REVIEW ARTICLE

Negative outcomes and mortality in the frail elderly undergoing major surgery: which risk factors have the greatest impact?

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ABSTRACT

The elderly, often frail, are patients susceptible to numerous complications, both immediate and in the short, medium and long term, following surgical interventions. Depending on their comorbidities, a comprehensive approach should be taken to achieve the best condition of the organs prior to surgery and attempt to maintain it during and after the intervention. Considering the statistical strength of negative outcomes, specifically mortality in elderly patients undergoing major surgery, is truly a challenge. This even extends to other fields such as bioethics, raising a dilemma about dysthanasia when resorting to certain risky interventions in those with a fearful life prognosis. Recently, interesting evidence estimating the incidence, mortality risk and factors associated with negative outcomes in elderly patients undergoing major surgery has been published, suggesting possible modifications in decision-making algorithms for future clinical practice guidelines in surgery. The objective of this review is to analyze updated evidence on which risk factors would have the greatest impact on negative outcomes and mortality in elderly patients undergoing major surgery. A literature search was conducted using the search terms "Major Surgery" and "Elderly," in addition to synonyms, in the PubMed, ScienceDirect, Web of Science and MEDLINE databases. In general surgery and subspecialties, it is very complex to determine precise risk factors that can be extrapolated to all surgical scenarios due to the complexity and specificity of certain organs and procedures. Evidence has found that frail adults undergoing surgery for colorectal cancer, liver metastasis, lung cancer, pancreatic disease and esophageal cancer have the longest hospital stays, and overall mortality is higher in those undergoing oncologic surgery. However, both physical and mental integrity are associated with worse outcomes, and surgical prehabilitation could positively impact this situation by improving functional reserve and post-surgical recovery time.

Keywords: Mortality; Aged; Surgical Procedures, Operative; Risk Factors (Source: MeSH NLM).

Desenlaces negativos y mortalidad en el anciano frágil sometido a cirugía mayor: ¿qué factores de riesgo impactan más?

RESUMEN

El adulto mayor, con frecuencia frágil, es un paciente susceptible a un sinnúmero de complicaciones, tanto inmediatas como a corto, mediano y largo plazo, posterior a una intervención quirúrgica. En función de las comorbilidades presentadas, se debe hacer un abordaje integral para alcanzar el mejor estado orgánico previo a la cirugía e intentar mantenerlo durante y posterior a la intervención. Considerar la fuerza estadística de los desenlaces negativos y, específicamente, de la mortalidad en adultos mayores sometidos a cirugía mayor, es verdaderamente un reto. Incluso, esto trasciende a otros campos como la bioética, al plantearse un dilema sobre la distanasia, cuando se recurre a ciertas intervenciones riesgosas en aquellos con un pronóstico de vida temeroso. Recientemente, se ha publicado evidencia interesante que ha estimado la incidencia, riesgo de mortalidad y factores asociados a desenlaces negativos en adultos mayores sometidos a cirugía mayor,

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planteando posibles modificaciones en los algoritmos de toma de decisiones en futuras guías de práctica clínica en cirugía. El objetivo de esta revisión consiste en analizar evidencia actualizada sobre qué factores de riesgo impactarían más sobre desenlaces negativos y mortalidad en el adulto mayor sometido a cirugía mayor. Se realizó una búsqueda bibliográfica utilizando los términos de búsqueda "Cirugía Mayor" y "Adulto Mayor", además de sinónimos, en las bases de datos PubMed, ScienceDirect, Web of Science y MEDLINE. En cirugía general y subespecialidades, es muy complejo determinar factores de riesgo precisos y extrapolables a todos los escenarios quirúrgicos, debido a la complejidad y especificidad de ciertos órganos y procedimientos. Existe evidencia sobre adultos frágiles que son sometidos a cirugía por cáncer colorrectal, metástasis hepática, cáncer de pulmón, enfermedad pancreática y cáncer esofágico, en donde se registra una mayor estancia hospitalaria; y de forma general, la mortalidad es mayor en aquellos sometidos a cirugía oncológica. No obstante, tanto la integridad física como mental se asocian con peores desenlaces, y la prehabilitación quirúrgica podría impactar de manera positiva sobre esta situación, al mejorar la reserva funcional y tiempo de recuperación posquirúrgico.

