Quality of Life and Longer Term Outcomes

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Learning Points

1. Longer-term outcome following ICU may be examined from the perspective of the patient, attendant staff or society. All of these perspectives are different and will require different measurement tools
2. Long term follow-up of critically ill patients should be extended until the gradient of their survival curves parallels that of a comparison group. This may require follow-up for up to four or more years and is probably country specific
3. The selection of a comparison group requires carefully consideration. Patients admitted to ICU are not a random selection of the normal population and so comparisons with age and sex matched normal populations may not be valid. Diagnosis on ICU admission affects long term survival and so the comparison group should be similar in this respect
4. Functional outcome measures physical and mental capacity, neuropsychological function and recovery. Functional outcome has been widely measured outside critical care but the psychometric properties of assessment tools have not been rigorously reported for use in the survivors of critical illness

Figure 1 plots two possible outcomes for a critically ill patient following rupture of an abdominal aortic aneurysm. After a protracted ICU stay involving mechanical ventilation, renal replacement therapy and a further laparotomy for an ischemic sigmoid colon, the patient is discharged to the general ward where he develops a hospital-acquired chest infection. After two months in hospital, the patient is considered well enough to return home. However, he is weak, his limbs are stiff, and he is having problems coping with his colostomy; understandably he is anxious and depressed.

At this stage his clinical course could diverge to follow one of several outcomes. For example, shortly after hospital discharge, the patient could suffer a cerebrovascular accident and develop a dense hemiparesis. Although he is re-admitted to hospital, he remains aphasic and wheelchair bound. As he cannot return to his previous employment, he loses his income and subsequently his home. On the other hand the patient could continue to make a gradual improvement and be well enough to return to his previous job. Unfortunately he dies in a road traffic accident three months later.

This clinical history usefully illustrates some of the problems when measuring the longer-term outcomes following critical illness. At present, survival is mea-

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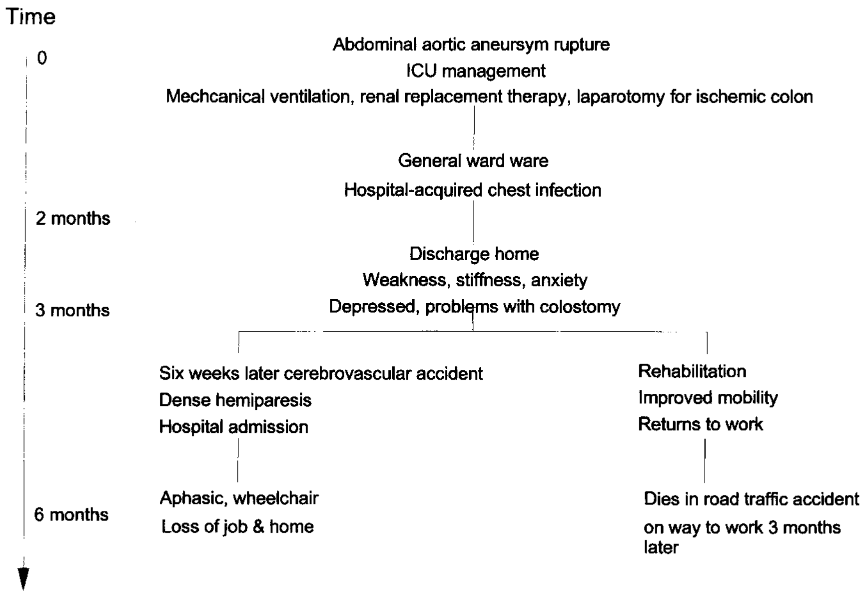

Fig. 1. Two theoretical outcomes of a patient following emergency aortic aneurysm repair

sured at arbitrary calendar periods after ICU admission. If survival was measured at six months in the above example, then the patient might have died in the road traffic accident. Unless his cause of death is known, this might be attributed to his critical illness rather than an unfortunate twist of fate. If quality of life is measured, then the patient in the wheelchair may not have too bad a quality of life because as a result of being so ill he is just grateful to be alive. Before his death, the quality of life of the patient who returned to work may not be as good as expected because he has lost his chances of promotion, enhanced salary and as a result his wife has left him. Clearly the functional outcome of this patient is much better that the patient who suffered the significant physical handicap due to the cerebrovascular accident.

