The Role of Patient-Reported Outcomes in Preoperative Decision-Making for High-Risk Patients

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"The Role of Patient-Reported Outcomes in Preoperative Decision-Making for High-Risk Patients"

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Abbreviations

ACP	Advanced care planning
AUC	Area under the curve
B.R.A.N.	Benefice Risk Alternative Nothing
CSF	Clinical frailty scale
CI	Confidence interval
DAH	Days alive at home
ePRO	Electronic patient-reported outcome system
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and drug agency
HRQoL	Health-related quality of life
OTP	Outcome Prioritization Tool
OSS	Operative stress score
PRO	Patient-reported outcome
PROMs	Patient-reported outcome measures
RCT	Randomized Controlled Trial
StEP	Standardise Endpoints in Perioperative Medicine Initiative
VAS	Visual analogue scale
WHO	World Health Organization
WHODAS	WHO Disability Assessment Schedule

Summary

Elderly and frail patients are increasing among the surgical population and are associated with an increased risk of postoperative mortality and major adverse events. Consequently, the preoperative decision-making process for this population is often complex, in particular to avoid situations of futility and overtreatment. Meanwhile, this high-risk surgical population also expresses different life and health priorities when facing difficult treatment decisions such as surgery. Most of the time, they are known to prioritize patient-reported outcomes (PROs) such as independence and quality of life, over survival and longevity.

PROs are assessed using patient-reported measures (PROMs), many of which have been widely used and validated for a long time in the perioperative period. PROs integration into clinical practice is known to enhances health outcomes by improving communication between patients and caregivers, facilitating the detection of potential serious but missed symptoms, and increasing patient engagement and satisfaction. However, PROs are still poorly used during preoperative decision-making and discussions.

Incorporating PROs into preoperative decision-making seems to be essential for several reasons:

- They help frame risk-benefit discussions according to life and health priorities that may be more meaningful for this high-risk population of elderly and frail patients.
- They could value non-operative alternatives according to potential benefits on PROs despite being less effective in terms of survival.
- They could support advanced care planning discussions by clarifying the potential impact of postoperative major adverse events on PROs.

To date, a major limitation of using PROs in surgical decision-making is the lack of reliable and tailored data for specific populations and procedures. This gap impedes the development of accurate predictive models that clinicians can trustfully use. However, today, some variables have been identified as potential predictors of deteriorated postoperative PROs, and predictive models are gradually emerging. Additionally, machine learning appears to enhance the accuracy of these models, though further validation is needed. This data on PROs must be developed to enable physicians to consider more relevant outcomes for this high-risk population and to empower patients and their relatives to make decisions that respect their values and priorities.

Introduction

Social and medical progress has gradually led to an ageing population in most developed countries, a trend that has become even more pronounced in recent decades[1]. In 2022, 2.9% of Europeans were 85 or older but this proportion is expected to more than double by 2050 and triple to 2100[2]. Advances in surgery, anaesthesia, and perioperative care, coupled with societal changes, have allowed an increasingly elderly population to benefit from interventions that were once deemed not feasible. Moreover, the proportion of elderly undergoing surgery is increasing even faster than the population ageing[3]. In the United Kingdom for example, by 2030, approximatively 20% of the 75 years and older age category will undergo surgery each year[3].

Chronological age itself, is a well-known factor associated with an increased risk of postoperative morbidity and mortality[4]. For example, elderly patients over 85 years old undergoing common abdominal surgery experience 50% more complications within 90 days compared to patients aged 65 and 69[4]. Using the same age groups comparison, mortality within 90 days is three times higher for patients over 85 years old[4]. These odds of complications and death were also found after adjusting for multiple variables such as demographic or patients, surgical and hospital characteristics.

However, chronological age is a complex variable to address due to a significant heterogeneity in the same age group. To improve categorisation of patients, the concept of frailty has gained a major interest during the last decade. Frailty is a syndrome defined as a decreased physiological reserve and increased vulnerability to stressors and is often but not exclusively associated with chronological age[5]. Frailty is more strongly associated with postoperative morbidity and mortality than age alone[6]. A recent systematic review and meta-analysis examining the association between frailty and postoperative complications in older surgical patients reported that frailty was associated with 6.62 higher odds of 30-day mortality, 3.11 times higher odds of postoperative complications, and 2.65 times higher odds of postoperative delirium[6]. This issue is increasingly concerning as the prevalence of frailty among the elderly population in hospitals appears to be rising over time[7]. We are therefore now witnessing a growing prevalence of an aging and frail population, which represent a high-risk perioperative group, especially for major surgery.

This demographic shift has made the development of perioperative medicine increasingly essential. In Europe, perioperative medicine is a multi-disciplinary approach often spearheaded by anaesthetists given that the latter have an extensive experience in

identifying both medical and surgical preoperative risks[8]. The traditional limited preoperative approach, often performed shortly before surgery, was increasingly perceived as insufficient to manage a growing at-risk population—not only increasing in prevalence but also increasingly undergoing major surgeries.

While there is no consensus on the definition of perioperative medicine, it can be broadly described as patient-centred care encompassing the time from preoperative preparation to postoperative recovery[9]. In practice, perioperative medicine focuses on the identification and management of patients at high risk of mortality and/or major adverse events[10]. For these patients, perioperative medicine aims to optimize preoperative mental and physical comorbidities, protect organs during the perioperative period, and enhance perioperative surveillance to promptly detect and treat postoperative complications. A key goal of this approach is to reduce 'failure to rescue' scenarios, ensuring that at-risk patients or those with complications are identified and managed effectively.

One of the additional and still underdeveloped tasks of perioperative medicine is to assess the relevance of the operation in the patient's overall context and discuss potential alternatives to it. Although the shared decision-making concept is aimed at all patients faced with a treatment decision, this approach is all the more important for this elderly and/or frail population faced with a major surgery or invasive procedure[11]. As the care and life priorities of this population are often directed towards priorities other than survival alone, it is essential to consider the existence of an alternative and discuss the issues involved. The acronym B.R.A.N. associated with shared decision-making describes the four points to be considered and distinguished: Benefit, Risk, Alternative and Nothing from the 'what if I do Nothing'[11].