Palabras clave: Mortalidad; Anciano; Procedimientos Quirúrgicos Operativos; Factores de Riesgo (Fuente: DeCS BIREME).

INTRODUCTION

With the advancement of science and technology, emergency and essential surgical care and outcomes have become important measures to assess the performance of healthcare practice in this field [1-3]. Based on social determinants of health and on health outcomes—morbidity, mortality, functional ability, life expectancy and health cost—according to international organizations and institutions regarding comprehensive healthcare, surgical decision-making should be solid enough to favorably weigh up these outcomes and obtain the greatest benefit for the patient [4-6]. For this purpose, it is necessary to know and have higher-quality evidence supporting the performance of an intervention, particularly in subgroups at higher risk [7].

The elderly, often frail, are patients susceptible to several immediate and short-, medium- and long-term complications, following surgical interventions [7-9]. Depending on their comorbidities, a comprehensive approach should be taken to achieve the best condition of the organs prior to surgery and attempt to maintain it during and after the intervention [10]. Despite there is not an absolute and definite definition of major surgery, it is presumed that it comprises all complex surgical interventions with high risk of complications, which involve the invasion of the organs with vital functions (generally located within the head, and the thoracic and abdominal cavities) and last at least 90 minutes [11,12]. Considering the statistical strength of negative outcomes, specifically mortality in elderly patients undergoing major surgery, is truly a challenge. This even extends to other fields such as bioethics, raising a dilemma about dysthanasia when resorting to certain risky interventions with fearful life prognosis.

Recently, interesting evidence estimating the incidence, mortality risk and factors associated with negative outcomes in elderly patients undergoing major surgery has been published, suggesting possible modifications in decision-making algorithms for future clinical practice guidelines in surgery [13-17]. Considering that there is very little evidence about this topic and thorough analyses comparing the estimates of clinical risk factors in Spanish to be taken into account in Latin America, the objective of this review is to analyze updated evidence on which risk factors would have the greatest impact on negative outcomes and mortality in elderly patients undergoing major surgery.

SEARCH STRATEGY

A literature search was conducted using the search terms "Major Surgery" and "Elderly," in addition to synonyms, which were combined with the operators "AND" and "OR," in the PubMed, ScienceDirect, Web of Science and MEDLINE databases. The search included any article available in full text assessing the factors associated with negative outcomes and mortality in the elderly undergoing major surgery. However, original studies, systematic reviews and meta-analyses had priority. A total of 125 potentially noteworthy articles were identified, the title and abstract of which were reviewed; and finally, 74 were selected. Articles published up to 2023 were included. The estimates and calculations found were expressed in their original measures: frequencies, percentages, confidence intervals (CI), difference of means (DM), relative risk (RR), odds ratio (OR) or hazard ratio (HR).

Frailty in the elderly and its impact on surgical decision-making

Aging is a physiological process that involves different organ modifications, which make human beings more susceptible to complications and death [18-24]. Currently, the prevalence of cardiometabolic, neurological and endocrine comorbidities as well as polypharmacy in elderly patients are extremely high. These conditions prevent adequate tolerance to some drugs, wound healing, movement, hygiene, recovery of functional ability, among many other key factors during the intra- and postoperative stage [18,20,21,25]. All of this leads to

the well-known frailty, which, in spite of being explained by some defined criteria, can be summed up as a clinical-biological syndrome with high vulnerability of the organs secondary to multi-organ dysregulation and decrease in physiological reserves [22-24], which is a common condition in the elderly with multimorbidity.

As previously mentioned, surgical decision-making is a complex process that depends on several factors, out of which the stability of the patient's organs is one of the most important. Besides frailty, the association between certain conditions—mostly heart disease, polypharmacy, renal disease, neuropathy and pneumopathy—and negative outcomes is very strong in the elderly [26-32]. Paradoxically, some authors have stated that this population has not been extensively studied through randomized controlled trials for general dissemination concerning different specialties, which represents a significant bias when trying to extrapolate results [18], despite the frail elderly are frequently seen in healthcare practice, particularly in low- and medium-income countries, where inequities in social determinants of health prevail. In general, frail subjects with polypharmacy are up to 5.3 (95 % CI: 2.3-12.5) and 2.3 (95 % CI: 1.2-4.4) times more likely to die and become disabled after going to the emergency room [21].