From the patient's perspective, survival, quality of life and functional outcome are the most important outcome measures after critical illness. However, the timing of measurement will influence the results and it may be difficult to unravel the effects of important socio-economic influences that may not be directly related to ICU management.

Introduction

The analytical tools chosen for outcome measurement depend upon the question being asked and how the result will be applied. Outcome from intensive care can be measured from at least three different perspectives: that of the patient and their relatives, that of the staff on the intensive care unit (ICU) and finally the perspective of health managers, economists and politicians. As none of these perspectives is similar, different measurement tools will be required to investigate the areas of interest to each of the three groups.

Patient-Orientated Outcomes

The patients and their relatives will be primarily interested in long-term outcome measures. Relatives will have a keen interest in knowing whether the patient will be capable of independent living and of returning to work, or will suffer permanent disability once they have recovered from their critical illness. Patients will be interested in the duration and quality of survival; however, what defines 'adequate' survival is a personal perception varying with the individual's view of the value of life, their expectations and possibly age. For the purposes of research, a standard definition of an acceptable duration of survival will be required. Calendar periods are used but evidence that one follow-up period is more representative and useful than another is lacking. A frequently used definition of adequate survival is when the patient returns home (not necessarily back to work since there may be good reasons why the patient was not working prior to ICU admission). Leaving hospital alive could be considered a health care success but it ignores the high post-hospital mortality in some patient groups.

Patients will also be interested in outcome measures such as complications and other adverse events occurring during critical illness. Adverse events and complications may reflect the standard of care delivered on the ICU and so will also be of interest to staff. Cross infection rates may reflect professional standards of practice and in Europe, higher rates of nosocomial infection have been linked to higher ICU mortality rates [1]. Adverse events and complications may be pathology dependent (for example, amputation of peripheries because of ischemia or extensive bowel resection leading to prolonged dependence on total parenteral nutrition) or they may be treatment dependent. Treatment dependent complications may be divided into general complications such as weight loss, critical illness neuropathy and joint stiffness, or specific treatment related complications such as tracheal stenosis following tracheostomy. Unfortunately, complications occur commonly on the ICU. Giraud et al. [2] recorded 316 iatrogenic complications in 124 out of 400 admissions (31%) in two centers in France. The commonest complications involved ventilator procedures or therapeutic errors. This distribution of complications was confirmed by the Australian Incident Monitoring Study (AIMS) which analyzed 610 complications involving drugs (28%), procedures (23%), patient environment (21%), airway (20%), and ICU management (9%) [3]. Some complications may be categorized as both treatment and pathology dependent. For example, the post traumatic stress disorder following acute respiratory distress syndrome (ARDS) has a reported incidence of 27.5% [4] which is similar to the incidence of post traumatic stress disorder following road traffic and industrial accidents and terrorism. Post traumatic stress disorder following ARDS may also have a specific and severe effect on health related quality of life of patients when compared to other forms of critical illness [4].

Other areas of interest to the patient are functional outcome and quality of life. Functional outcome encompasses physical impairment, handicap or disability. Functional outcome is not the same as quality of life, although it has been used, incorrectly, as being synonymous with quality of life. Functional outcome concentrates on physical and mental capacity and does not measure well being or sense of satisfaction. Quality of life measures cover a broad range of physical and psychological attributes (domains). For example, the Short Form 36 [6] has eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health), the Nottingham Health Profile [7] has five (activity level, pain, emotional reactions, sleep, social isolation and physical abilities) while the Sickness Impact Profile [8] has twelve (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior and communication).