The benefit of the surgery is traditionally placed in the hands of the surgeon. The question is not only the benefit of a given surgery but, for a population at risk, also and above all the potential absence of benefit. This is where the notion of futility comes in. The notion of futility has a long history in medicine, first enunciated by Hippocrates (430-330 BC): '*the aim of medicine is to refuse to treat those who are overwhelmed by their illness, knowing that in such cases medicine is powerless*'[12]. The higher the risk of an intervention, the more evident and substantial its benefit should be. Until recently, assessment of futility relied primarily on surgeons' personal experience and clinical judgment. However, it is only lately that several surgical research teams have begun to develop predictive models dedicated to this issue. Confronted with similar challenges in at-risk populations, these teams have also recognized the growing importance of this concern. An emblematic recent study published in JAMA Surgery sought to develop a model to predict futile up-front pancreatectomy in patients with

adenocarcinoma[13]. Despite certain limitations, this large-scale study demonstrated the interest and feasibility of such an approach. Predictive models for other elective or emergency surgeries have also emerged recently, some of which also making use of machine-learning[14,15].

However, this definition of futility is often limited to mortality or disease recurrence. Although essential, it does not necessarily address the objective of certain patients, especially at-risk populations. For many years, a large body of literature has clearly demonstrated that survival is often a secondary objective for elderly and frail patients. More than 20 years ago, a study published in the *New England Journal of Medicine* highlighted the influence of functional or cognitive complications on treatment decision-making[16]. The authors administrated a questionnaire about treatment preferences to 226 elderly patients with limited life expectancy, asking them if they would agree to receive a given treatment with different likelihood of complications. If the treatment was low burden and allowed patients to return to their current health, 98.7% chose to accept the proposed treatment. However, if the treatment resulted in severe functional impairment, only 25.6% of patients would choose it. Moreover, if the same treatment led to a severe cognitive impairment, acceptance dropped to just 11.2%.

Since then, multiples studies have replicated these findings across various contexts and populations. For example, a research group form the Netherlands included 350 elderly patients (median age 78.5) to assess the most important health outcome when facing a major treatment decision (such as cancer treatment or heart surgery)[17]. They used a validated instrument, the Outcome Prioritization Tool (OPT), consisting of four visual analogue scales on: life extension, preserving independence, reducing pain and reducing other symptoms. Facing this choice, the majority of patients ranked the maintenance of their independence as the most important outcome (55.2%), significantly outweighing the extension of life, which was the top priority for only 21% of patients.

When focusing specifically on cancer patients, several studies have explored the trade-off between length or quality of life, as patients may “trade” this quality of life to live longer. A systematic review including 30 articles revealed that while younger patients were more inclined to choose aggressive treatment to increase their survival time, older patients consistently prioritized quality of life over length of life[18].

Overall, despite its importance, mortality appears to be of less concern to most of the elderly and most of frail patients compared with other outcomes such as the maintenance of independence or quality of life[19]. As a result, the notion of futility cannot be confined to mortality or the absence of recurrence of disease. A treatment that does not enable the patient

to achieve his or her objective, whether is to maintain or improve independence or quality of life, return home, or reduce pain, must also be considered futile. If on the one hand we have a notion that we can call “raw futility” for mortality and the absence of disease recurrence, we can support a notion of “relative futility” for objectives specific to the patient. And these outcomes are mostly what we call Patient-Reported Outcomes (PROs).

PROs, which we will discuss at length in this review, are defined as “*any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else*”[20]. PROs increase the resolution with which caregivers can perceive the patient, beyond focused anamnestic questions, clinical examination, vital signs or lab results for instance. By bridging the gap between the caregiver's perception and the patient's lived experience, PROs provide deeper insights into the patient's needs, preferences, and expectations. As previously mentioned, while beneficial for all patients across various settings, PROs specifically address the primary objectives of many elderly and frail patients, for whom survival is not always the foremost concern. This paradigm shift, using PRO as the primary outcome, has already been underway for some years. A major perioperative study published in 2018 in the New England of Medicine did not have crude survival as its primary outcome, but disability free survival[21]. In other words, the authors raised the issue that the outcome of the intervention in question (fluid management for major abdominal surgery) should not only study the effect on survival alone, but a survival that was meaningful for most patients studied, in other words a survival free of major disability.

A similar shift is needed in how risk is addressed during the shared decision-making process through the B.R.A.N. approach discussed earlier. For now, risk discussions primarily focus on mortality and organ complications. However, for the elderly and/or frail population, the assessment of risk should prioritize PROs. More specifically, the degree to which an intervention represents a risk to independence, quality of life and other PROs, discussed earlier and explored further thereafter. While data on these outcomes is crucial, it remains insufficient.

The limited availability of data is likely one of the most significant current barriers to the effective use of PROs in perioperative medicine, particularly within the preoperative decision-making process. These data are essential not only for patients and their families but also for clinicians struggling to make shared, informed decisions. Improved understanding and prediction of these outcomes would enhance the shared decision-making process, either by validating the value of the proposed intervention and clarifying its associated risks, or by emphasizing the importance of non-operative alternatives (the "A" in B.R.A.N.) or the

necessity of a palliative approach (the "N" in B.R.A.N.). In this respect, the development of predictive models for PROs appears to be crucial in the coming years. As discussed in more detail later, some models are already emerging, although their development is often constrained by the limited availability of the underlying data.

This narrative review will discuss PROs, their importance in medicine, particularly in perioperative care, their potential role in preoperative decision-making and the promising integration of predictive models in this context.

