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The impact of frailty on outcomes following emergency laparotomy: Enhancing risk prediction and clinical decision-making

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The impact of frailty on outcomes following emergency laparotomy: Enhancing risk prediction and clinical decision-making

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Department of Surgery, Institute of Clinical Medicine, Faculty of Medicine, University of Tartu

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To my beloved wife Kristina and
children Karl Mattias,
Karl Joosep and Sandra

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to the text per their Roman numerals:

I **Isand KG**, Hussain S, Sadiqi M, Kirsimägi Ü, Bond-Smith G, Kolk H, Saar S, Lepner U, Talving P. Frailty Assessment Can Enhance Current Risk Prediction Tools in Emergency Laparotomy: A Retrospective Cohort Study. *World Journal of Surgery* 2023;47(11):2688–2697.

II **Isand KG**, Hussain S, Sadiqi M, Kirsimägi Ü, Bond-Smith G, Kolk H, Saar S, Lepner U, Talving P. Impact of frailty on outcomes following emergency laparotomy: a retrospective analysis across diverse clinical conditions. *European Journal of Trauma Emergency Surgery* 2024;50(6):3299–3309.

III **Isand KG**, Aim A, Bahhir A, Uuetoa M, Kolk H, Saar S, Lepner U, Talving P. Impact of preoperative frailty on outcomes in patients subjected to emergency laparotomy: a prospective study. *European Journal of Trauma Emergency Surgery* 2025;51(1):34.

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Papers I–III: contributed to the study conception and design, material preparation, data collection, data analysis and interpretation of the results, writing of the draft and critical revision, submission and correspondence.

ABBREVIATIONS

ACS-N SQIP	American College of Surgeons National Surgical Quality Improvement Program
ADLs	Instrumental Activities of Daily Living
AIC	Akaike Information Criteria
ANZELA	Australian and New Zealand Emergency Laparotomy Audit
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
DTS	Delay to Surgery
EGS	Emergency General Surgery
EL	Emergency Laparotomy
EPR	Electronic Patient Records
FI	Frailty Index
HR	Hazard Ratio
ICD	International Classification of Disease
ICU	Intensive Care Unit
IQR	Interquartile Range
IRR	Incidence Rate Ratio
LOS	Length of Stay
mFI	Modified Frailty Index
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NELA	National Emergency Laparotomy Audit
OR	Odds Ratio
POSSUM	Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity
P-POSSUM	Portsmouth- Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity
ROC	Receiver Operating Characteristic
RPT	Risk Prediction Tool
RR	Risk Ratio

1. INTRODUCTION

The demographic landscape of modern healthcare is being fundamentally reshaped by an increasingly ageing global population. As longevity improves and birth rates decline, the proportion of older adults is evolving across high- and middle-income countries alike. This demographic shift presents considerable challenges to healthcare systems, not least in the domain of acute and emergency surgical care, where older patients now constitute a growing proportion of those undergoing high-risk procedures (He et al., 2015; Pérez-Zepeda et al., 2021).

Frailty, a multidimensional syndrome characterised by diminished physiological reserve and increased vulnerability to stressors, has emerged as a crucial construct for understanding variability in outcomes among older adults (Buta et al., 2016; Church et al., 2020). Unlike chronological age or comorbidity alone, frailty provides a more comprehensive framework for evaluating a patient's functional status and resilience in the face of illness or surgical intervention (Clegg et al., 2013). In particular, the Clinical Frailty Scale (CFS) has gained prominence for its ease of use, strong prognostic value, and applicability across diverse clinical contexts (Rockwood et al., 2005; Rockwood & Theou, 2020; Church et al., 2020).

There is currently robust evidence linking frailty to increased 30-day mortality and other short-term postoperative outcomes in patients undergoing emergency general surgery (EGS), including emergency laparotomy (EL) (Hewitt et al., 2015; Kennedy et al., 2022; Park et al., 2024). Yet, despite its predictive value, frailty is not routinely incorporated into established surgical risk-stratification models, and its role in guiding clinical decision-making remains underdeveloped (Barazanchi et al., 2020; Eliezer, 2020; Vaughan et al., 2022).

The impact of frailty on long-term outcomes in EL remains relatively underexplored. EL is performed for a broad range of indications across diverse clinical settings, and it is not yet clear whether the poorer outcomes observed in frail individuals are partly attributable to differences in surgical indication, or clinical presentation compared to non-frail patients (Nally et al., 2020; Park et al., 2024).

Importantly, frailty is not an irreversible condition. Emerging research suggests that when inadequately addressed, frailty may predispose patients to further loss of independence and long-term functional decline following EL (Zattoni et al., 2021; Tan et al., 2019; Hwang et al., 2023). These findings highlight the need for a better understanding of frailty's role in shaping postoperative trajectories.

The aim of this doctoral thesis is threefold: firstly, to assess whether existing surgical risk prediction tools can be improved by incorporating frailty; secondly, to describe long-term outcomes following EL and examine whether the effects of frailty are confounded by differences in indication and clinical presentation; and thirdly, to characterise the prevalence of frailty and its impact on surgical outcomes in patients undergoing EL in referral health-care facilities in Estonia.