Staff-Orientated Outcomes

The effects of disease and the consequences of new medical interventions resulting in changes in mortality are important. New therapeutic options are frequently introduced on the basis of reduced mortality. For example, the improved survival of patients with human immunodeficiency virus (HIV) following the introduction of highly active anti-retroviral therapy [9] has improved the prognosis of such patients following ICU admission [10]. Prior to the introduction of such therapy, the prognosis of critically ill patients with acquired immunodeficiency syndrome (AIDS) was so poor as to be considered almost futile.

Long-term mortality is also of interest to intensivists because, in the face of increasing ICU demand and the relative paucity of resources, ICU physicians have to carefully triage patients in order to direct resources towards patients with the best chance of long-term survival. Sprung et al. [11] have shown that the decision whether or not to admit a patient depends upon the number of ICU beds available, the admission diagnosis, the severity of disease, age and surgical status. Three of these factors (diagnosis, severity of illness and age) all influence long-term survival. Other studies have shown that while some patients may survive having been declined ICU admission, the majority suffer a higher mortality [12]. It is therefore important that physicians recognize the consequences of declining admission and be certain that the information upon which they base their decision is as robust as possible. As a large quantity of resources are expended on patients who do not survive intensive care [13], attempts to identify potentially ineffective care are being made. For example, Esserman et al. [14] have developed a model where, if the product of the APACHE III risk estimates on day 1 and day 5 is greater than 0.35, then the specificity for a prediction of death is 98%. This, and similar prognostic tools, may help physicians in their difficult task of directing ICU resources to those patients who are likely to benefit the most.

Society-Orientated Outcomes

Health managers, economists and politicians are not necessarily interested in an individual's prognosis or clinical problems. Their task involves distributive justice to maximize the good for the whole of society. They are required to make rational decisions about health care resourcing based on accurate and reliable data. They must resolve conflicts concerning areas of health care, not only within hospital but also in trying to establish the appropriate balance between primary and secondary health care. Their decision making should be based upon rigorous economic evaluation using techniques of cost-minimization, cost-effectiveness, cost-benefit and cost-utility analyses. The data required for such outcome measures will probably be of little interest to the critically ill individual presenting to the ICU. However, for the professionals involved in intensive care, one of the pressing tasks must be to produce accurate and reliable information to allow rational decision making.

Long-Term Survival

Difficulties with Survival Analysis

Theoretically, measurement of mortality should be easy, but the reliability of information concerning survival depends upon a national system that collects this data centrally. For example, the Scandinavian countries have developed an effective system for identifying deaths based upon the individual's unique social security number. In the United Kingdom, the Office for Population Census and Survey uses the patient's National Health Service (NHS) number which is not the same as their hospital number or any other nationally used identifier. If the NHS number is not available, then identifying the patients depends upon their address and date of birth. With a mobile population, patients can easily be lost. Contact with their primary care physician may be fruitless if no follow-up details are provided by the patient on moving. Therefore, unless the national system for recording deaths can easily interact with the hospital system, following patients is more difficult because of data collection inadequacies.

When performing survival analysis, either special statistical methods must be used to compensate for censored observations or all the patients must be followed for a specified minimum period of time. Statistical tests include actuarial (or life table) analysis and hazard function calculation. However, one of the most frequently used analysis tools is the Kaplan-Meier product limit method and the graphical representation of such analysis is the step-wise decreasing Kaplan-Meier curves. Ninety-five percent confidence intervals for the survival curves can be calculated for both the actuarial and Kaplan-Meier analyses. If there are no censored observations, then two survival curves may be compared with the Wilcoxon Rank Sum test, but if censored observations are included then the Gehan (otherwise known as the Breslow) test or the log rank test should be employed. Modeling survival needs advanced techniques such as Cox's proportional hazard modeling. Details of such advanced statistics for survival analysis are available [15].

As mentioned above, survival has been reported at differing times following the onset of critical illness or admission to ICU. There is no standardized time at which survival figures are consistently reported. This makes interpretation and comparison of the survival figures difficult. Furthermore, reporting survival at different times allows other influences to confound the results. Survival is most frequently reported at ICU or hospital discharge, and then at various calendar periods up to many years following admission. Each of these reported survival periods has its shortcomings.