Methodology

This narrative review was conducted to address two primary objectives:

1. Summarize the current concepts and knowledge about patient-reported outcomes (PROs) in medicine, with a specific focus on the perioperative setting.
   To achieve this, I relied on my existing knowledge of the literature, reviewed embedded references within relevant systematic reviews and clinical guidelines, and conducted targeted searches for additional references when necessary. These searches were performed using Medline and Google Scholar to ensure comprehensive coverage of key publications in the field.
2. Explore the potential utility of PROs in preoperative decision-making and the potential value of predictive models.
   For this objective, a structured search strategy was employed across Medline, EMBASE, and Google Scholar, without publication date restrictions.
   The search utilized a combination of keywords and MeSH terms, including: Surgery (surgical); Patient-reported outcomes (patient-reported outcome, patient reported outcomes, patient-reported outcome measures); Prediction model (predictive model, prediction models, predictive models) and Machine learning (machine-learning).
   Relevant studies, systematic reviews, and guidelines were screened for inclusion based on their relevance to PROs in preoperative decision-making and prediction modelling. Only the more relevant articles were fully analysed and integrated in this review to provide a meaningful synthesis of current knowledge and emerging trends in the field.

Patient-Reported Outcomes – An Overview of the perioperative applications and potential benefits

PROs have been implemented in surgical care for years. Interestingly, one of the first study referenced on PubMed was published in 1974 in The Lancet and investigated the effect of early surgery for spina bifida on survival and quality of life[22]. Most of the following surgical studies mainly targeted specific procedures with substantial functional impact, especially in fields like orthopaedic and urology. But it is only in the last decade that studies have begun to investigate the impact of comorbidities and perioperative management on PROs. Since then, the integration of PROs in the perioperative medicine has gained considerable popularity in recent years, including in daily clinical practice.

In 2018, the American Society for Enhanced Recovery issued a special consensus statement of the importance of PROs in an enhanced recovery pathways[23]. To introduce the importance of PROs, the authors also point out that traditional measures, such as complications and hospital length of stay, do not capture post-discharge outcomes that are meaningful to patients, such as function or freedom from disability. By constituting a group of international experts, the working group agreed on several recommendations. Among these, the two key ones were: 1) PROMs in the perioperative setting should be collected in the physical, mental and social domains. 2) The data should be collected preoperatively at baseline, during the immediate postoperative period and after hospital discharge. The statement concluded that future research should focus on the consistent application of PROs measures in an enhanced recovery pathways to determine their ability to support clinical decision making, improve recovery via a biopsychosocial approach, and provide benchmark quality metrics on a population level.

More broadly, and as discussed above, PROs provide a deeper and more comprehensive understanding of patients' needs, preferences, and expectations. This is further supported by a robust and growing body of evidence indicating that the systematic use of PROMs enhances communication between caregivers and patients, improves treatment monitoring, facilitates early detection of complications, increases patient engagement and satisfaction, and contributes to better health outcomes[24,25]. Moreover, PROMs could have a major impact on decision making as we will discuss it later.

Improvement of communication

The impact of PROMs on the communication between caregivers and patients has been studied in multiples studies, including large RCTs[26]. A prospective, randomized crossover trial evaluated the efficacy of health-related quality of life (HRQoL) assessment through systematic

question completion in facilitating the communication between physicians and patients undergoing palliative chemotherapy[26]. Physicians identified more patients with moderate to severe HRQoL issues and, all physicians and the vast majority of patients found that this intervention facilitated the communication and expressed the wish to continue its use. Several studies have confirmed this benefit, but limitations, such as a lack of adequate training, have hindered the daily implementation of PROs in clinical practice. Recently, a Danish team addressed this by developing a concise manual called 'PROmunication,' which provides a clear, practical guide to conducting PRO-based consultations but further studies should test it in different settings[27].

Treatment monitoring and early detection of complications

The improvement in communication between caregivers and patients using PROMs can significantly enhance the detection of often overlooked symptoms. A notable study compared the accuracy of chemotherapy side effects as detected by clinicians with those reported simultaneously by prostate cancer patients undergoing chemotherapy[28]. The study revealed that clinician reporting was neither sensitive nor specific to detect chemotherapy adverse effect, with a Cohen's kappa coefficient of just 0.15. Clinicians missed symptoms like pain or dyspnoea in over 65% and 77% of cases, respectively.

Years later, a post-hoc analysis of a HRQoL study on chemotherapy outpatients with solid tumours found that integrating patient-reported outcome system (ePRO) into routine care was associated with an increased survival compared to standard care[29]. This unexpected finding opened a reflexion on the potential ability to use PROMs as an additional alert system to improve early responsiveness to potential adverse treatment effects and prevent downstream consequences. However, it is only in recent years that studies have started to explore the integration of PROMs in this role. For instance, a recent pilot study provided 40 patients discharged after abdominal surgery for cancer with an ePRO via a smartphone app to assess symptoms at discharge and weekly thereafter[30]. An integrated algorithm guided the patients according to the symptoms they reported. The smartphone app could simply give a self-management advice, advice the patient to contact a clinician but it could also directly contact itself a clinician in case of an alarming symptoms. Of the 197 ePRO completed, 36% prompted advice to contact a clinician, while 5% triggered a direct clinician alert, indicating that the reported symptoms were deemed sufficiently concerning and potentially missed otherwise.

Increase patient engagement and satisfaction.

In its resolution 72.6, the World Health Organisation (WHO) clearly addressed the necessity to integrate patients and their representant at all level of healthcare to improve their safety and autonomy[31]. In line with this consideration, PROMs are now increasingly recognized as an essential tool to capture and integrate patients' experiences and needs. In fact, since 2010, the Patient Centered Outcomes Research Institute, established under the Affordable Care Act in the United States of America, made PROs a central component of healthcare policy and reform[32]. Similarly, in 2017, the European Union, through the Organisation for Economic Co-Operation and Development (OECD), launched the PaRIS initiative to support and develop PROs in health care policy across the European Union[33]. Today, most of the international and national medical societies, grant funds, scientific journals and governmental policy institutions now require or strongly recommend the use of PROs in a research or quality project.