2. REVIEW OF THE LITERATURE

2.1 Aging Population

The global demographic landscape is undergoing a significant transformation, characterized by a rapidly increasing proportion of older individuals. This trend is primarily driven by declining birth rates and improved life expectancy due to advancements in social welfare and medical care. Worldwide, the proportion of individuals aged 65 and older is projected to rise from approximately 10% to nearly 25% by 2050 (He et al., 2015).

This demographic shift poses significant challenges. As the working-age population declines, an increasing proportion of resources must be allocated to pensions, social welfare, and healthcare to support the expanding elderly population. The impact of population aging varies across socio-economic contexts. While developed countries are already facing its consequences, developing nations are expected to undergo similar transitions, often at a more rapid pace. For example, in Canada, individuals aged 65 and older constituted 17.2% of the population in 2018, a figure projected to approach 30% by 2030 (Pérez-Zepeda et al., 2021). In Europe, the population aged 65 years and older accounted for approximately 20% in 2021 and is anticipated to reach 30% by 2050, with fewer than two working-age adults per older individual (European Comission, 2023).

2.2 Frailty

The aging population presents significant challenges to the healthcare sector. The care of an increasing number of elderly individuals depends on a shrinking workforce. At the same time advancing age is associated with greater social, psychological, and physical health needs (Collard et al., 2012; O'Caoimh et al., 2021). However, not all older adults require the same level of care, and some younger individuals may have more complex healthcare needs compared to their older counterparts (Pérez-Zepeda et al., 2021). This variability is measured by frailty, a state characterised by diminished function and physiological reserve, resulting in increased vulnerability to stressors. In a clinical context, such stressors may include acute illness, injury, or medical treatment (Buta et al., 2016; Church et al., 2020).

The concept of frailty emerged in geriatric medical literature around the mid-20th century (Sobhani et al., 2021). In 1978, the U.S. Federal Council on Aging introduced the term "frail elderly" to describe older individuals, typically over the age of 75, who require multiple health services for activities of daily living due to multimorbidity (Lewis, 1978). Since then, the definition of frailty has been refined, and efforts have been made to develop objective assessment tools to better characterise and measure it.

Although frailty is a core concept in geriatric medicine and gerontology and is widely recognised, researchers have yet to establish a universally accepted defi-

nition, conceptual framework, or standardized operational model for frailty (Sobhani et al., 2021). While frailty is often associated with advanced age and multimorbidity leading to adverse clinical outcomes, a definitive definition remains elusive, as frailty is neither an inevitable consequence of aging nor a disease with a clearly defined onset. It is generally accepted as distinct from disability and comorbidity, supported by a consensus document by Rodríguez-Mañas (Gobbens et al., 2010; Rodríguez-Mañas et al., 2013), although some authors consider these conditions to overlap with frailty (L. P. Fried et al., 2004).

Currently, approximately 70 different frailty definitions and assessment tools exist across the literature and in clinical settings, which can be broadly categorised into two models: (1) those focusing on the physical aspects of frailty and (2) those defining frailty through the accumulation of deficits (Buta et al., 2016; Fehlmann et al., 2022; Roller-Wirnsberger et al., 2020).

In 2001, Fried et al. introduced the "frail phenotype," a model that defines frailty based on physical manifestations. An individual is classified as frail if they meet three or more of the following criteria: (1) unintentional weight loss of ≥4.5 kg in the past year or ≥5% of body weight over the same period, (2) weakness, measured by reduced handgrip strength, (3) diminished endurance and energy, (4) slowed walking speed, and (5) reduced physical activity levels (Fried et al., 2001). This model is regarded as the foundation of the contemporary concept of frailty and remains one of the most widely used definitions (Kojima et al., 2018). However, despite its strong validation, it focuses exclusively on the physical dimension of frailty and is therefore often referred to as "physical frailty." Moreover, the frail phenotype does not fully capture frailty as a continuous spectrum of functional impairment (Sobhani et al., 2021).

The other major approach to defining frailty conceptualises it as a complex multidimensional state characterised by the accumulation of deficits across various health domains, including physical, cognitive, and psychosocial aspects. The more deficits an individual comprises, the higher their frailty level, indicating increased vulnerability to adverse health outcomes. The Frailty Index (FI) was developed by Rockwood and Mitnitski et al. using the Canadian Study of Health and Aging in 2004 (Mitnitski et al., 2004; Rockwood et al., 2004). It is based on the widely recognized Comprehensive Geriatric Assessment (CGA) and incorporates health impairments across physical, mental, and cognitive domains, accounting for the influence of social and environmental factors. The FI has been extensively validated and has been found to be superior in predicting mortality in a head-to-head comparison with frailty phenotype (Rockwood et al., 2007). However, the FI was first introduced with 92 items making it too time-consuming and impractical for routine use in most clinical scenarios (Rockwood et al., 2005). As a result, numerous assessment tools have been developed based on the deficit accumulation model to enhance feasibility in clinical practice. Among the most frequently cited are the Edmonton Frailty Scale and the Clinical Frailty Scale (CFS) (Buta et al., 2016).