ICU mortality is frequently quoted and, while it provides a global impression of ICU performance, it can be affected by various factors. Some of these factors are well recognized and include case-mix, severity of illness, co-morbidity, and age of patients. However, there may be more subtle effects that influence ICU mortality figures; for example, a discharge policy whereby no terminal care is given on the ICU with hopelessly ill patients being discharged to the general ward. Such practice will reduce the ICU mortality rate. Similarly, if the ICU workload has a large elective surgical component, these low risk patients should depress the overall mortality figure.

Hospital mortality is frequently quoted as an outcome measure following critical illness. However, hospital mortality is influenced by care outside the ICU physician's control and really reflects the institution's performance. Unfortunately, the in-hospital mortality rate following intensive care is surprisingly high. Goldhill [16] reported a 27% 'post-ICU but in-hospital' mortality rate in 12,762 patients. Most deaths occurred in elderly patients who had spent a short time on the ICU. In Norwich, the post-ICU discharge mortality rate of medical patients is 21% with a median survival of only 40 days after ICU admission [17]. This is alarming when many of the patients are returned to a general ward with the expectation that they will survive.

Wallis et al. [18] reviewed the causes of hospital death following ICU discharge in 1700 patients in a district hospital over a five-year period (Table 1). The main causes of death on the general wards following ICU discharge were pneumonia, hypoxic or structural brain damage, cerebrovascular accident, malignancy, myocardial infarction, renal or multiple organ failure, and sepsis. The management of four of these conditions, namely pneumonia, renal or multiple organ failure, and sepsis, are certainly within the realms of the critical care services and it is disappointing to see these conditions being responsible for patients' deaths.

Long-term survival is dependent upon a combination of the degradation of physiological reserve by critical illness and the natural progression of the underlying pathology that precipitated critical illness. With appropriate follow-up, it is possible to draw a survival curve for a group of critically ill patients. However, interpretation of the patients' survival requires comparison with an appropriate control group. Two new problems then need careful consideration. First, which individuals should make up the control group? The ICU patient population is not a representative sample of the general population because ICU patients tend to be chronically ill with pre-existing physiological derangement due to co-morbidity. Comparing their survival with that of an age and sex matched normal population may not be appropriate. Even so this comparison has been most frequently

Table 1. Causes of death on the ward following ICU discharge [18]

Cause of death	Number	%
Pneumonia (no other major precipitating factor apart from recent critical illness)	43	28.1
Hypoxic brain damage	21	13.7
Structural brain damage (trauma, surgery or cerebrovascular accident prior to ICU admission)	13	8.5
Cerebrovascular accident (occurring during or after critical illness but not the primary event)	12	7.8
Malignancy (direct cause of death)	11	7.2
Myocardial infarction	10	6.5
Renal failure	9	5.9
Multiple organ failure	8	5.2
Sepsis	8	5.2
Thrombo-embolism	5	3.3
Pulmonary aspiration	4	2.6
Hepatic failure	1	0.7
Miscellaneous	4	2.6

reported because of the relative ease of obtaining death rate data in the national population. Comparing ICU survivors with hospital patients would be a more representative comparison but there may still be real differences due to case-mix. For example, patients with advanced cancer are frequently admitted to hospital but not necessarily to the ICU. Ideally ICU survivors should be compared with a group of hospital patients with the same disease who did not develop critical illness and so did not require ICU admission (Fig. 2). Unfortunately it is difficult to identify this group of patients and even then such a comparison would determine the effect of critical illness on survival rather than the influence of ICU management.

Second, the question of how long to follow-up the patients arises. The ICU survivors should be followed until the gradient of their survival curve parallels that of the control group. However, the length of time taken for the gradients of the survival curves to become parallel depends upon the control groups chosen (Fig. 2). It will take the longest time with an age and sex matched normal population and probably the shortest time with hospital patients with the same condition. When the curves of the critically ill patients match those of a comparable population, then the effects of critical illness in combination with the underlying pathological process will have run their course. However, not all the long-term mortality observed in critically ill patients is due to the effects of the disease that precipitated their ICU admission. For example, the survival of patients following esophagogastrectomy is dependent upon their tumor histology, while their ICU admission is required for cardiorespiratory observation and monitoring after long and difficult surgery.

