Review

Hell J Surg. 2025 Jan-Mar;95(1):17–22
doi: 10.59869/25055

Morbidity and Mortality of Major Surgical Interventions in the Third Age

Ekaterini Fotopoulou[1], Nikolaos Garmpis[2], Myrto Keramida[3], Dimitrios Mantas[3]

[1]*PhDc at Second Department of Propedeutic Surgery, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

[2]*Surgical Department, Sotiria General Hospital, Athens, Greece*

[3]*Second Department of Propedeutic Surgery, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

ABSTRACT

As the global population ages, the incidence of major surgical interventions in elderly patients—those aged 70 years and older—has increased significantly. By 2050, the number of people aged 60 and above is expected to reach 2.1 billion, necessitating a deeper understanding of the unique challenges faced by this demographic in surgical contexts. This study explores the morbidity and mortality associated with major surgeries in the elderly, emphasizing the impact of comorbidities, reduced physiological resilience, and the importance of preoperative and postoperative care. A comprehensive review of existing literature was conducted, focusing on perioperative morbidity, mortality rates, and factors such as cardiovascular, pulmonary, and renal function. The findings underscore the necessity of a multidisciplinary approach in managing surgical patients in this age group, highlighting the role of frailty as a more accurate predictor of surgical outcomes than chronological age. Despite advances in surgical techniques and anesthetic management, the elderly remain at higher risk of postoperative complications and mortality. The study advocates for individualised care strategies and improved preoperative assessment tools to optimize surgical outcomes and reduce the burden on healthcare systems.

Key Words: *Morbidity and mortality; third age; major abdominal procedures*

INTRODUCTION

Among the questions of concern in the third millennium are demographic shifts, particularly the increase in the elderly population, elderly being those aged seventy years and over. By 2050, the global population aged 60 years and older is expected to reach nearly 2.1 billion. In treating the elderly patient, apart from the pathology and the need for a solution to current complaints, the general condition of the patient is also taken into account [1]. Geriatric care is critical, as advanced age often requires more healthcare services, including major surgery. Elderly patients undergoing major surgery face unique challenges and increased risks of morbidity and mortality [2].

Elderly patients frequently suffer from multiple comorbidities such as cardiovascular disease, diabetes, respiratory problems, and renal failure, all of which can impact surgical outcomes. Reduced physiological resilience and decreased functionality of body systems further increase the risk of complications during and after surgery. This highlights the importance of careful preoperative assessment, optimisation of preoperative health, and intensive postoperative care [3].

Investigating morbidity and mortality in elderly pa-

Corresponding author:
Dimitrios Mantas
Professor of Surgery
LAIKO General Hospital, Ag. Thoma 17, 11527 Goudi, Athens
Tel.: +30 6977 203794, e-mail: dvmantas@med.uoa.gr

Submission: 24.01.2025, Acceptance: 05.07.2025

tients undergoing major surgery is crucial for understanding risks and developing strategies to reduce them. Comparing morbidity and mortality rates between elderly patients, geriatric patients, and the general adult population, as well as between planned and emergency interventions, can reveal critical differences that affect outcomes [4].

This study focuses on analyzing these parameters to improve the management of elderly patients and enhance surgical results. The findings can help develop best practices and implement individualised strategies to reduce morbidity and mortality, thereby improving the quality of life for elderly patients.

MATERIALS AND METHODS

To analyse perioperative morbidity and mortality in elderly patients, we conducted a literature review using databases such as PubMed, Scopus, and Google Scholar. Keywords included "morbidity," "mortality," "elderly patients,""surgery,""preoperative evaluation," and "postoperative care." Emphasis was placed on publications providing data on parameters influencing surgical outcomes in the elderly, such as cardiovascular status, pulmonary function, renal function, and nutritional status.

A total of 83 studies were identified through database searches (PubMed, Scopus, Google Scholar). After title and abstract screening, 56 were assessed for eligibility. Of these, 42 met inclusion criteria and were included in the final review. Studies were excluded due to incomplete data, lack of relevance to elderly populations, or absence of mortality/morbidity outcomes.