2.3 Validated Frailty Assessment Tools

The assessment of frailty and its severity should be conducted using a validated tool (Dent et al., 2019; Liau et al., 2021; Partridge et al., 2022; Roller-Wirnsberger et al., 2020). It is now widely recognised that frailty cannot be reliably evaluated through a quick visual judgment, commonly referred to as "the eyeball test," without a standardised and validated assessment method. Hii et al. (2015) conducted a prospective observational study on 47 elderly emergency inpatients in a cardiology department, comparing clinicians' quick foot-of-the-bed frailty assessments to the Reported Edmonton Frailty Scale. Their findings indicated poor agreement both between clinicians and the Edmonton Scale, as well as among the clinicians themselves (Hii et al., 2015). Similarly, Ahmed and co-authors assessed the reliability of the eyeball test in a prospective study of 100 patients referred for transluminal or surgical valve therapy. They found that the eyeball test results did not align with objective frailty testing in 38% of cases (Ahmed et al., 2016). Notably, surgical risk classification was revised in 26% of cases when surgeons were provided with objective frailty measures. Walree et al. (2020) examined 55 cancer patients, comparing a specialist geriatric assessment with clinical judgments made by a cancer specialist, a general practitioner, and the patient's self-assessment. Their results showed negligible correlation coefficients between different clinical judgments and only a weak association between clinical judgment scores and geriatric assessment outcomes (Walree et al., 2020). Similarly, Dam et al. (2022) studied 736 emergency department patients and found poor agreement between physicians' clinical judgments of frailty and the Identification of Seniors at Risk–Hospitalized Patients tool, a validated frailty assessment instrument (Cohen's kappa of 0.36) (Dam et al., 2022). Interestingly, agreement was even lower when comparing either the validated tool or physicians' judgments with the patients' self-perceived frailty (Cohen's kappa of 0.30 for both).

2.4 Clinical Frailty Scale

The CFS is a simple yet robust tool that categorises patients based on physical fitness and loss of independence in activities of daily living. Developed in the 1990s and published by Rockwood et al. in 2005, the CFS was originally a 7-point scale designed for the Canadian Study of Health and Aging to assess overall fitness or frailty and summarise the comprehensive geriatric assessment (Rockwood et al., 2005). In 2007 the scale was updated to the current 9-point scale where a higher score reflects a more severe grade of frailty. Notably, level 4 represents a transitional phase from robustness to frailty, often referred to as pre-frailty.

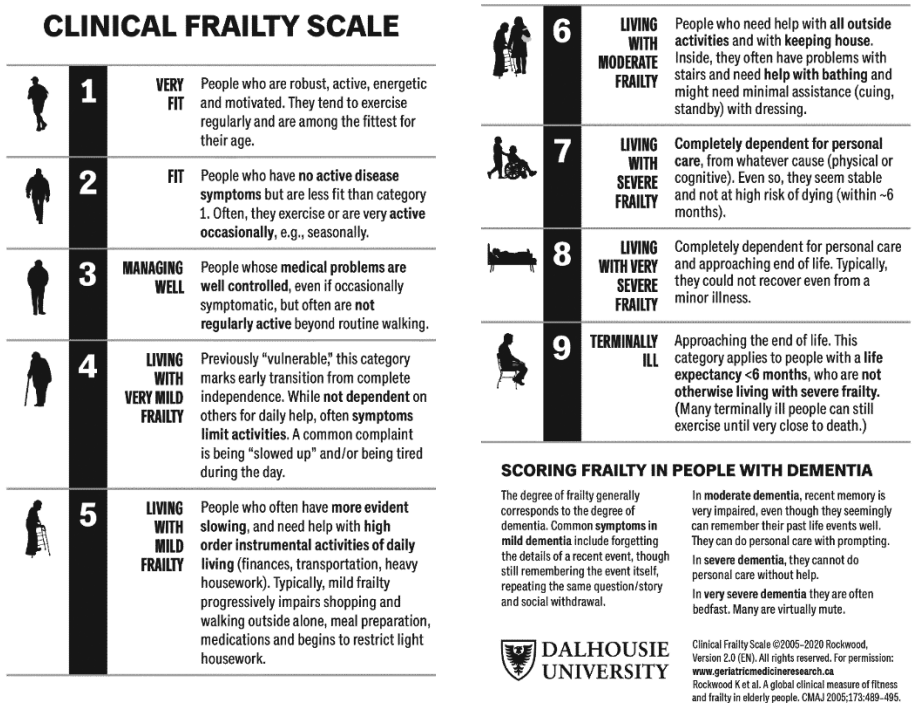

Figure 1. Clinical Frailty Scale

Although the CFS is based on the accumulation of deficits concept of frailty, it is not a questionnaire but rather a tool that relies on clinical judgment following a thorough patient evaluation. Central to this assessment is an interview with the patient and, when applicable, their caregivers.

The scale emphasises easily observable factors that do not require specialist training, including mobility, balance, reliance on walking aids, and the ability to perform tasks like eating, dressing, shopping, cooking, and managing finances. These activities of daily living (ADLs) are essential for self-care and independent living and are classified into two categories: instrumental ADLs and basic ADLs. Instrumental ADLs involve more complex skills required for independent living and functioning within a community, such as shopping, managing finances and medications, meal preparation, and housekeeping. Basic ADLs, on the other hand, encompass fundamental self-care tasks required for physical functioning and survival, including dressing, toileting, bathing, and eating. A key principle is that frailty progresses in stages, with individuals typically first experiencing difficulty in performing instrumental ADLs, followed by impairments in more basic functions as frailty advances.

In contrast to Frieds frail phenotype, the CFS is a multidimensional tool that extends the assessment well beyond the physical aspects of frailty. As such, it incorporates a broader range of factors, including disability, comorbidity, and

mental health issues such as mood disorders and dementia (Rockwood et al., 2005; Rockwood & Theou, 2020).