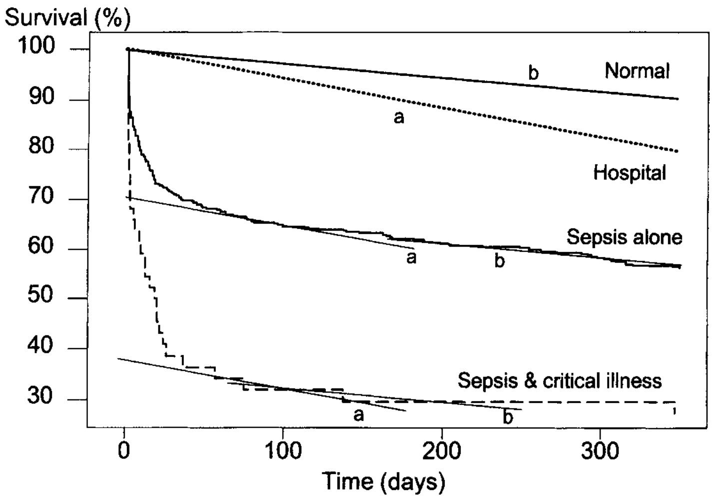

Fig. 2. The theoretical survival curves for four patient groups (normal individuals, hospital patients, patients suffering from sepsis but not ill enough to warrant ICU admission, and critically ill septic patients). Lines marked 'a' or 'b' are parallel with each other, thus represent when the survival curves of patients with sepsis parallel the other two possible control groups

Long-Term Survival

Unfortunately most of the studies that have followed critically ill patients have matched their survival to that of a normal population. There is conflicting data concerning the length of time taken for survival curves to parallel the normal population. Niskanen et al. [19] followed 12,180 Finnish patients for five years. The 5-year survival rate was 66.7% and overall the survival rate paralleled that of the general population at two years. However, the time at which this happened varied with diagnostic category. For example, the survival of trauma victims and patients with a cardiovascular diagnosis equaled that of the general population after three months (Fig. 3). If they survived the initial episode, patients admitted following cardiac arrest had a similar mortality rate to the general population after one year. In contrast, there were more deaths than expected throughout the follow up period among patients with respiratory failure and attempted suicide.

Dragsted et al. [20] followed 1,308 patients in Denmark and reported an overall 5-year survival rate of 58%, although once again certain subgroups had much poorer survival (e.g., cancer, medical and older patients). In Sweden, Zaren and Bergstrom [21] looked at 980 adult patients admitted to the ICU, and at the end of one year 73.6% survived compared to 96% for the normal population. The authors concluded that follow up was only required for one year.

In Scotland, it took four years for the survival of 1,168 critically ill patients to match that of a normal population by which time 55% of patients survived [22]. Results from East Anglia confirm that the survival of critically ill patients does not match a normal population for at least two and a half years (Fig. 4) [17].

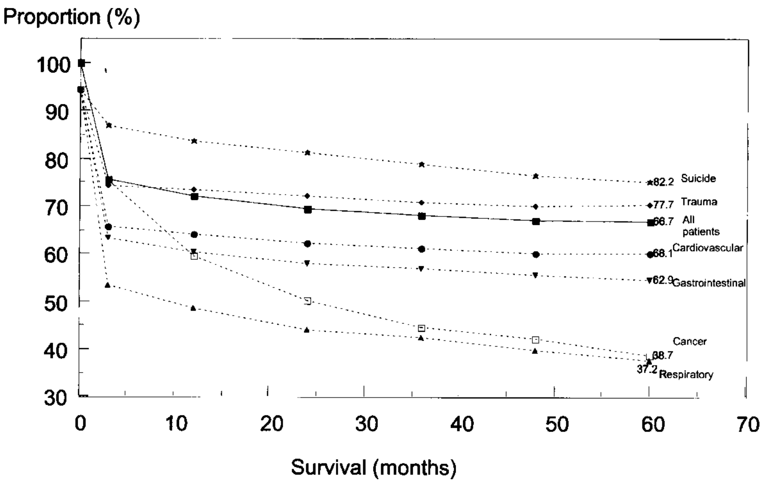

Fig. 3. The long-term survival of critically ill patients stratified by diagnosis (modified from Niskanen et al. [19]).