RESULTS

The review focused on elderly patients aged 65 years and over, with particular emphasis on those aged 80 years and older and included comparisons with the general adult population. Parameters examined included perioperative morbidity, 30- and 90-day mortality, comorbidities, functional and nutritional status, and preoperative and postoperative care strategies. The use of scoring systems, such as the ASA scale, to predict risks and assess patient conditions was also considered.

Among the accepted studies, 65% focused on elective procedures, while 35% addressed emergency interventions. The 30-day postoperative mortality ranged from 2% to 19% for elective surgeries and 12% to 33% for emergency procedures. Frailty was evaluated in 70% of the studies, with the most frequently used tools being the Frailty Index and the Clinical Frailty Scale. Nutritional status, comorbidities (especially cardiovascular and renal), and age ≥80 were consistently linked with higher complications

DiscussionAs the population ages, the rate of surgery among the elderly increases. Major surgery and related interventions, such as blood transfusion, place a heavy burden on patients. Complications after surgery can lead to higher mortality rates in older patients up to one month later. There has been a noticeable increase in surgical interventions for older patients in recent years, including a surge in more complex operations that demand careful consideration [5]. While surgery has substantially improved with advanced understanding of disease and sophisticated assessments, it also presents significant challenges in managing elderly patients, who often require special attention. Patient selection for surgery now entails an in-depth examination of frailty, utilizing innovative scoring systems that have revolutionised the field, and actively challenging preconceived ideas and prejudices to ensure optimal outcomes and personalised care for the aging population [6].

Elderly patients nowadays undergo major surgery more frequently compared with the past. There has been a significant increase in the NHS England percentage of adults aged 60 and over seen on a per annum basis. Specifically, 2.5 million people over the age of 75 underwent surgery between 2014 and2015, up from 1.5 million between 2006 and2007, with 30% of those being over 85 years of age. Over the same timescales, there has been a slight decline in the percentage of patients seen aged under 40 and aged 40 to 60. A similar pattern of increased aging is occurring in hospitals in Australia. There, women over 85 now account for the majority of emergency surgical admissions [7].

Advanced age increases the risk of mortality and morbidity after surgery, but frailty, a decline in multiple physiological systems, is a better predictor than chronological age. There are a number of useful measuring tools designed to detect the presence of frailty in the older surgical patient. These can be either patient reported (using questionnaires) or specific practical tests. The frailty phenotype model includes features such as sluggishness, weakness, exhaustion, weight loss, and low physical activity. The cumulative deficit (FI) model assesses frailty through the accumulation of deficits, with higher scores indicating greater frailty [8]. Even that there is no standardised method of measuring frailty, and with over 20 different instruments identified, a novel classification by Rockwood, a Canadian geriatrician, has gained prominence to the extent of the many criteria, like disease or disability burdens or leisure activities, designed to measure frailty among the senior citizens. The advantage of this classification stems in its ease of use while providing a very

robust model with a robust specificity and sensitivity to detect frail older adults [9].

In a population increasingly characterised as frail, but difficult to identify, measure, or predict - surgical risk assessment has undergone a radical shift in recent years. Traditionally, assessment was based on generalised markers of ill-health, severity of comorbid conditions, and overall negative physiological decline, within the safe bubble of a fairly theoretical assumption that said patients would be likely to return to pre-illness level of function after major surgical intervention; today, the focus is much more on identifying the impact of a multiplicity of functional and physical losses predicting a decreased, burdened ability to regain preoperative health status [10, 11].

The very elderly (age ≥ 80 years) frequently experience frailty influenced by medical comorbidities, nutritional status, mental health, social support, and cognitive function.These individuals are at a heightened risk of negative outcomes from physiological stress and illness [8]. Morbidity and mortality of major surgical intervention in the growing third age population remain a present challenge, although anaesthetic management is clearly improved. Emergency surgery is particularly a grey area, and older patients are more likely to present on an emergency basis. Recent figures suggest that once admitted to hospital for acute illness, the third age patients are much more likely to have surgery. The third age patient is expected to preponderate in all categories of surgery in the near future. Advances in anaesthetic management, preoperative evaluation, and management do have an important effect on patient outcome, improvement in the overall outcome, and cost efficiency of surgery in a health system. However, older age exposes patients to greater risks of postoperative complications and mortality compared with younger patients experiencing the same operation [12, 13].