To avoid confusion with PROs, an additional measurement should be mentioned when addressing patient's experience and implication in healthcare: patient-reported experiences measures (PREMs)[34]. While PROs correspond to patient's outcome, PREMs measure patients' perception of their personal experience of receiving healthcare. They need to be differentiated from satisfaction survey as they measure objective patient experiences. PREMs are primarily designed to assess the quality and performance of specific health services or systems but can also indirectly enhance patient engagement in their clinical itinerary by uncovering previously unrecognized or underestimated barriers.

Improving health outcome

Overall, PROs can enhance health outcomes by improving communication between caregivers and patients, serving as an additional alert system to prevent potential downstream consequences of missed or delayed complication identification, and increasing patient engagement in their care.

Patient-Reported Outcomes Measures (PROMs)

PROs are measured with patient-reported outcome measures (PROMs). PROMs are standardized questionnaires that assess a wide range of health dimensions, including pain, disability, physical and mental health, health-related quality of life (HRQoL), symptom burden, mental health, regret or recovery (**Table 1**). PROMs questionnaires require psychometric validation to ensure they effectively measure their intended purpose[35]. Key psychometric properties include reliability, validity, responsiveness (ability to detect change) and

interpretability. Interpretability is closely tied to the concept of Minimal Clinically Important Difference (MCID), which defines the smallest change in a measurement that a patient perceives as meaningful and significant[36]. Moreover, the feasibility of PROM is similarly important, i.e. the questionnaire must be practical for both patients and healthcare providers in term of time, effort and cost. Finally, PROM needs to be validated for different cultures and languages. This point is essential as either interpretation or scoring could differ among different countries, sometimes even with significant and clinically relevant difference[37].

Pain
Visual Analogue Scale (VAS)
Numeric Rating Scale (NRS)
Brief Pain Inventory (BPI)
McGill Pain Questionnaire (MPQ)
Disability
World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)
Katz Index of Independence in Activities of Daily Living (Katz ADL)
Health-related quality of life
European Quality of Life-5 Dimensions (EQ-5D)
Short-Form 36 Health-Survey (SF-36)
World Health Organization Quality of Life (WHOQOL)
European Organisation For Research and Treament of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30)
Functional Assessment of Cancer Therapy – General (FACT-G)
Mental health
Hospital Anxiety and Depression Score (HADS)
Regret
Decision Regret Scale (DRS)
Recovery
Quality of Recovery-15 (QoR-15)
Death and dying
Quality of Dying and Death (QODD)

Table 1. Examples of relevant perioperative patient-reported measures (PROMs)

PROMs are divided in two main categories: condition-specific and generic[38]. Condition-specific questionnaires are more sensitive in detecting changes with precision; however, they may overlook important aspects of the patient's experience by losing a broader, holistic perspective. In contrast, general questionnaires are less sensitive but provide a more extensive assessment, enabling comparisons across different populations.

Several factors may limit the integration of PROMs into daily practice[39]. At the patient-level, barriers include the time required to complete the PROMs; difficulty or inability to fill them out (due to literacy, memory issue or severely diminished health), and a perceived lack of relevance of the PROMs to their personal experience. These challenges underscore the critical importance of an early involvement of patient partners in the selection and

development of PROMs to ensure their relevance and usability in both research and clinical settings. At the level of the health care provider, obstacles include the time required to administer the PROMs, a lack of expertise in the interpretation of PROMs (particularly in determining intervention threshold) and a perceived lack of utility of PROMs in clinical practice. Addressing these challenges will mainly require additional data to demonstrate their impact on clinical outcomes and patient/proxies' satisfaction.

An essential consideration regarding PROMs is the mode of administration. For decades, PROMs have been delivered through various methods, including paper questionnaires (with or without supervision), telephone interviews, web-based platforms, and face-to-face interviews. While these different approaches are generally effective, they can introduce slight variability in results depending on the mode of administration, which should be acknowledged when interpreting data[40]. In recent years, the widespread adoption of digital technologies has led to a significant increase in the use of PROMs via smartphone apps and dedicated websites (ePRO). While this digital approach offers numerous advantages, such as convenience and adaptability, it may introduce a potential selection bias[41]. Individuals unable to use digital devices, whether due to chronic conditions, temporary impairments, or lack of access, could be excluded from the process. This issue is particularly relevant in perioperative settings, where patients may be physically incapacitated or otherwise unable to respond to digital questionnaires, leading to disappointingly low participation rates[42]. Addressing these challenges is so essential to ensure the inclusivity and reliability of PROM data across diverse patient populations.

Patient-Reported Outcomes & Preoperative Decision Making

In the years to come, the integration of PROs into the decision-making process is likely to become increasingly important for several reasons.

Firstly, as previously discussed, certain populations, particularly elderly or frail patients, often prioritize outcomes beyond survival or the avoidance of complications. Their main focus is typically on PROs such as maintaining independence or preserving HRQoL. To align with their expectations, discussions on the benefits and risks of surgery need to be framed with these goals in mind.

Secondly, acknowledging the value of non-operative alternatives for this demographic group requires the availability of comprehensive and relevant information including outcomes on PRO. Non-operative alternatives, even when they are less effective in terms of survival, may

resonate positively with these patients and their families if they offer potential advantages in terms of PROs.

Finally, given the higher likelihood of serious complications and their significant impact in this population (such as organ damage, disability or cognitive decline), it is essential to strengthen pre-operative advanced care planning[43]. However, effective discussions on potential care limitations should not only reflect patient's life priorities but also be informed by a reliable quantification of potential risks to PROs, particularly regarding new disability or a decline in HRQoL resulting from a specific procedures or complications. Physicians' frequent discomfort in addressing these issues may stem from a lack or reliable data on such outcomes.

Avoiding over-expectation and addressing postoperative regret

Whatever PROs are included in a discussion, patients make the decision to undergo surgery with expectations about the effectiveness of the surgery and their post-operative recovery. However, multiple set of data revealed the risk of over-expectation for PROs. For example, one year after kidney transplant, it appears that most patients expected improvement in several domains of HRQoL that, at the end, did not change[44]. The same observation was retrieved for patients undergoing cancer surgery where preoperative expectations were poorly correlated with postoperative physical HRQoL[45].