The CFS has been utilised in various research contexts worldwide. While it is the most applied frailty assessment tool in Canada and the United Kingdom, its use has also extended to Asia, South America, and other parts of Europe (Church et al., 2020). The CFS has been found to correlate well with adverse outcomes including mortality, comorbidity, disability, length of hospitalization, re-admission, institutionalization, cognitive function and falls. Additionally, its good correlation with other frailty assessment tools supports its convergent validity. Although the CFS has been most frequently used in cardiology and geriatric medicine, its application has expanded in recent years to a variety of clinical settings, including intensive care, general medicine, emergency medicine, dialysis, and surgery. Initially validated for individuals over 65, the CFS has also been shown to correlate with mortality and other adverse outcomes in younger adults (Hewitt et al., 2019).

The ease of use and reliability of the Clinical Frailty Scale (CFS) have likely contributed to its widespread adoption and growing popularity in recent years. The CFS assessment can typically be completed within minutes and does not require a specialist physician trained in geriatric medicine, making it particularly valuable in clinical settings where assessments are often conducted by junior medical staff and nurses. Young & Smithard (2020) examined the consistency of CFS assessments among 124 healthcare professionals from various specialties, including consultants, junior doctors, nurses, and allied health professionals, who rated seven clinical scenarios. Their observations demonstrated broad agreement within and between professional groups, with median scores typically differing by no more than one point (Young & Smithard, 2020). Similarly, Ringer et al. (2020) assessed 159 patients and found good inter-rater reliability between nurses and physicians using the CFS (weighted kappa of 0.76) (Ringer et al., 2020). Loand co-authors further confirmed this in a study of 100 emergency department patients, reporting almost perfect inter-rater reliability between assessments conducted by a nurse and a geriatric medicine-trained physician (weighted kappa = 0.90) (Lo et al., 2021).

To enhance usability, Theou, Rockwood, and colleagues have developed multiple aids and training materials for CFS novices, available at https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html. These resources include a classification tree, which has been validated in a prospective study of 115 patients, demonstrating strong agreement with assessments made by geriatricians (inter-class correlation coefficient of 0.833) (Theou et al., 2021).

One of the key advantages of the CFS is its applicability in emergency settings. Frailty is defined as a person's baseline state of vulnerability, distinct from the acute deterioration observed at the onset of illness. A previously healthy person may appear frail during an acute episode; however, accurate prognosis requires assessing both their baseline frailty and the severity of their acute condition. This distinction presents challenges for tools like Fried’s Frailty Phenotype in emergency admissions, where the walking speed or grip strength can-

not be reliably measured and may not reflect the baseline frailty (Stiffler et al., 2013). In contrast, the CFS is specifically designed to assess a person's baseline state, capturing their condition two weeks prior to admission (Rockwood & Theou, 2020). The CFS has been shown to be more favourable than other frailty assessment tools in emergency settings (Lewis et al., 2019; Moloney et al., 2023), and its use in emergency medicine continues to increase (Fehlmann et al., 2022).

In addition, the CFS allows for frailty assessments retrospectively based on medical records. Shears et al. (2018) found no statistically significant differences between CFS scores generated from chart reviews and those obtained via patient interviews in a prospective study of 150 ICU patients. While there was a trend toward underestimating frailty when relying solely on medical records, this difference was not statistically significant (Shears et al., 2018). Similarly, Stille et al. (2020) demonstrated in a cohort of 60 hospitalised elderly patients that CFS scores can be reliably obtained retrospectively from medical records. They reported high agreement between retrospective and prospective assessments (weighted Cohen's kappa of 0.89) and found no significant differences between the two methods, though a minor trend toward underestimating frailty in chart reviews was observed. Additionally, repeated retrospective CFS scoring showed excellent inter-rater agreement, with minimal clinically insignificant bias (Stille et al., 2020).

A cross-sectional study of 145 hospitalised patients in Sweden confirmed these findings, reporting substantial agreement (weighted Cohen's kappa = 0.66) between CFS scores derived from medical records and those obtained via patient interviews. However, this study also noted a statistically significant tendency to assign lower CFS scores when using medical records alone (Jackwert et al., 2024).

Kay et al. (2022) further supported the validity of retrospective CFS assessments, finding low bias (0.23) between prospectively assigned geriatrician CFS scores and retrospective CFS scores assigned by non-geriatricians. Interestingly, they observed a non-significant trend toward overestimating frailty when assessments were based solely on medical records. Their study also found good inter-rater reliability for retrospective CFS scoring (Cohen's kappa = 0.76) (Kay et al., 2022).

2.5 Prevalence of Frailty

Prevalence in Community-dwelling Older Adults

The prevalence of frailty among older adults varies widely depending on the assessment method used and geographic region. The first systematic review of frailty prevalence was published in 2012 by Collard et al., who analysed 21 studies on community-dwelling adults aged 65 and older from high-income Western countries (Collard et al., 2012). They reported an average frailty prevalence of 10.7% and 41.6% for pre-frailty. However, they observed that studies using

the physical frailty phenotype consistently reported lower prevalence rates than those employing the accumulation of deficits model.

