Predicting outcome in critical care

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Each day, physicians decide which patients to admit to an Intensive Care Unit (ICU) and how vigorously to treat them. Such decisions are in large part based on outcome prediction, i.e., on the need or potential benefit of ICU treatment. Unfortunately, the rapid advances in diagnostic and therapeutic technology have rarely been evaluated rigorously to define their specific value for patient care. Instead, philosophy, logic and pragmatism have dictated that many of these new technologies and the patients who might benefit from them be concentrated within ICUs.

Why do we need to improve our ability to predict outcome? The first reason is so we can treat more precisely individual patients, ensuring they receive all necessary treatment but avoiding futile care. The second reason is so we can do a better job of comparing the performance and quality of intensive care units. To achieve this goal of predicting outcome within a diverse ICU patient population, we need to understand clearly the factors that determine patient outcome.

Factors influence outcome

When an acutely ill individual is admitted to an ICU, his or her outcome will be primarily determined by the factors listed in Table I. Together these factors represent a conceptual model for assessing outcome. The following sections review important concepts about measuring each of these factors in outcome prediction.

Type of disease

A careful, objective and reproducible method for describing disease is the foundation of any attempt to predict outcome. This is because, inherent in our labelling of disease, we incorporate knowledge of aetiology when it is known and, for selected diagnoses, such improved information leads to better treatment. Disease labelling should be natural. It should recognize the basic mechanism or aetiology of the disease and the major organ systems involved. This concept of labelling disease using aetiology and organ system has recently been reviewed by

Gonnella *et al.*¹ Their approach meets two other important criteria for a good disease classification system. First, it is exhaustive; i.e., all potential patients can be classified. Secondly, it is disjointed, implying that a patient will always be classified into one category; e.g., a patient with septic shock always has an infectious aetiology involving the cardiovascular system.

Physiologic reserve

The ability to survive an acute illness is also related to a patient's condition before its onset. Previous analyses have documented the independent impact of advanced chronologic age on the ability of ICU patients to survive acute illness.² This is most likely due to the decrease in organ system function that accompanies aging.³ Age, however, is not a sensitive indicator of physiologic reserve since there are wide variations among individuals with the same chronologic age.

Chronic health problems (e.g., severe emphysema or cirrhosis) can also accelerate the loss of physiologic reserve and thereby decrease the probability of survival. Unfortunately, we lack objective, reliable methods for measuring the impact of chronic organ system dysfunction on physiologic reserve. As is the case with disease classification, currently we must rely on relatively crude definitions of these important measures of co-morbidity.

Severity of disease

For most critically ill patients, severity of disease is defined by focusing on the extent of injury, impact on function, or the degree of physiologic disturbance. Among trauma patients, for example, the extent of injury has been defined by the Injury Severity Scoring System (ISS).⁴ For patients with acute burns, the Burn Index measures severity by taking into account the extent of surface area burned.⁵ The level of neurologic function is the major determinant for assessing severity of acute head injury using the Glasgow Coma Score.⁶

TABLE I Factors influencing outcome

Patient factors	Treatment factors
Type of disease	Type of therapy
Physiologic reserve	Amount of therapy
Severity of disease	Application of therapy
Response to therapy	

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PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE				
	+4	+3	+2	+1	0	-1	-2	-3	-4	
TEMPERATURE — rectal (°C)	≥ 41*	39*–40.9*		38.5*–38.9*	36*–36.4*	34*–35.9*	32*–33.9*	30*–31.9*	≤ 29.9*	
MEAN ARTERIAL PRESSURE — mm Hg	≥ 160	130–159	110–129		70–109		50–69		≤ 49	
HEART RATE (ventricular response)	≥ 180	140–179	110–139		70–109		55–69	40–54	≤ 39	
RESPIRATORY RATE — (non-ventilated or ventilated)	≥ 50	35–49		25–34	12–24	10–11	6–9		≤ 5	
OXYGENATION: A-aDO ₂ or PaO ₂ (mm Hg)										
a. FIO ₂ ≥ 0.6 record A-aDO ₂	≥ 500	350–499	200–349		≤ 200					
b. FIO ₂ ≤ 0.6 record only PaO ₂					PO ₂ > 70	PO ₂ 61–70		PO ₂ 55–60	PO ₂ < 55	
ARTERIAL pH	≥ 7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	≤ 7.15	
SERUM SODIUM (mMol/L)	≥ 160	160–179	150–159	150–154	130–149		120–129	111–119	≤ 110	
SERUM POTASSIUM (mMol/L)	≥ 7	6–6.9		5.5–5.9	3.5–5.4	3.3–4	2.5–2.9		≤ 2.5	
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥ 3.5	2–3.4	1.5–1.9		0.6–1.4		≤ 0.5			
HEMATOCRIT (%)	≥ 60		50–59.9	46–49.9	30–45.9		20–29.9		≤ 20	
WHITE BLOOD COUNT (total/mm ³) (in 1,000)	≥ 40		20–39.9	15–19.9	3–14.9		1–2.9		≤ 1	
GLASGOW COMA SCORE (GCS) Score = 15 minus actual GCS										
A) Total ACUTE PHYSIOLOGY SCORE (APS) Sum of the 12 individual variable points										
Serum HCO ₃ (venous mMol/L) (Not preferred, use if no ABGs)	≥ 52	41–51.9		32–40.9	22–31.9		16–21.9	15–17.9	≤ 15	