In addition to the gap between expectations and reality, an often overlooked and potentially linked PRO is decisional regret. Identifying populations at high risk of experiencing postoperative decisional regret could play a critical role in the decision-making process for physicians, patients and their relatives. Even more considering that decisional regret can affect not only patients but also physicians and relatives, underscoring its potentially strong implication. A systematic review published in 2017 reported that the prevalence of postoperative decisional regret ranged from 6,4 to 24%[46]. However, most studies focused on relatively young patient populations. Similarly, a systematic review we recently conducted on relatives' decisional regret highlighted the same issue, with the majority of studies addressing paediatric or young adult patients, and none focusing on the elderly and frail population[47]. This lack of data is particularly concerning given that the elderly and frail population is likely to experience a higher prevalence of decisional regret, which could profoundly impact preoperative decision-making[48]. Addressing this gap seem essential to improve decision making in this high-risk population.

Recently, a research group conducted a secondary analysis on decisional regret on a prospective, multicentre cohort study of elderly patients who underwent elective noncardiac

surgery[48]. Decisional regret was measured at 30 days, 90 days and one-year after surgery using a 3-point ordinal scale "no; unsure, yes". After adjusting for confounders, frail patients exhibited a higher risk of decisional regret with an odds ratio of 1.68 (95% CI 0.84-3.36). However, several limitations were exposed by the authors underlying the complex association between frailty and decision regret that need to be further explored.

What is limiting the use of PRO in decision-making process and the perspective of predictions models?

In addition to the general limitations of using PROMs discussed earlier, the very limited integration of PROs into the decision-making process likely stems from one key factor: the lack of data and, consequently, reliable predictive models, particularly for at-risk, elderly, and frail populations. Currently, the integration of PROs into decision-making relies largely on general knowledge applied to specific situations, rather than on robust, data-driven frameworks. It is only recently that predictive models for postoperative PROs have begun to emerge as we will discuss it later. However, they are expected to expand in parallel with the increasing availability of raw data and advancement in machine-learning models. Beyond simply identifying associations between variables and outcomes, prediction models are designed to select the most relevant predictors, address data quality issues (including missing values), incorporate variables that optimize predictive performance, and undergo evaluation using calibration and discrimination metrics[49].

Today, most prediction models are still aimed at classical clinical outcomes such as mortality and complications[50]. As discussed earlier, emerging new interesting models are targeting potential futility specific to specific surgery[13–15]. But prediction models dedicated to PROs are still rare and should be encouraged.

To illustrate the potential integration of PROs into the preoperative decision-making process for high-risk patients, I will focus on two examples particularly relevant to perioperative care for elderly and frail patients: disability and health-related quality of life (HRQoL).

Disability

As defined by the WHO, disability is any condition of the body or the mind (impairment) that makes it more difficult for the person with the condition to do certain activities (limitations) and interact with the world around them (restriction)[51]. Disability can severely impact the independence of the patient, especially in the elderly with fewer compensating mechanism availability[52]. As discussed earlier, maintaining independence is

one of the most important PRO prioritized by elderly regarding the treatment decision making[17]. However, it is important to recognize that the measurement of disability is primarily functional and does not fully capture the suffering associated with such limitation. In other words, even if patients can perform all their daily tasks, these activities may be accompanied by severe pain or other distress, something often overlooked in disability questionnaires but captured by most HRQoL questionnaires (discussed later).

Among all the PROMs measuring disability, the StEP consensus in Perioperative Medicine (Standardise Endpoints in Perioperative Medicine Initiative) has recommended the use of the 12 items WHODAS 2.0 (WHO Disability Assessment Schedule)[53]. The WHODAS 2.0 is a validated questionnaire to assess disability in adult patients across 6 domains: understanding and communicating, getting around, self-care, getting along with people, life activities and participation in society (**appendix 1**). For each question, the patient scores from 0 (no difficulty) to 4 (extreme difficulty). Total score ranges from 0 to 48 points, with higher score indicating higher disability[54]. The score is expressed in percentage of disability with, according to WHO guidelines, none (0–4%), mild (5–24%), moderate (25–49%), severe (50–95%), and complete (96–100%). A minimal clinically important difference has been determined for perioperative patients, with a change of WHODAS 2.0 score of 5% or more after surgery considered clinically relevant[55]. The same study defined a new onset clinically significant moderate disability as "*an increase in WHODAS score of at least 5% to a final WHODAS score of at least 35%*"[55].

In 2018, by using the WHODAS 2.0, a princeps perioperative study published in the New England Journal of Medicine shifted the paradigm of classical postoperative knowledge and perception[21]. This international trial randomized 3000 at-risk patients undergoing major abdominal surgery between liberal and restrictive fluid therapy. Raw survival was relegated to one of the secondary outcomes, while the primary outcome was disability-free survival at 1 year. Using the validated WHODAS questionnaire, disability was defined as a persistent impairment in health status lasting more than 6 months, measured by a WHODAS score of at least 24 points[54]. This pragmatic study revealed, among the survivor, an incidence of persistent disability of 11.5% and 11.1% respectively (*liberal versus restrictive fluids arms*) at one year after surgery. Beyond these results, this large-scale study has further established the growing notion that raw survival is gradually losing its significance in the light of both demographic trends and medical advances. Subsequently, further perioperative studies used the same outcome, confirming its major interest.

A large prospective study followed patients > 55 years old who underwent elective non cardiac surgery up to one year after surgery[56]. Postoperative disability was defined according to the MCID discussed earlier[55]. WHODAS 2.0 was stratified according to an operative stress score (OSS), with OSS 1 corresponding to very low stress to OSS 5 corresponding to very high score. Of the 2921 patients included, 13% experienced disability at three months and 10% at one year after surgery. The patients who underwent more stressful surgery (OSS 4-5) reported an increasing and higher disability at three months and one year after surgery.