A more recent review and meta-analysis by O'Caoimh and colleagues. (2021) provided the prevalence of frailty globally in their analysis of population-level studies from 62 countries (O'Caoimh et al., 2021). These authors estimated that, across different frailty measures, the overall prevalence of frailty in individuals aged 50 or older is 17%, while pre-frailty affects 45%. The study confirmed that frailty prevalence varies by assessment method. When using physical frailty measures, the global prevalence was 12% for frailty and 46% for pre-frailty. In contrast, when applying the deficit accumulation model, the frailty prevalence was substantially higher at 24%, with pre-frailty at 49%. Regardless of the frailty measure or region, frailty prevalence increased with age, although the correlation was weak. Consistent with previous research, both frailty and pre-frailty were more prevalent in females than males, possibly due to a greater accumulation of frailty-associated deficits over a longer lifespan. The meta-analysis also identified significant regional differences. The lowest frailty prevalence was observed in Europe (8% using physical frailty measures and 22% using the accumulation of deficits model), while the highest prevalence was found in Africa (22% using physical frailty) and Oceania (31% using the deficits accumulation model).

Within Europe, the Survey of Health, Ageing and Retirement in Europe (SHARE) is a longitudinal micro-data infrastructure established in response to a 2000 European Commission communication to the Council and the European Parliament. This initiative identified population ageing and its associated social and economic challenges as among the most pressing issues for growth and prosperity in the 21st century. Several studies using SHARE wave 6 data have been conducted to map frailty prevalence across different European countries. Manfredi et al. (2019) analysed a sample of 60,816 individuals aged 50 or older from 18 European countries, estimating the overall prevalence of physical pre-frailty at 42.9% (ranging from 34.0% in Austria to 52.8% in Estonia) and physical frailty at 7.7% (ranging from 3.0% in Switzerland to 15.6% in Portugal) (Manfredi et al., 2019). For Estonia, physical frailty and pre-frailty rates were 8.5% and 52.8%, respectively, based on a sample of 4,865 individuals. Notably, frailty prevalence is likely significantly higher when using the accumulation of deficits model (Pitter et al., 2024).

Pitter et al. (2024) expanded on this effort by developing a Frailty Atlas covering 42 European countries. Using SHARE data from all available survey waves across 29 countries, they analysed data from 311,915 individuals to estimate frailty prevalence stratified by age and gender. Their analysis incorporated adaptations of both the physical frailty phenotype and the Frailty Index to provide comprehensive prevalence estimates. Additionally, they employed mixed linear regression in combination with gross domestic product (GDP) per capita to predict frailty prevalence for countries not included in SHARE. This work resulted in the creation of an interactive Frailty Atlas, which is available at https://bbsri.shinyapps.io/share-vitalo/ (Pitter et al., 2024).

Prevalence in Hospitalised Patients

The prevalence of frailty and pre-frailty in specific clinical settings often differs from that observed in community-dwelling individuals.

Kojima et al. (2015) conducted a meta-analysis of nine studies involving 1,373 patients, estimating the prevalence of frailty in nursing homes at 52.3%. However, the included studies exhibited high heterogeneity, with prevalence ranging from 19.0% to 75.6% (Kojima, 2015).

Handforth and co-authors (2015) performed a systematic review to estimate frailty prevalence in cancer patients, including 20 studies with 2,916 patients. Their findings reported a median frailty prevalence of 42%, with a range of 6%–86% (Handforth et al., 2015).

A more recent meta-analysis by Veronese et al. (2021) aimed to estimate frailty prevalence by setting, including population-based, ambulatory, nursing home, and hospital settings. This analysis included 177 studies with a total of 56,407 patients, using the Multidimensional Prognostic Index, a frailty measure derived from the Comprehensive Geriatric Assessment. As expected, frailty prevalence was lowest in population-based studies (13.3%), followed by ambulatory settings (18.5%) and hospital settings (29.8%), with the highest prevalence in nursing homes (51.5%) (Veronese et al., 2021).

In 2018, Hewitt et al. conducted a meta-analysis examining frailty prevalence among older general surgical patients. Seven studies using various frailty measures were included, reporting pre-frailty prevalence between 31.3% and 45.8%, and frailty prevalence between 10.4% and 37.0% (Hewitt et al., 2018).

2.6 Screening for Frailty

Most recent clinical practice guidelines recommend that elderly patients be routinely screened for frailty (Dent et al., 2019; Geriatric Emergency Department Guidelines Task Force, 2014; Liau et al., 2021; Partridge et al., 2022; Roller-Wirnsberger et al., 2020). This is further supported by consensus documents on frailty (Morley et al., 2013).

In the UK, the NHS Long Term Plan mandates that elderly patients in the Emergency Department receive a clinical frailty assessment within 30 minutes. To further enhance the identification and management of frailty, NHS England introduced a Commissioning for Quality and Innovation indicator in 2023.

In Europe, the Joint Action ADVANTAGE program was launched in 2017 as a three-year initiative to develop a common European framework for addressing frailty in response to population ageing. The program involved 22 European Union member states, including the United Kingdom at the time. Its primary objective was to harmonise frailty prevention, detection, assessment, and management strategies across Europe to promote healthy ageing, with a specific emphasis on frailty screening.