To understand the relevance of this syndrome regarding surgical outcomes, the role of physical prehabilitation and rehabilitation in postsurgical patients should be recognized. Recovery and maintenance of organ functionality are accompanied by their integrity and the body's ability to perform the activities required to achieve this regulation [22,23]. Nevertheless, in the frail elderly, who—at the molecular level—have a significant degree of mitochondrial dysfunction, cellular senescence and poor intercellular communication, this generates failures in the immune system, glucose metabolism and autonomic dysfunction, which makes prompt modulation of organs difficult and also generates disorders in the musculoskeletal, metabolic and stress response systems. This is a cyclic and negative physical frailty phenotype defined by fatigue, which leads to weight loss and weakness and, consequently, slow gait and low physical activity, thereby causing persistent fatigue, and the cycle repeats itself [22,23,24,29]. Therefore, this type of patient is more susceptible to thromboembolic events because of immobility, a higher rate of surgical site or nosocomial infections because of impaired glucose metabolism and immune system, and disability because of difficulty in the rehabilitation process [29] (Figure 1). This would obviously be more severe in major surgery, which is more invasive and involves higher risk.

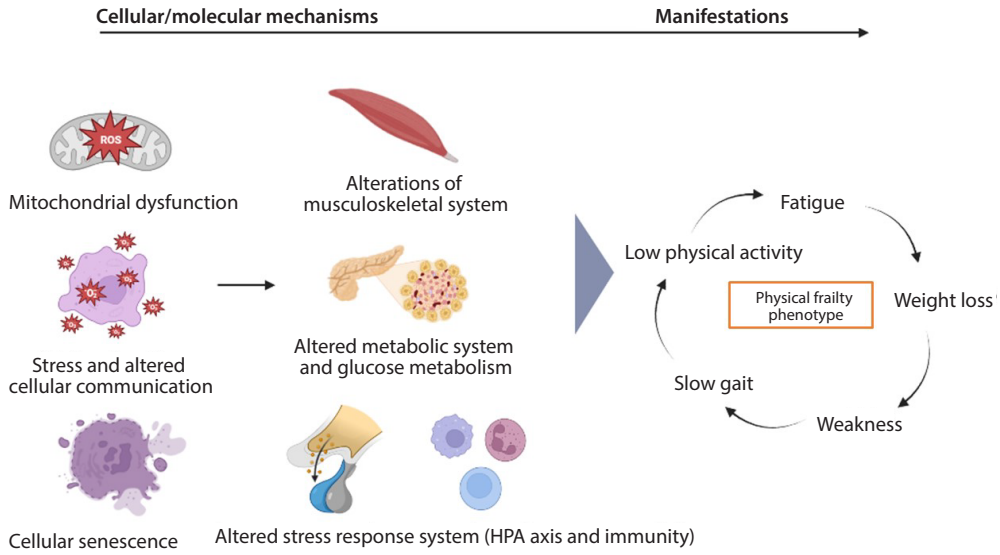

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Figure 1. Graphic description of monocellular and cellular mechanisms that trigger alterations in different organs to generate the physical frailty phenotype [32-36]. HTP: hypothalamic-pituitary-adrenal.

Therefore, surgery of frail patients must include a preoperative risk assessment and optimization process, besides considering the surgery suitability, combining some scales, e.g., the Rockwood clinical frailty scale [33] and the NELA (National Emergency Laparotomy Audit) model [34]. If surgery is performed, intraoperative management should be optimized by avoiding hypothermia, using restrictive fluid therapy and anesthetic agents with wide therapeutic window, considering intensive monitoring and, during the postoperative period, by constantly evaluating and reevaluating organ stress until being sure that the functional recovery process can start (Figure 2). For this reason, some reviews have demonstrated that frailty in the elderly is a predictor of complications, long hospital stay and postoperative mortality [35-37]. From this risk variability, some authors set forth surgical frailty phenotypes based on different domains, which have the potential to predict complications, hospital readmission and quality of life [38].