B) AGE POINTS:
Assign points to age as follows:

AGE (yrs)	Points
≤ 44	0
45–54	2
55–64	3
65–74	5
≥ 75	6

C) CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:

a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:
LIVER: Biopsy proven cirrhosis and documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.
RENAL: Requiring chronic dialysis.
IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g. immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemic, lymphoma, AIDS.

APACHE II SCORE
Sum of A) + B) + C)

A) APS points: _____

B) Age points: _____

C) Chronic Health points: _____

Total APACHE II: _____

FIGURE 1 The APACHE II severity of disease classification system.

For the vast majority of ICU patients, severity of disease implies the degree of physiologic disturbance and is measured by acute physiologic changes. Which physiologic measures to use and how much importance or weight to give each one are important decisions. There are two major ways these weighting decisions can be made.

The first is to select the physiologic variables before you study the patients and decide the importance of each one by using past studies or expert opinion. This is the approach used in the acute physiology score of the APACHE II severity of disease classification systems (Figure 1), and in other systems based on APACHE's principles.^{7–9}

The second is to examine a large number of critically ill patients whose outcome is known, divide them into survivors and non-survivors, and then contrast the physiologic characteristics of the two groups. The physiologic measures are then given weights or importance based on how often they were associated with survivors versus non-survivors. This is the method used by Shoemaker *et al.*,¹⁰ and more recently by Teres *et al.*¹¹

In principle, both methods and various combinations of the two are correct. A few precautions, however, should be kept in mind. First, selection and weighting by

computer requires testing or validation in two independent groups of patients — the group from which the physiologic data was first obtained, and then an independent validation group. If the objective of severity measurement is to predict patient outcome by estimating risk of death prior to treatment, neither method should rely extensively on physiologic or other information collected over time. This confuses severity measurement with a different prognostic indicator — response to treatment.

Response to therapy

Predictive accuracy is limited by our incomplete understanding and description of the patient factors that determine outcome. One way to increase precision is to use information obtained after we begin treatment. This is collected best using physiologic data rather than the therapy used, since not all patients are treated in the same way. Standard physiologic data over time (for example, the number and type of organ system failures) enable you to calculate daily estimates of the probability of survival.

Treatment-type, amount and application

Studies comparing the type, skill and timing of intensive medical therapy indicate wide variations in

practice at different institutions.¹²⁻¹⁴ Such variations make it mandatory to closely examine treatment variations when evaluating outcome. The type and amount of treatment is best measured using the Therapeutic Intervention Scoring System (TISS).^{15,16} TISS uses assigned weights from 0 to 4 to grade 76 therapeutic, diagnostic, and monitoring tasks commonly used in ICUs. It is essential, however, to keep patient and treatment factors separate. We cannot evaluate the impact of therapy if we use treatment factors as part of our description. We also cannot rely too heavily on specific treatment factors to estimate individual prognosis since this would require identical treatment for all critically ill patients.

Information on the timing and process of treatment is also essential when assessing patient outcome. This is because variations in the skillfulness of medical care can markedly influence prognosis. Timing of therapy, i.e., differences in the interval from onset of illness to the initiation of treatment, so-called lead time bias, should be carefully recorded.¹⁷ If some ICU patients are extensively treated and stabilized prior to ICU admission while others are promptly admitted, differences in admission status may reflect variations in institutional practice rather than individual patient risk. Part of this problem can be overcome by precisely measuring the time interval between onset of illness and ICU treatment.

Types of predictions

Outcome estimates for critically ill patients usually have two distinctly different purposes: outcome prediction for groups of acutely ill patients and outcome prediction for individual patients.

For group prognostication, information about disease, physiologic reserve, and severity of disease is usually available before admission to an ICU. We can use these factors to prognostically stratify or rank patients by their relative risk of death prior to treatment. Information on response to therapy is only available after we have begun to treat the patient. When combined with information about therapy, these factors can provide prognostic estimates for similar patient groups in the future.