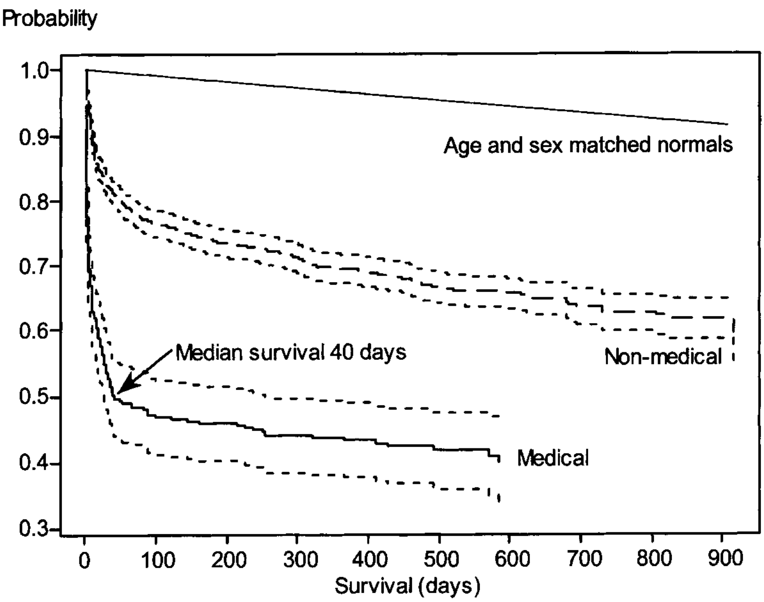

Fig. 4. The survival of critically ill patients divided into those referred from medical and non-medical specialties (95% confidence intervals shown). Note the median survival of medical patients is only 40 days. Neither survival curve matches that of an age and sex matched normal population

In summary, these studies indicate that in most patient groups it is possible to determine when the survival curve of ICU patients matches that of the general population (accepting that this may not in fact be a valid comparison). Overall, depending upon the population studied, the follow-up time required for satisfactory results may be anywhere between one and four years for entire cohorts of critically ill patients but may be more variable if certain subgroups are examined.

Non-Mortality Outcome Measures

Non-mortality outcome measures are vitally important to the surviving patients as they encompass all the aspects of life that concern the patient. While the patient is critically ill on the ICU, the most frequently asked question is whether or not the patient is going to survive. However, having left the ICU, the patients and their relatives become more interested in how the patient is going to survive. The long-term consequences of critical illness now become prominent and these are reflected in the non-mortality outcome measures.

Problems with Non-Mortality Outcome Measures

Critical care is a relatively modern specialty and so the consequences, both physical and mental, of life threatening critical illness are also new. Attempts to measure these are hampered by a number of difficulties. First, such assessment needs the selection of special tools or measurement devices. Generally such measurement tools have been designed for use in other areas of medicine or different populations of patients. The performance of such tools may not be as good in a new population, such as critical illness survivors, when compared with the patient group for whom the tool was designed. Second, the results obtained will depend upon case-mix, patient selection and the confounding influences of socio-economic changes that affect the whole population. For example, Figure 5 represents the theoretical recovery of pre-morbid quality of life in the survivors of critical illness.