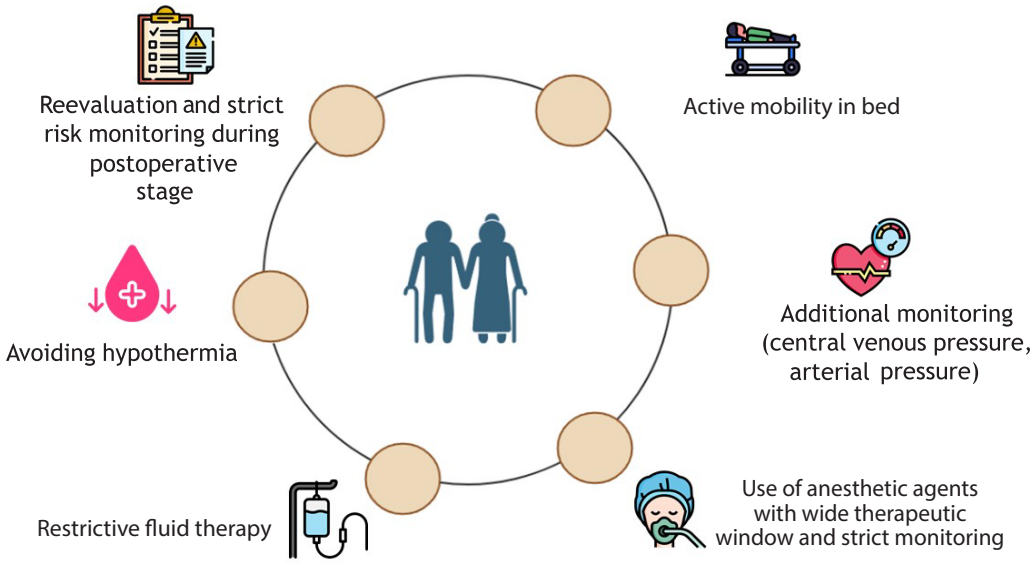

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Figure 2. Basic considerations in intraoperative approach to frail elderly patients [32-37].

Much translational research is still needed to assess and determine the drugs, inputs, times, settings and other variables exerting more influence on this type of outcomes, apart from the optimization of low-resource scenarios, where it is not possible to perform a strict monitoring, to have the chance to choose the safest therapeutic scheme or to provide a comprehensive rehabilitation set with the best quality [39-41]. Nevertheless, recognizing these factors allows the healthcare team to customize, without doubt, the context of frail elderly patients to obtain the best results.

Risk factors associated with negative outcomes and mortality in the elderly undergoing major surgery

In general surgery and subspecialties, it is very difficult to determine accurate risk factors that can be extrapolated to all surgical scenarios because of the complexity and specificity of some organs and procedures. It is evident that some subspecialties involve higher risks than others, which are even more critical in the frail elderly undergoing major surgery. Evidence has demonstrated that frail adults undergoing surgery for colorectal cancer, liver metastasis, lung cancer, pancreatic disease and esophageal cancer require the longest hospital stay. Morbidity is higher in patients undergoing surgery for colorectal and esophageal cancer and repair of an abdominal aortic aneurism. Therefore, higher mortality has been reported particularly in cancer surgery [42]. Also, despite heterogeneous results have been found [43,44], mortality trend in this subgroup has been associated with emergency surgeries and open surgery techniques [45]. Other risk factors described for postsurgical morbidity and mortality [46-48] are the extension of the operative period, malnutrition, fractures caused by osteoporosis, and preoperative blood transfusion.

As to the 30-day survival data, some studies report that postoperative mortality risk increases by 10 % every year after 70 years of age and rises significantly if it is also associated with admission to the intensive care unit and use of inotropes or vasopressors [49]. At the neurological level, the factors associated with the occurrence

and prolonged persistence of delirium are diabetes mellitus, history of stroke, long-standing therapy with benzodiazepines, alcohol consumption and emergency surgical interventions—all of which could be explained by the lack of preoperative optimization [50-52]. For more than 15 years approximately, frailty, based on the criteria and scales defining it, has had the potential to predict postoperative complications (*OR* 2.06; 95 % CI: 1.18-3.60), hospital stay (*OR* 1.69; 95 % CI: 1.28-2.23) and loss of functional ability to perform basic daily activities (*OR* 20.48; 95 CI %: 5.54-75.68) [53]. Even patients in prefrailty condition have shown a higher rate of complications compared to those who are not in such condition (34.7 % vs. 27.5 %; *OR* 1.78; 95 % CI: 1.04-3.05), and it is associated with a long hospital stay [54].