2.7 Risk Factors for Frailty

Age is one of the strongest known risk factors for developing frailty. However, not all elderly individuals are frail, and some younger individuals may exhibit signs of frailty. Feng et al. (2017) conducted a systematic review of 23 longitudinal studies, identifying a multitude of risk factors associated with frailty. They classified risk factors into sociodemographic factors, including older age, female gender, lower education, lower income, and lower socioeconomic status; physical factors, such as obesity and lower functional status; biological factors, including certain immune and endocrine markers such as low vitamin D levels; lifestyle factors, encompassing smoking, alcohol consumption, and dietary habits; and psychological factors, such as depression and cognitive impairment. These risk factors have been corroborated by several more recent studies, with only minor variations (Dent et al., 2023).

2.8 Adverse Outcomes of Frailty

Frailty is a condition characterised by increased vulnerability to stressors and a state of impaired ability to recover from them (Clegg et al., 2013). It is associated with numerous adverse outcomes in both community-dwelling individuals and clinical settings. In the community, frailty has been linked to lower quality of life, falls, depression, cognitive decline, dependence in everyday life, increased risk of infections, and a higher likelihood of hospitalisation. In clinical settings, it is associated with increased mortality, prolonged hospital stays, higher risk of complications, and greater likelihood of readmission (Church et al., 2020; Hoogendijk et al., 2019; Kojima et al., 2018; McIsaac et al., 2020).

There is also compelling evidence that frailty is associated with increased health-care utilisation and costs, increasing in proportion to the degree of frailty. While specific figures vary depending on the setting, methodology, and health-care system, it is evident that the increased costs stem primarily from greater utilisation of healthcare services across inpatient, post-acute, and outpatient care settings (Hoogendijk et al., 2019).

2.9 Managing Frailty

Potential for Reversal

Despite its strong association with increasing age, frailty is not an irreversible, one-way trajectory toward disability or death but rather a dynamic process that can involve both improvement and progression (Hwang et al., 2023; Kojima et al., 2019; Stolz et al., 2022; Ward et al., 2021).

Kojima et al. (2019) found in their meta-analysis of 16 studies that over an average follow-up period of 3.9 years, 13.7% of individuals improved, 56.5% maintained their frailty status, and 29.1% experienced progression of frailty.

Hwang et al. (2023) demonstrated in their longitudinal study of 3529 patients who managed to improve their frailty score (either with the frailty phenotype or FI) showed the same mortality risk as those who remained robust/pre-frail (Hwang et al., 2023). Moreover, recent research has focused on whether the rate of change in frailty is predictive of mortality than the current status. Stolz et al. conducted a prospective observational study of 508 older adults with an average of four repeated FI measurements every 9 months (Stolz et al., 2022). They found that adding the within-person FI change as a predictor to the model, decreased the size effect of the current frailty status and even rendered it statistically non-significant concluding, that the rate of change is more predictive of mortality, than the current status.

Managing Frailty in the Community

Frailty management is inherently multidimensional. A recent consensus statement and clinical practice guideline by Dent et al. (2019) emphasises the importance of a tailored Comprehensive Geriatric Assessment and an individualised management plan for frail individuals living in the community. Such a plan should systematically address key domains, including polypharmacy, sarcopenia management, treatable causes of weight loss, and factors contributing to exhaustion, such as depression, anaemia, hypotension, hypothyroidism, and vitamin B12 deficiency (Dent et al., 2019).

A systematic review and meta-analysis of 66 randomised controlled trials by Negm et al. (2019) identified physical activity interventions combined with nutritional support as the most effective strategies for improving frailty (Negm et al., 2019). This finding was corroborated by a separate review by Apóstolo et al. (2018). However, despite evidence suggesting potential benefits from various other interventions, significant uncertainty persists regarding their overall efficacy (Apóstolo et al., 2018).

Medication management in frail older adults requires careful prescribing and deprescribing, maintaining an up-to-date medication list, regular medication reviews, regimen simplification where feasible, considering the individual's capacity to manage their medications, and an awareness of medication-related harm, particularly given the influence of geriatric syndromes on drug effectiveness (Liau et al., 2021). Presently, no medication treatment recommendations (such as hormone replacement) can be given in frailty management (Dent et al., 2019).

Beyond physiological improvements, frailty management should incorporate strategies to enhance coping mechanisms and social support (Andreasen et al., 2015). have demonstrated efficacy in enhancing physical performance and function, their impact on long-term clinical outcomes remains uncertain (Pérez-Zepeda et al., 2022).

Managing Frailty in Hospitalised Patients

Physical exercise interventions have also been shown to benefit frail patients during hospitalisation. A recent randomised controlled trial by Pérez-Zepeda et al. (2022) demonstrated that such interventions significantly improve physical and multidimensional frailty in hospitalised older adults, particularly those with higher baseline frailty levels. The study included patients admitted to an acute care ward, primarily for cardiovascular conditions, who participated in a tailored physical exercise programme consisting of morning and evening sessions over a median hospital stay of six days. This intervention reduced their Frailty Index (FI) from 0.25 to 0.20, whereas the control group experienced a decline, with their FI worsening from 0.25 to 0.27 (Pérez-Zepeda et al., 2022). These findings build on previous randomised controlled trials demonstrating improved physical function in acutely hospitalised frail older adults following tailored exercise programmes lasting five to seven days (Martínez-Velilla et al., 2019, 2020; Sáez de Asteasu et al., 2019).