The line representing recovery following cardiac surgery exceeds pre-morbid levels because surgery had a therapeutic effect and the patient's quality of life is improved. The other two lines represent two patients recovering following emergency aortic aneurysm repair. One patient made a good recovery in terms of quality of life but the other, as in the clinical example above, suffered a stroke two months after ICU discharge. This resulted in a dense hemiparesis, and despite some recovery, significantly impaired long-term quality of life. Quality of life after the stroke will be poor but unless precise details about the timing of the stroke are elicited, this poor recovery of quality of life will be ascribed to the aneurysm repair and associated critical illness. Third, the rate of recovery of the individual components such as quality of life and functional outcome following critical illness is unknown. It is unlikely that the rates of physical recovery and quality of life are identical and follow the same time course. There will be a balance between allowing as full a recovery of quality of life as possible and avoiding other socio-economic influences which impinge upon quality of life but may only be indi-

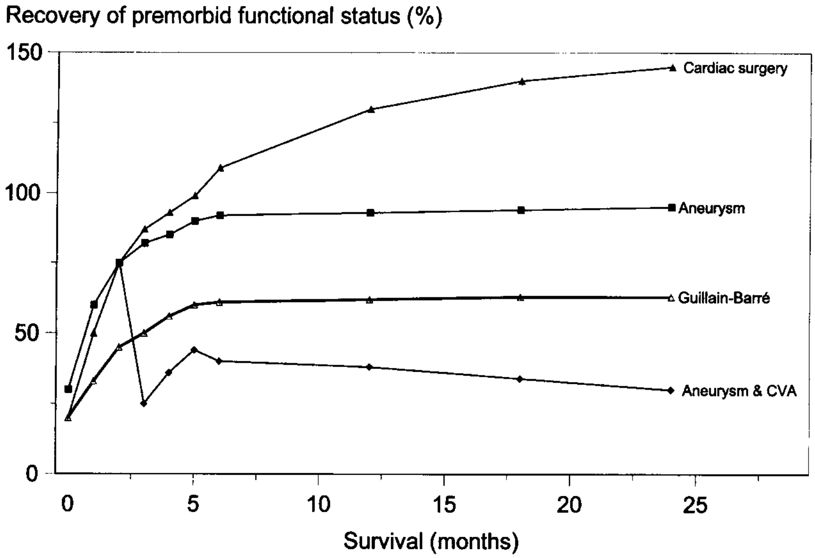

Fig. 5. Theoretical recovery of premorbid quality of life after cardiac surgery and emergency aneurysm repair. CVA: cerebrovascular accident

rectly associated with critical illness. Major life events such as marriage, divorce, unemployment may make the interpretation of changes in quality of life in relation to intensive care much more difficult (and hence dangerous). Not enough is known about the recovery of quality of life to make recommendations concerning appropriate measurement points. Many of the non-mortality outcome measures have been designed for or applied to patients with chronic diseases such as hypertension and arthritis. Theoretically, clinical changes in such conditions should be gradual rather than the faster recovery usually expected after critical illness. The responsiveness of tools designed for more chronic and stable conditions may not be adequate for critical care. Finally, any changes need to be compared to a suitable baseline as there is little evidence to suggest that ICU patients have the same distribution of pre-morbid physical and psycho-social attributes as the general population. Medical and nursing staff should not offer their own assessment of a patient's quality of life as these have been shown to be erroneous [23]. Only very close relatives or partners who care for the patients are really qualified to act as proxy respondents, and even then surrogate answers are more reliable in the physical rather than the psycho-social domains [24–26].

Non-Mortality Outcome Measures

A number of non-mortality outcome measures have been used following intensive care and these may be broadly categorized into six classes:

1) *Physical impairment and disability.* Physical impairment and disability will be common after severe trauma but its measurement may not be appropriate for

other causes of critical illness. Because ventilation is a key therapeutic modality on the ICU, measures of physical impairment have concentrated on the respiratory system and have included spirometry, diffusing capacity and bronchoscopy. Alas, these outcome measures have rather limited application in outcome analysis except for those patients admitted with acute lung injury and other causes of severe respiratory impairment.