However, as previously mentioned, these estimates vary according to subspecialties. For example, in vascular surgery, prior studies have found a strong and directly proportional relationship between the loss of functional ability and the need for assistance or death within 30 days in the frail elderly (62 % vs. 22 %, *OR* 12.1; 95 % CI: 2.17-66.96; $p < 0.01$) [55]. As to elective surgery, in this group of patients, the frequency of complications ranged between about 25 %, where cognitive impairment (*OR* 2.01; 95 % CI: 1.44-2.81), depression (*OR* 1.77; 95 % CI: 1.22-2.56) and history of smoking (*OR* 2.43; 95 % CI: 1.32-4.46) are predictors of postoperative complication [56,57]. It should be noted that very recent evidence showed that cumulative risk of major surgery over a five-year period was higher in frail elderly patients compared to those who were not in such condition (incidence of 10.3 vs. 6.6 per 100 person-years) [14]. Then, despite age is not an associated risk factor [58,59], in settings with inequities of social determinants of health—where aged patients do not have resources for a balanced diet, live in a polluted environment without access to potable water, with little or no education and an unhealthy lifestyle—a high prevalence of comorbidities is obviously expected due to the intake of hypercaloric diets and little exercise, among other variables. Thus, frailty syndrome is triggered, and negative outcomes occur when a surgical intervention is required. For this reason, studies to determine which factors have the greatest impact according to the sociodemographic and cultural settings, the health of the elderly in a community, the healthcare scenario, the surgical specialty involved and the capacity to optimize healthcare are needed.

Surgical prehabilitation in elderly adults: what impact does it have?

Based on the foregoing, it is evident that surgical prehabilitation is essential to control risk factors, but how essential?

A systematic review identified that, in effect, surgical prehabilitation in the frail elderly promoted positive postoperative outcomes. However, it was specified that, for such purpose, validated scales for surgical patients should be used and the approach included physical exercise, nutrition and psychological assessment, precisely to be able to reduce the intensity or remove factors from the psychosomatic axis [60]. As to colorectal cancer, a slight decrease in the rate of postoperative complications in those who have, at least, two comorbidities (35.9 % vs. 45.5 %) has been found [61]. Concerning oncologic patients, some authors state that it is imperative to make a transition from only assessment to optimization since rehabilitation is still more complex in these patients given that additional factors should be taken into account and, probably, some organs should be given more emphasis than others. Moreover, mental resilience, muscular strength and cardiorespiratory fitness are essential for the evolution and prognosis of frail elderly patients with oncologic pathology [62].

To date, most existing studies that have assessed surgical prehabilitation are related to the frail elderly with some type of gastrointestinal cancer [63] and, unfortunately, there is still a lack of higher-quality evidence of the cost-effectiveness relationship for better decision-making [61]. PRAEP-GO (Pre-habilitation of elderly frail or pre-frail patients prior to elective surgery) trial is currently conducted. It seeks to assess the impact of prehabilitation on the frail elderly undergoing elective surgery regarding care dependence for 12 months, based on multidisciplinary management and decision-making [64]. This is one of the best studies to date, which allows expanding the view of available evidence. Nevertheless, it should be concluded that prehabilitation does cause a favorable trend in functional recovery and reduction of complications and should be suggested to surgical teams.

Future perspectives

Taking care of the elderly at risk is a real challenge because it involves the close relationship with the end-of-life care and quality of life itself [65-67]. Based on the foregoing, the Economic Commission for Latin America and the Caribbean (ECLAC), the Inter-American Development Bank (IDB) and the United Nations (UN) have emphasized the promotion of strategies and plans that contribute to strengthen inclusion, care in the long term, quality of life and rights of older adults.

To date, innovative strategies to promote postsurgical care in different scenarios have been discussed [68,69]. Nevertheless, knowing the current situation of health systems in Latin America and the Caribbean [70,71], it is presumed that it would be difficult to implement such care in the near future. Consequently, evidence about this subject should be spread, knowledge gaps should be accurately identified, and research studies should be formulated to answer possible difficult questions regarding

the problems and allow applying the results in order to obtain serious results.

CONCLUSIONS

Frail elderly are people with inherent high surgical risk because of their systemic instability, the prognosis of which is seriously affected when undergoing major surgery, particularly as to their morbidity, dependence, quality of life and mortality. There are several factors associated with negative outcomes and mortality which depend on the surgical specialty involved and type of surgery performed. However, both physical and mental integrity are associated with worse outcomes, and surgical prehabilitation could positively impact on this situation since it improves functional reserves and postsurgical recovery time.

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