this important aspect of critical care practice.

2.8. How did the study change your career?

It changed everything. From 1985 until 2000, when the APACHE methodology was sold to the Cerner Corporation (Kansas City, MO), working on improvements to the system, talking about its development, and encouraging and supporting its use in ICUs across the United States and throughout the world were my professional life. Through

these efforts, I was privileged to meet some of the most interesting and dedicated professionals in any field. I traveled to countries and continents and was introduced and welcomed into an international world of science and medicine. It was an exciting, inspiring, and challenging period of my life. I will always be in debt to the wonderful professionals that offered us their help and their friendship.

2.9. If you have to conduct the same study today, will you do anything different?

No. As mentioned hereinabove, for most of my career, APACHE II has been the most widely accepted version of the APACHE system. I recall a close friend and colleague returning from an aborted attempt to climb Mt Everest during which she was injured. When she awoke in the hospital in Katmandu, Nepal, the first thing she saw was a copy of the APACHE II scoring sheet taped to the wall. APACHE II helped establish severity measurement as a key component of the description and assessment of critically ill patients throughout the world. My colleagues and I could ask for no more than this in return for our efforts.

2.10. Do you have any additional comments?

APACHE II was one of the early applications on what is a never-ending exploration of how to describe severely ill patients in the most accurate and useful ways. We began the effort with 3 principles I listed hereinabove: a commitment to accountability, respect for the individual, and a belief that the future can be better. During this century, there will be greatly enhanced electronic data capture and a rapidly

growing capability to measure precise physiologic, biologic, and genetic markers. These will make our current descriptions of patient severity crude by comparison. So one of the great challenges facing biology and medicine during this century will center around detecting the intricate relationships among genetic, environmental, and lifestyle choices and common diseases and, most importantly, determining how such information can and should be used. As we said in the concluding paragraph of the APACHE II article,

Regardless of the number of patients studied . . . providing medical care to individuals will always require experienced clinical judgment and careful integration of objective data with other relevant information, such as the individual reaction and personal wishes of the patient.

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