2) *Functional status.* Functional status measures may be broadly classified as disease specific or general measures. The New York Heart Association classification [27] has been used in critically ill patients but this tool was originally designed for patients suffering from congestive cardiac failure. The classification grades physical activities. Generic measures of functional status include the activities of daily living (bathing, dressing, toileting, moving, continence, and feeding) [28] and these have been modified into the instrumental activities of daily living (using the telephone, shopping, using transport, cooking, housekeeping, taking medicine, and handling finances) [29]. Unfortunately most outcome measures examining functional status were developed for use in other fields. For example, Katz's activities of daily living were originally developed from results obtained from elderly patients with fractured neck of femur. The application of the activities of daily living as a primary outcome measure to critical care survivors may therefore be flawed.
3) *Mental function.* As with functional status, mental function outcome measures may be divided into generic measures including the Profile of Mood State (POMS) [30]. This scale was developed to assess mood in psychiatric outpatients. The scale assesses mood by ranking 65 adjectives on a five-point scale. The Hospital Anxiety and Depression Scale (HADS) was developed in non-psychiatric patients to measure mood disorders and depression [31]; it contains 14 items asking about depression and anxiety. Disease specific mental function tests include the Impact of Events Scale [32] and this assesses psychological distress following trauma. Mental function assessment has not been closely nor frequently measured after critical illness.
4) *Neuro-psychological function.* This measures cognitive function and examples include Trailmaking Tests A and B [33], Wisconsin Card Sorting Test [34], and Benton's test for visual retention [35]. The tests are generally complex and used as part of a battery of investigations assessing neuro-psychological function; because the tests are complex, they usually require face to face interviews. They measure attention, perception, cognitive flexibility, information processing, and visual memory. These tests have been used for patients with head injury, but are probably rather limited for the general ICU patient because of their complex application.
5) *Measures of recovery.* The extent of recovery may be measured in a multi-item scale such as the Glasgow Outcome Scale which has four grades of recovery (good, moderate disability, severe disability, and vegetative state) [36]. The scale was originally intended to assess recovery six months after head injury. Simple single items scales such as returning to work or independent living have been used but their simplicity limits their usefulness as there are many grades of employment and varying levels of support available to maintain independence.

6) *Quality of life.* Measures of quality of life have been widely used outside critical care. Such measures may be disease specific or general. In the critical care setting, quality of life has been most frequently measured using tools such as the Sickness Impact Profile [7], Nottingham Health Profile [6] and the Short Form 36 [5]. Gill and Feinstein [37] randomly selected 75 articles reporting quality of life and found that 136 out of 159 of the instruments used had been used only once. When assessing critical care, investigators frequently fail to report the psychometric properties (validity and reliability) of the instrument they use and rarely report the steps they have taken to ensure adequacy of the sample size. Investigators should be encouraged to select the tools that are specifically designed for the area of outcome in which they are interested (physical impairment, functional status, mental or neuro-psychological function, recovery or quality of life).

Non-Mortality Outcomes

Although the outcome measures listed above have been used in critical care survivors, apart from quality of life and functional status measures, such non-mortality outcomes may not actually measure what troubles the patients. While follow-up clinics have only recently been established and are few in number, their results do provide an insight into the problems experienced by patients. During critical illness it is possible to lose 2% of the body's muscle mass per day. Not only does this lead to severe weakness and fatigue but also poor muscle co-ordination and difficulty swallowing and coughing. Anxiety and depression are common and this may strain relationships with partners and limit social interaction. More severe psychological upset may present as nightmares and delusions. These may be consequences of the initial trauma or the results of the psychological disturbances that developed in the ICU. The patient's lack of memory, compounded by a lack of understanding or explanation may aggravate these disturbances. Such non–mortality consequences of critical illness will certainly impinge on quality of life. Therefore it may be more fruitful initially to look at specific outcomes perceived as problems by the patient rather than attempt to interpret the results of global non-mortality outcome measures.

Conclusion

Unfortunately there are still many problems and inadequacies with our understanding and appreciation of outcomes following critical care. Until follow-up of patients is standardized in terms of duration, it will be difficult to fully explore the influences that affect survival. Many non-mortality outcome measures have been used but their application to critical care survivors may not have been appropriate. Follow-up clinics have identified the types of long-term problems experienced by patients and it may be more appropriate to rigorously quantify these problems prior to investigating global changes in quality of life or functional status.

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