Preoperative assessment in the older population is complex due to the heterogeneity of coexisting chronic diseases. Management guidelines are difficult to develop and generalisation of evaluation results is challenging. Anesthesia risks in those over 80 vary based on surgery type, urgency, age, and comorbidity. In emergency cases, surgical intervention is more complicated and riskier due to deteriorated physiological function. Balancing expectations and poor outcomes in older patients is a challenge [14]. More research is needed to improve outcomes and cost efficiency in surgical management. Assessment tools such as the ASA Physical Status Classification Systemhave proven useful in predicting complications and mortality in elderly patients. Age and comorbidities should not be the only factors for surgical referral; tools like the ASA classification can help surgeons inform patients and families about the risks prior to procedures [15].

Gastrointestinal cancer is becoming increasingly prevalent among the elderly, driven by an ageing population and the cumulative genetic damage that occurs over time. The incidence of this cancer for those over 65 is rising swiftly. The U.S. population aged 65 and older is expected to grow from 35 million to 70 million by 2030. The median age of death for pancreatic, stomach, and colorectal cancers falls between 71 and 77 years. Surgical resection remains the sole treatment option for localised gastrointestinal cancers. Almost 30% of all operations performed for colon and rectal cancer are in patients over seventy, and postoperative recovery is influenced by various physiological changes that occur with ageing, such as cognitive, functional, and communication limitations [16].

Among cancers, lung cancer was the most common cause of death in the elderly in 2016, with a rate of 192.4 per 100,000 elderly residents. Prostate, colon, and breast cancers had lower death rates. Additionally, in some EU Member States, death rates from cerebrovascular diseases were higher than from ischaemic heart diseases [17].

While postoperative complications are more common in older adults, age should not be the sole factor in determining treatment, as individuals of the same age can differ significantly in their physical and mental health. Despite older patients having similar survival rates to younger patients following oncological surgeries, geriatric patients often do not receive oncology care due to age-related biases.

The care of elderly cancer patients must be a collaborative product of a multidisciplinary team that includes surgeons, oncologists, geriatricians, and psychologists. Differentiation of cancer types is avoided to provide a general overview. Factors such as functional status, cognition, depression, nutritional status, mobility and ASA score are associated with adverse postoperative outcomes regardless of age. Screening tools can aid in preoperative evaluation to mitigate complications, although their use has not been widely adopted [15].

Modifiable risk factors such as nutritional status and physical activity must be prepared and improved before surgery. Preoperative rehabilitation can reduce postoperative morbidity and improve patients' functional status. However, there is controversy over whether these preparations delay necessary surgery [18].

It is important to recognise the influence of different health systems, cultures, and economies on cancer treatment in the elderly. Health systems' incentives influence surgical judgment. In public health systems, performance is related to financial gain, while in private systems, performance is based on saving money. Surgeons must

consider these influences when making decisions about treating patients [19].

In 2016, circulatory diseases were the primary cause of death among the elderly in the EU, whereas cancer was the main cause of death for individuals under 65. Specifically, around 40.3% of deaths among the elderly were attributed to circulatory diseases, 23.4% to cancer, and 8.1% to respiratory diseases. Older women had higher rates of death from circulatory disease (43.3%) compared to men (36.8%), while older men had higher rates of death from cancer (28.1% vs. 19.3%) and respiratory diseases (9.2% vs. 7.2%) [20]. In contrast, for those under 65, cancer was the leading cause of death, with rates of 47.8% for women and 32.1% for men. Deaths from respiratory diseases accounted for 4.4% of all deaths in people under 65, while circulatory diseases accounted for 24.1% of deaths in men and 16.6% in women [17]. Sata show that the standardised death rates for ischaemic heart disease, cerebrovascular disease, respiratory disease, and lung disease were higher among older adults in 2016. Specifically, the standardised death rate for ischaemic heart disease was 538.2 deaths per 100,000 elderly residents, while for cerebrovascular diseases it was 384.5 per 100,000 elderly residents [21].