Several factors were associated in the literature with the onset or worsening of postoperative disability including frailty, comorbidities, nutritional status, type and complexity of surgery, as well as postoperative factors such as complications and the quality of rehabilitation. Interestingly, to our knowledge, there is no clear data indicating that age itself is associated with postoperative disability[57]. One study found a statistical but clinically irrelevant association between age and disability, with the outcome being a composite measure with mortality[56].

Parallelly, the specific impact of frailty on postoperative disability trajectory remains complex and seems to be dependent of the timing of assessment. A prospective multicentre study investigated the association of frailty with death or new disability 90 days after major elective surgery[58]. Interestingly, in the multivariate analysis, frailty was the only significant predictor of death or new disability. The main limitation of the study was related to its pragmatic design dedicated to preoperative decision making. In this context, disability was measured as a composite outcome with death. Specific results for new disability only were not available. Another large prospective multicentre cohort study investigated specifically the association of preoperative frailty with postoperative disability in the year following major elective noncardiac surgery[59]. Interestingly and as highlighted in other observational studies, in both frail and non-frail groups, patients had a slight increase of their disability in the first postoperative month. At one year, most of the patients with preoperative frailty experienced an improvement of their disability while patients without preoperative frailty had no significant improvement or deterioration of their baseline disability. One severe limitation of this study was that most patients concerned orthopaedic surgery and disability mostly related to mobility. A recent prospective pilot study investigated the association between preoperative frailty and postoperative disability at 3 months after cardiac surgery[60]. The study confirmed an improvement of disability but to a lesser extent in frail patients compared to non-frail. Frail

patients had a lower likelihood of being alive and free of disability at three months following cardiac surgery but, in the other hands, had a higher preoperative disability score.

To date, only one model was specifically developed and validated to predict postoperative death or disability in older patients 6-month after surgery[61]. Disability was defined as a WHODAS score of 16% or greater. Clinically significant disability defined as a WHODAS score 35% or greater was used as a secondary analysis. The prospective study included patients of 70 years old or older, undergoing elective and nonelective surgery (cardiac and non-cardiac). At 6 months after surgery, 12% of the 2176 patients had died, 42% were dead or disabled and 19% had a significant disability. The predictive model had a good discrimination in the internal and external validation data sets with respective AUC of 0.74 (95% CI, 0.69-0.79) and 0.77 (95% CI, 0.74 to 0.80). Unexpectedly, frailty was not considered among the predictor variables, likely because it was not measured in the cohort used for the external validation.

Further and more discriminative predictive models will probably emerge in the near future. Although not specifically focused on high-risk patients, a recent publication used machine learning models to predict disability and pain at one year after lumbar disc herniation surgery[62]. This prospective, multicentre study analysed more than 21’000 patients. The discrimination (C statistic) ranged from 0.81 to 0.84 and only minor heterogeneity was found in calibration slopes and intercepts. Even more interestingly, the authors used a Shapley Additive Explanations (SHAP) values summary plot to display the impact of each variable of the model on the disability outcome (**Figure 1**). This example of variable visualization could be particularly valuable for clinicians, as it enhances their understanding of each variable's impact on the model and facilitates the integration of the model's results with their clinical judgment.

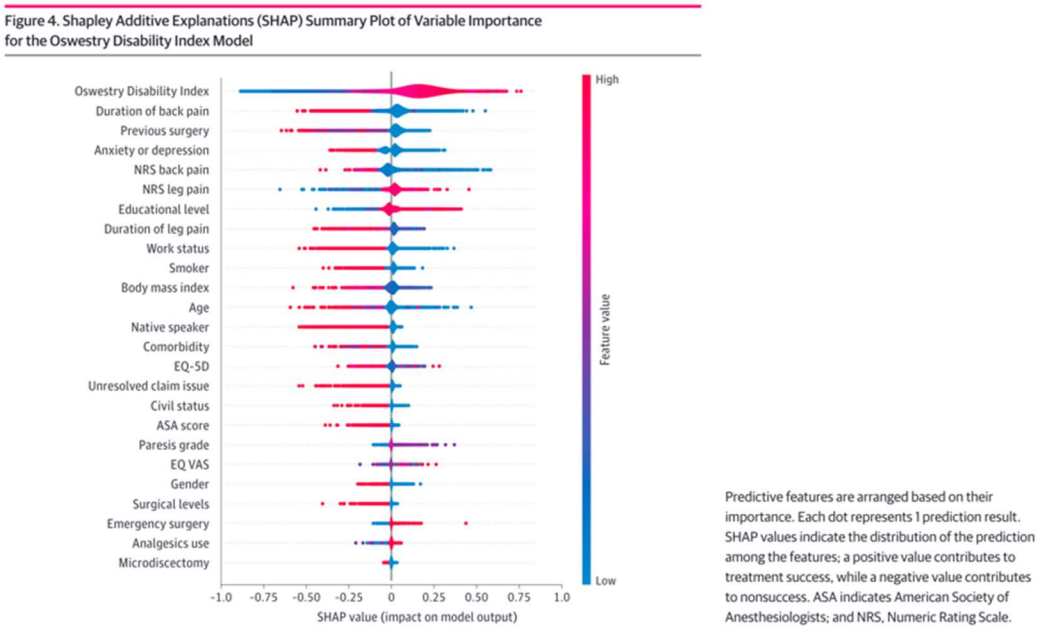

Figure 1: From Berg B et al. Machine Learning Models for Predicting Disability and Pain Following Lumbar Disc Herniation Surgery. JAMA Netw Open 2024; 7:e2355024

Health-related quality of life

In 1948, the WHO defined health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity[63]. This definition immediately sets itself apart from the narrower concept of disability discussed above. Later, the WHO more specifically defined the quality of life as the "*individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*"[64]. However, to date, there is no universally accepted definition of the widely used term "health-related quality of life" (HRQoL). However, the US Food and Drug Administration (FDA) issued an interesting definition of HRQoL which is often used as "*a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life*"[20].