Advance Care Planning

Frail older adults often receive more aggressive treatment than they prefer. Given their high risk of complications and reduced ability to recover to their previous state, they frequently face a significant care burden and an increased likelihood of further loss of independence. Research suggests that some individuals living with frailty may even prefer death over enduring a heavy care burden or experiencing further deterioration in physical or cognitive function (T. R. Fried et al., 2002, 2007; Heyland et al., 2013, 2013; Hopkins et al., 2020).

Advance care planning has demonstrated benefits across various patient groups and settings, increasing the likelihood that individuals receive end-of-life care aligned with their preferences. A systematic review by Sharp et al. (2013) found that while 61%–91% of elderly patients would like to discuss their end-of-life preferences, only 2%–29% have the opportunity to do so with a healthcare professional (Sharp et al., 2013). Furthermore, a prospective multicentre study in Canada by Heyland et al. (2013) revealed that despite many severely frail patients having expressed their treatment preferences, concordance between patients' stated end-of-life wishes and documentation in their medical records was only 30.2% (Heyland et al., 2013).

2.10 Emergency General Surgery

EGS refers to urgent, non-elective general surgical procedures, primarily involving the gastrointestinal tract (Ingraham et al., 2022; Shafi et al., 2013). In the United States, EGS has been recognised as a subspecialty within general surgery, supported by dedicated training pathways and certification. Conversely, in the United Kingdom and continental Europe, EGS is not formally recognised as a

distinct subspecialty, though some centres have established specialised units or services to manage EGS cases (Lipping et al., 2024; Ramsay et al., 2018).

To define EGS procedures, Shafi et al. (2013) initially utilised International Classification of Disease (ICD)-9 codes, which were subsequently translated to ICD-10 codes by Ingraham et al. (2022). Scott et al. (2016) further refined the classification by identifying seven key procedure groups that account for 80% of all EGS procedures, 80.3% of associated deaths, 78.9% of complications, and 80.2% of costs in the United States. These procedure groups include appendectomy, cholecystectomy, adhesiolysis, small bowel resection, large bowel resection, stomach or duodenum ulcer repair, and exploratory or re-laparotomy. A cross-sectional population-based study in the UK noted that appendectomy and cholecystectomy were the most commonly performed EGS procedures. In contrast, adhesiolysis, small bowel resection, large bowel resection, and other laparotomies collectively accounted for only 9.4% of all EGS operations (Ramsay et al., 2018).

Emergency Laparotomy

EL encompasses a range of urgent surgical interventions; however, its definition lacks consistency in the literature (Nally et al., 2020). In their review, Nally et al. (2020) highlighted discrepancies in the term “emergency,” which has been variously defined as “non-elective,” “surgery not planned the day before,” or classified according to surgeon or anaesthesiologist assessment. Some studies include trauma patients, while others do not. Studies referencing the National Emergency Laparotomy Audit (NELA) often rely on National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classifications, categorising surgeries as “expedited,” “urgent,” or “emergency” based on permissible delays. Additionally, some studies use ICD-10 codes for classification.

The term laparotomy refers to a surgical procedure involving a (long) abdominal incision to access the abdominal cavity. It derives from the Greek lapara ("flank") and -tomy ("incision") (Rajaretnam et al., 2025). Traditionally performed via a midline incision, alternative approaches include the subcostal Kocher’s incision and the transverse suprapubic Pfannenstiel incision (Kocher, 1903; Pfannenstiel, 1900). Advances in minimally invasive techniques have enabled many procedures to be performed laparoscopically, using smaller incisions with a camera and specialised instruments. Both laparotomy and laparoscopy are widely used across surgical specialties, including urology, gynaecology, vascular, and general surgery. Within general surgery, these techniques are commonly employed for procedures involving the gastrointestinal tract, hepatopancreato-biliary system, and abdominal wall.

Nally et al. (2020) noted that some studies on EL also included laparoscopic surgery despite it traditionally being considered an alternative to laparotomy. While some studies included only laparoscopic cases converted to open surgery, others encompassed fully laparoscopic procedures. Furthermore, while some studies considered emergency procedures across all surgical specialties, those

based on NELA excluded non-general surgical cases and even certain general surgical procedures, such as appendectomy, cholecystectomy, and hepato-pancreato-biliary surgeries.

Consequently, the terms EGS and EL are not uniformly defined in the literature. Some studies show significant overlap between the two, while others define EL as a subset of EGS procedures, typically representing more extensive operations performed via either an open or laparoscopic approach.

Public Health Burden of Emergency General Surgery

EGS represents a substantial global public health burden. Stewart et al. (2014) estimated that approximately 49 million general surgical procedures were performed annually in the early 2000s. Their review further highlighted that general surgical emergencies accounted for approximately 10% of all major operations in high-income countries, whereas in middle- and low-income countries, the proportion ranged between 21% and 90% (Stewart et al., 2014).

In the USA the annual case rate for EGS patients exceeds that of all new cancer diagnoses, with 11% of all hospitalisations being due to EGS diagnoses (Gale et al., 2014; Lee et al., 2020; Scott et al., 2016). The population-adjusted EGS admission rate was 1,290 per 100,000 individuals in 2010, reflecting a 27.5% increase over the preceding decade (Gale et al., 2014). Similarly, in Scotland, the EGS admission rate reached 1,818 per 100,000 individuals in 2016, representing a 9.4% increase over a 20-year period (Wohlgemut et al., 2020). Gale et al. (2014) also highlighted a significant increase in the proportion of EGS admissions requiring surgical intervention. In contrast, Wohlgemut (2020) observed that although the overall number of EGS admissions had increased, the proportion of patients undergoing surgery had significantly declined over two decades.