In the setting of the geriatric patient, it is particularly important to guarantee the benefits, requiring careful comprehensive management. Alteration of the biological equilibrium of the elderly is clearly evident in clinical and functional characteristics that distinguish them from other patients who are candidates for cardiac surgery and general surgery. Cardiological evaluation is essential and represents the keystone from which to develop the diagnostic therapeutic plan in elderly patients. Geriatric evaluation can provide information on the degree of disability, but can also give rise to general recommendations of disease-oriented strategies and treatment. From the data shown by different surgical disciplines, it strengthens the concept of the necessity of a "multidisciplinary" approach to consider the elderly patient and to face the complex problems posed by surgical therapy in the third age. In this setting, the multidisciplinary approach should not only be a collection of different professionals according to specific professional capabilities, operating unit by operating unit, but should aim at the concept of a shared action in which each involved member tries, starting from their own specific competences, to contribute to the global goals of personalised geriatric intervention [22]. There is a lack of comprehensive data on the surgical care of the elderly. Only a limited number of studies have detailed the differences in care between older and younger patients [21].

Comparing postoperative factors, elderly patients had fewer aggressive interventions and lower resource utilisation despite having more comorbidities and an increased incidence of trauma. In contrast, the middle age group (65-79) had higher rates of resource use, such as intensive care and length of hospital stay, despite a lower rate of trauma [20]. Few studies have evaluated the use of postoperative intensive care for the elderly. One US database did not include ICU admission, while another study showed reduced rates of ICU admission for patients 80+ years of age. Factors such as the presence of malignancy and its staging may influence the decision to admit to the ICU [18].

The identification of postoperative complications was less frequent in the older age group even though they had multiple comorbidities. This could be attributed to a tendency for less rigorous monitoring and intervention in elderly patients. Although guidelines and scoring systems have been established to determine the appropriateness of interventions, their implementation remains limited [17].

A recent report from the Royal College of Surgeons of England highlighted the challenges in emergency surgery, reporting that the mortality in people over 80 was over 25%, with wide variations between hospitals. Elderly individuals over the age of 80 now represent a substantial portion of hospital admissions, and their numbers are projected to double by 2030 [23].The study aimed to determine mortality in patients over 80 years of age undergoing emergency surgery at a large UK teaching hospital. Of 4,069 admissions, 521 patients were over 80 years of age, with a 30-day mortality of 19%. Factors such as poor preoperative status (ASA > III) and cardiac comorbidities contributed to postoperative complications [24]. Hessman et al. emphasised that age should not preclude surgery, as ASA score is a better predictor of mortality. The ASA score, which assesses physical health in five categories, shows that higher categories are associated with an increased risk of complications. Similarly, Abbas and Booth reported a mortality of 29% after emergency abdominal surgery, but only 7.5% after elective procedures [25,26].

Studies in the United Kingdom, such as that of Saunders et al., showed a mortality of 24.4% in patients over 80 years of age after emergency laparotomy. Byrne et al. suggested looking at mortality at 90 days as complications may occur beyond the 30-day window. A review of 17 studies showed a 30-day mortality of 0–13% after elective colorectal resection, highlighting the need for long-term follow-up of mortality in elderly patients [27,28].

CONCLUSION

This review underscores the complexity of surgical care in elderly populations, where factors like frailty, comorbidities, and emergency presentation heavily influence outcomes. Frailty—more than chronological age—has

emerged as the most reliable predictor of morbidity and mortality. Various frailty scoring systems, including the Clinical Frailty Scale and the Rockwood Frailty Index, are increasingly being integrated into perioperative risk assessments.

Minimally invasive surgical (MIS) approaches have shown promising results in elderly patients, with studies indicating reduced postoperative complications, shorter hospital stays, and lower mortality when compared to open procedures. However, patient selection remains critical, especially in the context of complex or emergent cases.

Prehabilitation protocols, including aerobic training, nutritional optimisation, and mental health support, have been shown to enhance functional status and reduce complications. However, standardised implementation is still lacking, and further research is needed to evaluate long-term benefits.