Although incompletely defined, HRQoL is a PRO of major importance in healthcare. As early as 1985, the FDA recommended that a favourable effect on HRQoL was an equivalent alternative to survival for the approval of an anti-cancer treatment[65]. In 1996, the FDA even stipulated that, after survival, HRQoL was the most important outcome for assessing the efficacy of an anti-cancer treatment[66]. From a perioperative perspective, in 2018, the British Journal of Anaesthesia published a series of "systematic review and consensus definitions for standardised endpoints in perioperative medicine" using multiround Delphi consensus process with numerous perioperative clinicians and researchers. In the issue

addressing cancer outcomes, HRQoL was ranked between first and second place, alongside 5-year overall survival, depending on the round[67].

The main limitation of the use of HRQoL as a PRO, is the heterogeneity of HRQoL PROMs[53]. This variability may also explain the lack of a universal definition, as HRQoL is defined by the specific domains and symptoms it assesses. HRQoL is a multidimensional concept encompassing at least three key domains: physical, mental, and social. Despite this heterogeneity, the StEP consensus in Perioperative Medicine has recommended the use of the European Quality of Life-5 Dimensions (EQ-5D) to assess general perioperative HRQoL[53]. The EQ-5D is fast and easy to administer, though its scope is limited to five domains: mobility, self-care, daily activities, pain, and anxiety/depression (**appendix 2**)[68]. One particularly interesting feature of the EQ-5D is its ability to generate negative scores, indicating a state potentially perceived as "*worse than death*"[69]. However, the EQ-5D primary limitation lies in its broad range of the MCID, reported between 0.03 and 0.52, as well as normative differences across age groups, potentially reflecting its limited capacity to assess aspects beyond basic functionality[70,71]. An important point to consider when using HRQoL PROMs is the common availability of an overall score (i.e. EQ-5D VAS; EORTC Global QoL). Overall scores often do not correspond to the sum of the domain-specific scores (e.g., physical, emotional, social), but instead serve as distinct, independent measures[72]. This distinction is crucial to capture because, while overall scores might suggest equivalence between diseased and a healthy populations, individual domain scores can vary significantly, potentially revealing differences that the overall measure fails to capture[72]. To address this issue, some PROMs have introduced summary scores derived from scoring algorithms[73]. Some of these algorithms have demonstrated equal or greater discriminative ability compared to the best-performing single-domain scales within the same measure[74].

Numerous studies investigated the evolution of perioperative HRQoL in different surgical and populational setting. One interesting point is that, as disability, the clinical trajectory of postoperative HRQoL is dependent of the timing of assessment. Most studies, particularly those on cancer surgery, have found that HRQoL typically declines in the initial months following surgery before returning to baseline within 6 months to a year[75]. However, certain domains may remain affected even in the long term[76].

Despite the apparent recovery one year after surgery, a major limitation of observational studies is their reliance on cohort averages (e.g., mean and median). This approach may obscure the presence of outlier patients whose outcomes are masked within these seemingly reassuring results. A multicentre cohort study exploring the effect of surgical

valve replacement on HRQoL found that in all age group explored, between 11.6 to 22.1% of the patients experienced HRQoL deterioration (**Figure 2**)[77]. In this study, frailty was not measured but increasing age was associated with a higher risk of postoperative deterioration in HRQoL. Another prospective study investigating elderly patients (>70 years old) before and after major elective cancer surgery appears to support this possibility, showing that frail patients tend to experience worse postoperative HRQoL[78]. However, by including only elderly patients, the study was unable to investigate the impact of age on HRQoL. Additionally, frailty was assessed using a limited tool rather than the Clinical Frailty Scale (CFS), which is currently the most robust tool to predict postoperative mortality[79].

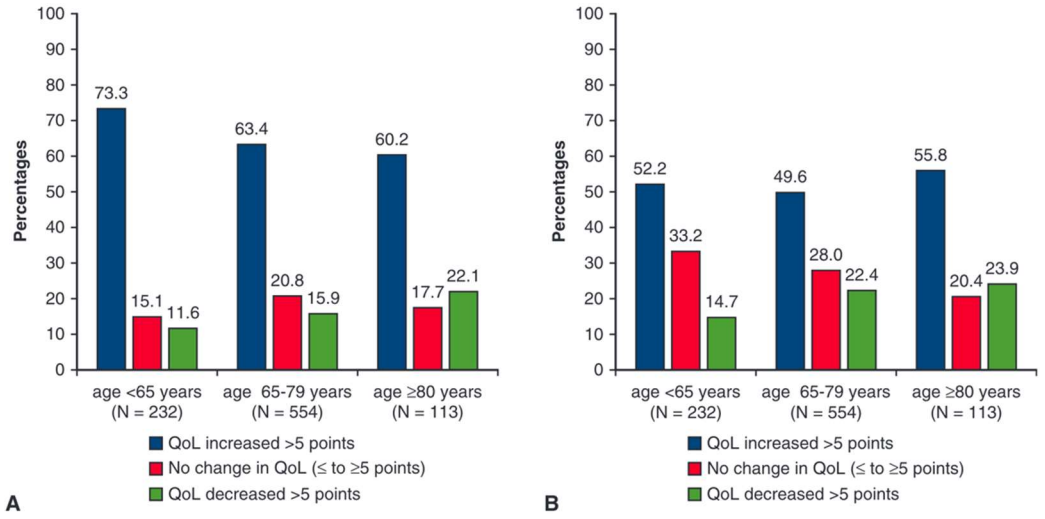

FIGURE 2. A, Difference in quality of life of patients with surgical aortic valve replacement: Physical Component Score. Differences between baseline and 1-year follow-up per age group in the quality of life physical component score; cut-off value 5 points. B, Difference in quality of life of patients with surgical aortic valve replacement: Mental Component Score. Differences between baseline and 1-year follow-up per age group in the quality of life mental component score; cut-off value 5 points. *QoL*, Quality of life.