The principles employed in risk stratifying groups of patients are also useful when estimating prognosis for individuals. An important distinction, however, is the relative precision in estimating how much of the variation in outcome the results explain. When comparing groups, we are willing to accept substantial degrees of unexplained variation since we are interested in group risk. When estimating prognosis for individuals, we demand much greater precision. This is especially true when the prediction is used to supplement decisions to either limit or stop treatment.

Statistical confidence in prediction

Regardless of the method chosen to measure patient

TABLE II Statistical confidence levels in relation to number of patients in an outcome study*

<i>Number of patients studied with no survivors</i>	<i>Maximum probability of survival for next patient†(%)</i>
10	30.0
20	15.0
30	10.0
50	6.0
100	3.0
1000	0.3

*Adapted from Hanley and Lippman-Hand¹⁸.

†Each estimate based on the upper 95 per cent confidence limits.

outcome, the number of patients upon which estimates of survival are based is critical. It is statistically impossible to ever state that an individual will or will not survive based on the records of previous patients. The most that can be said is that, considering past experience, no individual with a given set of characteristics survived, i.e., survival was unprecedented but not impossible. The confidence with which one can make such a statement varies directly with the number of patients studied.¹⁸ Examples of the relationship between the size of a group studied without any survivors and the maximum statistical probability of survival are given in Table II. From this table, you can see that even though there are no survivors among 1,000 patients studied, the maximum estimated mortality rate is still less than 100 per cent.

Prediction of group outcome

By collecting information on risk factors such as disease, severity of disease, and physiologic reserve, one can prognostically stratify many patient groups prior to treatment. This provides an estimate of the relative risk of death for patient groups with similar characteristics. By helping to answer the question "Were the control and treatment groups similar?", risk stratification can improve the precision of clinical research.

One of our recent studies illustrates the value of a group prediction approach. We evaluated outcome and compared treatment of 5,030 ICU patients at 19 ICU's in 13 U.S. hospitals.¹⁴ At the time of ICU admission, we prognostically stratified each hospital's ICU patients by their risk of death using disease and APACHE II score which incorporated information on severity, age, and chronic health status.

We used these individual pre-treatment risk assessments to predict the number of patients that would have died at each hospital, assuming their quality of care was average, and compared this prediction to the actual hospital death rate. We found one hospital performed significantly better ($p < 0.001$) than all others with an actual hospital death rate 41 per cent lower than predicted. Another hospital's performance was significantly inferior

Number of OSF	Day of Failure							
		1st	2nd	3rd	4th	5th	6th	7th
1	Percent Mortality*	22%	31%	34%	35%	40%	42%	41%
	No. Deaths	450	261	204	159	142	118	80
	No. Patients	2070	847	607	455	356	279	195
2	Percent Mortality*	52%	67%	66%	62%	56%	64%	68%
	No. Deaths	239	147	103	118	96	78	56
	No. Patients	458	219	156	191	171	122	82
≥ 3	Percent Mortality*	80%	95%	93%	96%	100%†	100%†	100%†
	No. Deaths	152	70	50	50	38	33	32
	No. Patients	191	74	54	52	38	33	32

FIGURE 2 Hospital mortality according to number and duration of organ system failure.

*To calculate confidence level: 95% confidence level (± 2 standard deviation [SD])

$$1SD = \sqrt{N P Q}$$

N = total number; P = percent death rate; Q = 1 - P.

For a patient with ≥ 3 OSF on the 4th day of OSF, N = 52, P = 0.96, Q = 0.04; therefore, $1SD = 1.4$ and $1.4/52 = 2.7\%$, so $\pm 2SD = 96\% \pm 5.4\%$.

Therefore, the next patient to have ≥ 3 OSF on the 4th day of OSF has a projected death rate from 90.6 to 100%. (Use of poisson distribution yields equivalent results).

†Survival unprecedented with maximal statistical probability of survival of 10% (with 95% confidence).

Projections are based on 2,719 patients from 13 hospitals. For definition of OSF, see text.

with 58 per cent more deaths than expected ($p < 0.01$).

Each hospital's performance appeared to be related to the involvement and coordination of their intensive care unit teams and the process of care – not to the administrative structure of the unit, the amount of unique ICU treatment used, or the hospital's teaching status. These findings suggest that the effectiveness of intensive care is now substantially influenced by the process of care and this may vary greatly between hospitals.

Prediction of individual outcome

As experience with life supportive technology has grown, it has become obvious that mechanical and pharmacological support of physiological function is not curative. Life support buys time – time during which the primary disease can be identified and treated. When this is not possible, treatment initially directed at saving a life may instead only prolong the dying process.¹⁹ Decisions to limit or withdraw life supporting therapy are plagued with uncertainty. One response to such uncertainty is to supplement clinical decisions by using objective estimates of prognosis.