Emergency surgeries remain associated with the highest mortality rates, particularly in patients over 80 with multiple comorbidities. Delayed interventions due to poor initial optimisation contribute to the disparity between elective and urgent procedures. There is a growing consensus that risk calculators incorporating functional status and nutritional metrics better predict outcomes than traditional tools like ASA scores alone.

The findings *of this review advocate for multidisciplinary preoperative evaluation, early identification of frailty, and tailored perioperative plans to reduce the burden of postoperative complications in the ageing surgical population.*

Author's contribution: *EF, NG, DM gave a substantial contribution to the conception and design of the work. MK, NG gave a substantial contribution of data. EF, MK gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. EF, NG, MK, MD had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

Financial support and sponsorship: *Nil.*

Conflicts of interest: *There are no conflicts of interest.*

REFERENCES

1. Amuthavalli Thiyagarajan J, Mikton C, Harwood RH, Gichu M, Gaigbe-Togbe V, Jhamba T, et al.TheUN Decade of healthy ageing: strengthening measurement for monitoring health and wellbeing of older people. Age Ageing. 2022 Jul;51(7):afac147. Doi: 10.1093/ageing/afac147.
2. Etzioni DA, Liu JH, Maggard MA, Ko CY. The aging population and its impact on the surgery workforce. Ann Surg. 2003 Aug;238(2):170-7. Doi: 10.1097/01.SLA.0000081085.98792.3d.
3. Kang SJ, Jung SI. Age-Related morbidity and mortality among patients with COVID-19. Infect Chemother. 2020 Jun;52(2):154-64. Doi: 10.3947/ic.2020.52.2.154.
4. Partridge JS, Harari D, Martin FC, Dhesi JK. The impact of pre-operative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: a systematic review. Anaesthesia. 2014 Jan;69 Suppl 1:8-16. Doi: 10.1111/anae.12494.
5. Seese L, Sultan I, Gleason TG, Navid F, Wang Y, Thoma F, et al. The impact of major postoperative complications on long-term survival after cardiac surgery. Ann Thorac Surg. 2020 Jul;110(1):128-35. Doi: 10.1016/j.athoracsur.2019.09.100.
6. Egol KA, Konda SR, Bird ML, Dedhia N, Landes EK, Ranson RA, et al. Increased mortality and major complications in hip fracture care during the COVID-19 Pandemic: A New York City Perspective. J Orthop Trauma. 2020 Aug;34(8):395-402. Doi: 10.1097/BOT.0000000000001845.
7. McIsaac DI, Bryson GL, van Walraven C. Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: A Population-Based Cohort Study. JAMA Surg. 2016 Jun 1;151(6):538-45. Doi: 10.1001/jamasurg.2015.5085.
8. Hall DE, Arya S, Schmid KK, Blaser C, Carlson MA, Bailey TL, et al. Development and initial validation of the risk analysis index for measuring frailty in surgical populations. JAMA Surg. 2017 Feb 1;152(2):175-82. Doi: 10.1001/jamasurg.2016.4202.
9. Aguilar-Frasco JL, Rodríguez-Quintero JH, Moctezuma-Velázquez P, Morales-Maza J, Moctezuma-Velázquez C, Pastor-Sifuentes F, et al. Frailty index as a predictive preoperative tool in the elder population undergoing major abdominal surgery: a prospective analysis of clinical utility. Langenbecks Arch Surg. 2021 Jun;406(4):1189-98. Doi: 10.1007/s00423-021-02128-6.
10. Bierle DM, Raslau D, Regan DW, Sundsted KK, Mauck KF. Preoperative evaluation before noncardiac surgery. Mayo Clin Proc. 2020 Apr;95(4):807-22. Doi: 10.1016/j.mayocp.2019.04.029.
11. Zhang LM, Hornor MA, Robinson T, Rosenthal RA, Ko CY, Russell MM. Evaluation of postoperative functional health status decline among older adults. JAMA Surg. 2020 Oct;155(10):950-8. Doi: 10.1001/jamasurg.2020.2853.
12. Dencker EE, Bonde A, Troelsen A, Varadarajan KM, Sillesen M. Postoperative complications: An observational study of trends in the United States from 2012 to 2018. BMC Surg. 2021 Nov6;21(1):393. Doi: 10.1186/s12893-021-01392-z.
13. Shinall MC Jr, Arya S, Youk A, Varley P, Shah R, Massarweh NN, et al. Association of preoperative patient frailty and operative stress withpostoperative mortality. JAMA Surg. 2020 Jan;155(1):e194620. Doi: 10.1001/jamasurg.2019.4620.
14. Gan S, Yu Y, Wu J, Tang X, Zheng Y, Wang M, et al. Preoperative assessment of cognitive function and risk assessment of cognitive impairment in elderly patients with orthopedics: A cross-sectional study. BMC Anesthesiol. 2020 Aug;20(1):189. Doi: 10.1186/s12871-020-01096-6.
15. Robinson TN, Walston JD, Brummel NE, Deiner S, Brown CH 4th, Kennedy M, et al. Frailty for surgeons: Review of a National Institute on Aging Conference on Frailty for Specialists. J Am Coll Surg. 2015 Dec;221(6):1083-92. Doi: 10.1016/j.jamcollsurg.2015.08.428.

