Patient-centered Endpoints for Perioperative Outcomes Research

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"The operation was a success, but unfortunately the patient died."

THIS trite but enduring cliché can be traced back to the late 19th century. The fact that it survived to this day indicates that perceptions of "success" can still differ widely between doctors and patients. For example, although the "1-yr graft patency" after coronary artery bypass surgery may be a highly meaningful outcome for a cardiac surgeon, it could have been achieved without any meaningful change in the patient's health status.[1] Mortality obviously is a patient-centered outcome. A high postoperative troponin level predicts future cardiac events including mortality,[2] but it is in itself not a patient-centered outcome. However, a postoperative myocardial infarction that results in new disability, such as extreme fatigue and decreased exercise tolerance with delayed return to work, clearly is. In a trial on the effectiveness of epidural analgesia, a difference of one point on the numeric pain rating scale may be statistically significant, but Number Rating Scale scores 2 *versus* 3 may have no meaning from the perspective of the patient.[3] Similarly, "cognitive decline" on a battery of postoperative neuropsychological tests may be important from a scientific viewpoint, but if not matched with new disability—as perceived by the patient or a close relative—it cannot be considered a patient-centered outcome. In this issue of Anesthesiology, Shulman *et al.*[4] propose "disability-free survival" as a new and truly patient-centered outcome that can be used as a valid endpoint in perioperative outcomes research.

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Outcomes that "matter to the patient" need to be distinguished from those that do not, and only patients can make that distinction. We are now entering a new era in medicine where differences in patient-centered outcomes will determine what constitutes medical success or failure, not only doctors' perceptions of success. Increasingly, healthcare purchasing decisions by third-party payers—and even individuals—will be based on such outcomes. Add to that mounting economic pressures to contain total healthcare expenditures. The value-based healthcare concept[5] simply boils down to seeking the highest value for the patient per healthcare dollar spent. More and more the patient will decide if his or her consent to a surgical procedure has resulted in the intended health improvement (cure or symptom relief).

While "disability-free survival" can be used as a valid patient-centered endpoint in perioperative outcomes research, it can be equally useful for shared decision making, quality metrics, and benchmarking quality of care. Disability-free survival is a combination of survival (1 – mortality) and a patient-reported assessment of disability measured with a validated questionnaire. The authors took an instrument, which was originally developed by the World Health Organization to measure disability from various chronic diseases in a wide range of national and cultural settings (World Health Organization Disability Assessment Schedule 2.0 [WHODAS]),[6] and validated it in 510 surgical patients. The short version of WHODAS 2.0 consists

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of 12 questions that ask the patient for perceived limitations in physical, cognitive, and social functioning.

Shulman *et al.*[4] performed an extensive psychometric evaluation of WHODAS in surgical patients with a focus on patient acceptability, validity, and reliability. Response rates were very high, especially considering that the patients were asked to fill in multiple questionnaires at four time points after surgery. Disability-free survival was compared with the Quality of Recovery Scale[7] at 30 days postoperatively, Quality of Life (EuroQoL EQ5D),[8] activities of daily living (Katz ADL),[9] and the extent to which pain interferes with daily activities (modified Brief Pain Inventory Short Form)[10] and correlated well with each of these specialized scales, but correlations were not so high as to make WHODAS redundant.

What would widespread adoption of disability-free survival as a primary endpoint for future perioperative medicine studies accomplish? Let's assume an investigator has recently started a randomized controlled trial investigating the benefit of a perioperative intervention designed to improve long-term outcomes. Explaining disability-free survival to the patient immediately makes the main study outcome understandable and meaningful to the patient. Shulman *et al.*[4] argue that perioperative outcomes researchers have often selected as primary outcome a "composite" of bad things that can happen during and after surgery, *e.g.*, the combined incidence of death, stroke, myocardial infarction, and acute kidney failure. They cite the landmark randomized Peri-Operative ISchemic Evaluation (POISE) trial[11] as a case in point. The POISE authors investigated metoprolol to prevent major complications in more than 8,000 patients, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest. Although administration of metoprolol reduced the occurrence of the primary (composite) endpoint (5.8% *vs.* 6.9%) and there were significantly less myocardial infarctions (4.2 *vs.* 5.2%), there were also more deaths in the metoprolol group (3.1 *vs.* 2.3%) and the stroke rate was double that of controls (1·0% *vs.* 0·5%). Pooling of bad outcomes into a composite endpoint suggests that these outcomes all have more or less equal weight in terms of patient burden. The problem with both stroke and myocardial infarction is that such diagnoses in themselves do not provide the information a patient requires: the disability caused by the event. Most people, however, would consider a disabling stroke a far worse outcome than a myocardial infarction. We certainly would. Then again, some people might disagree, depending on the nature and severity of the disability. In either case, a functional outcome such as WHODAS provides information on the burden of disability. One further step in designing studies with true patient-centered outcomes would be to elicit patient preferences as part of the design of clinical outcomes research.

It is sometimes tempting for clinical investigators to extend their composite outcome measure with an outcome that occurs more frequently, but is less severe in terms of patient burden, *e.g.*, "long length of stay" or some biochemical evidence of ischemic end-organ injury. This will have the effect of lowering the required sample size for the study, which can make the difference between a study that will actually be performed and one that never leaves the protocol stage. However, adding a prevalent but less severe outcome to the composite comes at a price: now the result of the entire study will be biased toward the effect of the intervention on that single outcome.

The concept of disability-free survival could also be helpful in deciding on the utility of a proposed surgical procedure. A patient's decision to consent to an operation is based on the expectation that it will relieve symptoms and restore function or that it will prevent future disability, including death. Although a small probability of harm must be accepted, the anticipated benefits should obviously outweigh any risk of serious harm. By framing the outcome in terms of the likelihood of surviving free from disability, patients can gauge the expected benefit of surgery in relation to its effectiveness as well as its risks. This could be especially important for older patients who may only be willing to submit to major surgery when there is a sufficiently large probability of surviving the operation without new disability. In addition, the incremental benefit of any proposed perioperative intervention or adjunct such as epidural analgesia, supplemental oxygen, β blockers, antifibrinolytics, steroids, statins, prophylactic antiemetics, total intravenous anesthesia, monitoring with transesophageal echocardiogram, or electroencephalography can be framed in the same terms.

In summary, perioperative outcomes research has come a long way. Starting with small trials and surrogate outcomes it moved on to adopt major complications—either alone or pooled in composites—as the benchmark outcomes for large perioperative trials. The time has now arrived to take the final step and include patient-perceived disability in our arsenal of relevant outcomes. Good doctors want to know if their efforts were able to accomplish the goals their patients were hoping for. Several medical specialties have recently set up large clinical registries with the aim to track and improve quality of surgical care. Such registries are equally in need of meaningful patient-centered outcomes to guide quality improvement. If disability-free survival would be adopted as a primary outcome both for randomized clinical trials and in observational clinical registries, there is an opportunity for both to converge. Such a development would allow clinical registries to form the basis of low-cost pragmatic trials and holds enormous promise for improving the quality of care.

Competing Interests

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