Figure 2: From Blokzijl F et al. The impact of surgical aortic valve replacement on quality of life—a multicenter study. The Journal of Thoracic and Cardiovascular Surgery 2021; 161:1204-1210.e7

To complement these data, we are currently finalising the follow-up phase of our observational study, which aims to measure HRQoL changes after major abdominal cancer surgery[80]. Our prospective observational cohort study included adult patients undergoing gastrectomy, esophagectomy, pancreas resection and hepatectomy. The primary outcome is the proportion of patients in each group with changes in HRQoL (improvement, stability and deterioration) at 6 months, with an additional follow-up at one year after surgery. By specifically assessing preoperative frailty (using the CFS) and other key preoperative variables, such as disability, we aim to identify patient groups at risk of postoperative deterioration in HRQoL.

The current lack of data, which we aim to partially address through the study described above, is crucial for the development of reliable prediction models. Prediction models addressing HRQoL after surgery are still rare and mainly concern breast cancer surgery without aiming at elderly or frail population[81,82]. Recently, a prediction model was updated for estimate the 1-year risk of low HRQoL in long-term CRC survivors with a good calibration and discrimination (AUC 0.75) but none of the predictors included frailty assessment[83].

Perspectives of Patient-Reported Outcomes in Preoperative Decision-Making for High-Risk Patients

As previously discussed, the number of high-risk patients undergoing moderate to major surgeries is expected to rise for numerous reasons. However, determining the balance between costs and benefits can be complex for these patients, particularly since they often have different health and life priorities. As surgery may not always be the only available option, physicians involved in preoperative decision-making need access to high-quality data. This data should support the development of reliable, probability-based predictions models for a patient's postoperative course, enabling informed discussion with the patient and their close relatives.

Beyond PROs, additional patient-centered outcomes are emerging, enhancing the ability to capture patients' perspectives with greater clarity and addressing their most relevant concerns. One example is "days alive at home" (DAH) which measures the time a patient spends alive and out of hospitals and institutions[84]. DAH may indirectly reflect multiple health burdens such as comorbidities, functional limitation, and hospital/institutions length of stay. This outcome is gaining importance and is recommended by the StEP consensus in Perioperative Medecine[53]. Other PROs may include symptoms or functions specifically impacted by a disease or surgery, often requiring the use of dedicated PROMs. When selecting which PROMs to use, priority should be given to those that have been rigorously validated and translated into the relevant language to ensure accuracy and applicability[85].

The core objective of perioperative medicine is to dedicate time and resources to high-risk patients to enhance informed decision-making, reduce complications, and prevent failure to rescue. In this context, the collection and analysis of perioperative PRO data should focus on high-risk patients by either deliberately including them in studies or identifying outliers within broader cohorts. Although patients who experience postoperative deterioration in PROs may represent a minority, they are the ones most in need of early identification and targeted interventions. Additionally, regardless of whether the treatment is surgical or an alternative, advanced care planning (ACP) should be prioritized for this population[86]. Here again, while not

yet formally tested, data on PROs following major complications and high-burden treatments could provide valuable insight to support ACP discussions.

In the near future, reliable perioperative prediction models are expected to efficiently assist clinicians in the preoperative decision-making process. While current models have limitations, recent studies, as discussed earlier, indicate increasing attention and progress in this field[13,15,61]. Some studies have compared traditional prediction models based on logistic regression with machine-learning models, yielding mixed results. Some machine-learning models outperformed linear models, while others have not[87,88]. One study specifically examined postoperative PROs prediction following hip and knee replacements, finding that machine-learning models outperformed linear models[89]. A recent systematic review focusing on several machine-learning models to predict PROs after surgeries seems to support this finding[90]. Regardless of which model proves superior in the future, the quality of raw data remains the cornerstone for developing reliable prediction models.

Medical and technological advancements have made it possible to care for increasingly frail patients. However, this progress comes with significant economic, demographic, and human costs. Over one-third of care provided in the final year of life is considered futile[91], often resulting in additional suffering for patients, their families and health-care workers[92,93]. As we confront the realities of an aging population and the expanding capabilities of modern medicine, we must also accept the responsibility to continually improve our knowledge and practices to ensure we make the best possible treatment decisions for and with the patients.

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Appendix

1. WHODAS 2.0 12-item version[54]

WHODAS 2.0

WORLD **H**EALTH **O**RGANIZATION
DISABILITY **A**SSESSMENT **S**CHEDULE 2.0

12-item version, self-administered

This questionnaire asks about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.

In the past 30 days, how much difficulty did you have in:						
S1	Standing for long periods such as 30 minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
S2	Taking care of your household responsibilities?	None	Mild	Moderate	Severe	Extreme or cannot do
S3	Learning a new task, for example, learning how to get to a new place?	None	Mild	Moderate	Severe	Extreme or cannot do
S4	How much of a problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	None	Mild	Moderate	Severe	Extreme or cannot do
S5	How much have you been emotionally affected by your health problems?	None	Mild	Moderate	Severe	Extreme or cannot do

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In the past 30 days, how much difficulty did you have in:						
S6	Concentrating on doing something for ten minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
S7	Walking a long distance such as a kilometre [or equivalent]?	None	Mild	Moderate	Severe	Extreme or cannot do
S8	Washing your whole body?	None	Mild	Moderate	Severe	Extreme or cannot do
S9	Getting dressed?	None	Mild	Moderate	Severe	Extreme or cannot do
S10	Dealing with people you do not know?	None	Mild	Moderate	Severe	Extreme or cannot do
S11	Maintaining a friendship?	None	Mild	Moderate	Severe	Extreme or cannot do
S12	Your day-to-day work?	None	Mild	Moderate	Severe	Extreme or cannot do

H1	Overall, in the past 30 days, how many days were these difficulties present?	***Record number of days*** ____
H2	In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition?	***Record number of days*** ____
H3	In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?	***Record number of days*** ____

This completes the questionnaire. Thank you.

2. EQ-5D questionnaire[68]

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