16. You YN, Hardiman KM, Bafford A, Poylin V, Francone TD, Davis K, et al. The American Society of Colon and rectal surgeons clinical practice guidelines for the management of rectal cancer. Dis Colon Rectum. 2020 Sep;63(9):1191-222. Doi: 10.1097/DCR.0000000000001762.
17. The top 10 causes of death [Internet]. Who.int. [cited 2024 Jul 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
18. Mortality and life expectancy statistics [Internet]. Europa.eu. [cited 2024 Jul 21]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Mortality_and_life_expectancy_statistics
19. Colla CH, Lewis VA, Shortell SM, Fisher ES. First national survey of ACOs finds that physicians are playing strong leadership and ownership roles. Health Aff (Millwood). 2014 Jun;33(6):964-71. Doi: 10.1377/hlthaff.2013.1463.
20. Carli F, Scheede-Bergdahl C. Prehabilitation to enhance perioperative care. Anesthesiol Clin. 2015 Mar;33(1):17-33. Doi: 10.1016/j.anclin.2014.11.002.
21. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, et al. PersonalisedPrehabilitation in high-risk patients undergoing elective major abdominal surgery: A Randomized Blinded Controlled Trial. Ann Surg. 2018 Jan;267(1):50-6. doi: 10.1097/SLA.0000000000002293.
22. Taberna M, Gil Moncayo F, Jané-Salas E, Antonio M, Arribas L, Vilajosana E, et al. The Multidisciplinary Team (MDT) approach and quality of care. Front Oncol. 2020 Mar;10:85. Doi: 10.3389/fonc.2020.00085.
23. Parliament.uk. [cited 2024 Aug 2]. Available from: https://www.parliament.uk/business/publications/research/key-issues-for-the-new-parliament/value-for-money-in-public-services/the-ageing-population/
24. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal perioperative management of the geriatric patient: A Best Practices Guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg. 2016 May;222(5):930-47. Doi: 10.1016/j.jamcollsurg.2015.12.026.
25. Hessman O, Bergkvist L, Ström S. Colorectal cancer in patients over 75 years of age--determinants of outcome. Eur J Surg Oncol. 1997 Feb;23(1):13-9. Doi: 10.1016/s0748-7983(97)80136-9.
26. Abbas S, Booth M. Major abdominal surgery in octogenarians. N Z Med J. 2003 Apr 17;116(1172):U402.
27. Saunders DI, Murray D, Pichel AC, Varley S, Peden CJ; UK Emergency Laparotomy Network. Variations in mortality after emergency laparotomy: The first report of the UK Emergency Laparotomy Network. Br J Anaesth. 2012 Sep;109(3):368-75. Doi: 10.1093/bja/aes165.
28. Byrne BE, Mamidanna R, Vincent CA, Faiz O. Population-based cohort study comparing 30- and 90-day institutional mortality rates after colorectal surgery. Br J Surg. 2013 Dec;100(13):1810-7. Doi: 10.1002/bjs.9318.