A landmark in this regard was the definition of irreversible coma by the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death.²⁰ More recently, Levy *et al.*^{21,22} have suggested a useful and accurate method for predicting poor outcome from hypoxic-ischaemic coma. Prognostic estimates are based on repeated neurologic evaluation

at admission, day 1, 3, and 7. The outcome predicted is neurologic status at one year classified according to three categories: no recovery or vegetative state; severe disability; and moderate disability or good recovery. Outcome estimates are provided according to both neurologic findings and the time of examination relative to admission. The most important result of this analysis was that predictions for no recovery or a vegetative state included few individuals (three per cent) who subsequently regained independent function.

We recently linked the number and duration of organ system failures (OSFs) to outcome at hospital discharge for each of 2,719 ICU patients.²³ For all medical and most surgical patients, a single OSF lasting more than one day resulted in a mortality rate approaching 40 per cent. Among both medical and surgical patients, two OSFs for more than one day increased death rates to 60 per cent. Mortality for 99 patients with three or more OSFs persisting after three days was 98 per cent. Because these estimates were obtained using previously derived, easily reproducible definitions of OSF that were based on objective physiologic measurements, they can be directly applied to similar patients. The estimates were obtained from a sufficient number of patients that the confidence levels are adequate for use in individual decision making (Figure 2).

Conclusion

This summary suggests that the systematic collection of

objective information on a patient's disease, the acute severity of the disease, their physiologic reserve and their response to treatment can improve our ability to predict outcome for critically ill ICU patients. These predictions can then be used to evaluate the quality of ICU services and improve the precision of treatment for individual patients.²⁴

References

- Gonnella JS, Hornbrook MC, and Louis DZ. Staging of disease. A case-mix measurement. *JAMA* 1984; 251: 637-44.
- Scheffler RM, Knaus WA, Wagner DP *et al.* Severity of illness and the relationship between intensive care and survival. *Am J Publ Health* 1982; 72: 449-54.
- Kenney RA. Physiology of aging: a synopsis. Year Book Medical Publishers Inc., Chicago, 1982.
- Baker SP, O'Neil B, Haddun W *et al.* The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974; 14: 187-96.
- Feller I, Tholen D, Cornell RG. Improvements in burn care, 1965 to 1979. *JAMA* 1980; 244: 2074-8.
- Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974; 2: 81-3.
- Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE - acute physiology and chronic health evaluation: a physiologically-based classification system. *Crit Care Med* 1981; 9: 591-7.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818-29.
- LeGall JR, Loirat P, Alpertovich A *et al.* A simplified acute physiology score for ICU patients. *Crit Care Med* 1984; 11: 975-7.
- Shoemaker WC, Appel P, Bland R. Use of physiologic monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. *A J Surg* 1983; 146: 43-50.
- Lemeshow S, Teres D, Pasioes H *et al.* A method for predicting survival and mortality of ICU patients using objectively defined weights. *Crit Care Med* 1985; 13: 519-25.
- Jennett B. Outcome of intensive therapy for severe head injuries: an inter-center comparison. *In: Major Issues in Critical Care Medicine*. Baltimore: Williams and Wilkins, 1984.
- Zimmerman JE, Knaus WA, Sharpe SM *et al.* The use and implications of do not resuscitate orders in intensive care units. *JAMA* 1986; 255: 351-6.
- Knaus WA, Draper EA, Wagner DP *et al.* An evaluation of outcome from intensive care in major medical centers. *Ann Intern Med* 1986; 104: 410-8.
- Cullen DJ, Civetta JM, Briggs BA *et al.* Therapeutic Intervention scoring system: a method for quantitative comparison of patient care. *Crit Care Med* 1974; 2: 57-60.
- Keene AR, Cullen DJ. Therapeutic intervention scoring system: update 1983. *Crit Care Med* 1983; 11: 1-3.
- Feinstein AR, Horwitz RJ. Double standards, scientific methods, and epidemiologic research. *N Engl J Med* 1982; 307: 1611-7.
- Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything right? *JAMA* 1983; 249: 637-44.
- Jennett B. Inappropriate use of intensive care. *Br Med J* 1985; 289: 1709-11.
- Beecher HK, Adams RD, Barger CA *et al.* Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death: a definition of irreversible coma. *JAMA* 1968; 205: 337-40.
- Levy DE, Bates D, Caronna JJ *et al.* Prognosis in non-traumatic coma. *Ann Intern Med* 1981; 94: 293-301.
- Levy DE, Caronna JJ, Singer BH *et al.* Predicting outcome from hypoxic-ischemic coma. *JAMA* 1985; 253: 1420-6.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ system failure. *Ann Surg* 1985; 202: 685-93.
- Knaus WA, Zimmerman JE. Prediction of outcome from intensive care. *Clinics in Anaesthesiology* 1985; 3: 811-29.