2.11 Mortality in Emergency General Surgery

A hallmark of EGS is its significantly higher morbidity and mortality rates compared to the same procedures performed electively (Havens et al., 2015). In a retrospective analysis of a prospective database, Havens et al. (2015) compared the outcomes of 26,068 EGS procedures with 42,597 corresponding elective cases, controlling for patient-specific factors. They found that nearly half of all EGS patients developed postoperative complications, with a 30-day mortality rate of 12.5%. EGS patients were generally older, had a higher prevalence of co-morbidities, and presented with greater acute illness severity. Even after adjusting for these factors, EGS remained an independent risk factor for 30-day mortality (OR 1.39) and postoperative complications (OR 1.20). Similarly, Ramsay et al. (2018) reported that in the UK, nearly 7% of all EGS patients and 20% of those over 75 years died within six months of admission, regardless of whether they underwent surgery.

A systematic review by Ng and Weber (2022) examining 15 studies found that 30-day mortality rates following EL ranged from 5.3% to 21.8%, while 1-year mortality rates varied between 9.2% and 47% (Ng & Weber, 2022).

Several national and international audit and quality improvement initiatives aim to reduce the substantial morbidity and mortality associated with EL. These include the NELA in the UK, the Australian and New Zealand Emergency Laparotomy Audit (ANZELA), and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). Since its inception in 2013, NELA has reported a decline in mean in-hospital 30-day mortality following EL from 11.8% to below 9.5% (NELA project team, 2015; NELA Project Team, 2024). Similarly, ANZELA recorded an overall in-hospital 30-day mortality rate of 7.1%, with a statistically significant reduction over time (Party et al., 2021).

Predicting Mortality Risk in Emergency Laparotomy

The risk of mortality and morbidity following emergency laparotomy is influenced by a combination of factors, including the patient's baseline health status, current physiological condition, underlying pathology necessitating surgery, and the complexity of the procedure. To optimise perioperative care and minimise postoperative complications, both the structure and delivery of care must be tailored to each patient's specific needs. Significant efforts have been made to identify high-risk patient subgroups and those most vulnerable to adverse outcomes. Various risk assessment models have been developed to aid in prognostication and decision-making. While these tools consider multiple patient- and procedure-related factors, including age, they do not explicitly incorporate frailty as an independent risk factor, despite growing evidence of its prognostic significance.

The Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) model, developed by Copeland et al. (1991), was later refined into the more accurate Portsmouth-POSSUM (P-POSSUM) by Prytherch et al. (1998) (Copeland et al., 1991; Prytherch et al., 1998). The P-POSSUM score integrates a physiological score, assessing the preoperative status of the patient, and an operative severity score, evaluating surgical complexity, to estimate 30-day postoperative mortality and morbidity risk. Although not specifically designed for EGS, P-POSSUM has been widely applied in this setting (Hewitt et al., 2024; Oliver et al., 2015).

Another widely used surgical risk assessment tool, developed within the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), was introduced by Bilimoria et al. (2013) (Bilimoria et al., 2013). Like P-POSSUM, the ACS NSQIP risk calculator was designed for both elective and emergency surgery. In contrast, the NELA risk assessment tool, developed by Eugene et al. (2018) and updated in 2020, was specifically tailored for EL (Eugene et al., 2018). These risk stratification tools have undergone external

validation across various healthcare systems, with the NELA and ACS-NSQIP scores generally demonstrating better discrimination than P-POSSUM.

Regarding calibration, P-POSSUM has been shown to overpredict mortality, whereas NELA and ACS NSQIP have exhibited variable calibration performance.

Eliezer et al. (2020) conducted an external validation study of the P-POSSUM, NELA, and ACS-NSQIP risk calculators in a retrospective multicentre study in Australia. Their findings indicated that the NELA assessment tool demonstrated the highest sensitivity (88.1% vs. 78.0% for both P-POSSUM and ACS-NSQIP), although this was not statistically significantly greater. Additionally, P-POSSUM was found to systematically overestimate mortality. While the NELA tool exhibited slightly greater accuracy than ACS-NSQIP, this difference did not reach statistical significance (Eliezer, 2020).

Barazanchi et al. (2020) performed a single-centre retrospective analysis of 758 patients in New Zealand, comparing the P-POSSUM, NELA, and ACS-NSQIP models. The NELA model had the highest discrimination (AUC of 0.83) and was the only tool considered well-calibrated ($p = 0.95$). In contrast, P-POSSUM significantly overpredicted mortality ($p < 0.001$), while ACS-NSQIP significantly underpredicted mortality ($p = 0.002$). Attempts to enhance discrimination by integrating the modified Frailty Index (mFI) with each tool did not yield significant improvements (Barazanchi et al., 2020).

Parkin and co-authors (2021) conducted a meta-analysis of six studies assessing the ACS-NSQIP model's accuracy in predicting mortality. The model exhibited good overall predictive performance, with an observed-to-expected mortality ratio of 1.06. However, substantial heterogeneity was noted ($I^2 = 57.5\%$, $p = 0.035$), with four studies underestimating mortality and two overestimating it (Parkin et al., 2021).

Lai et al. (2021) compared the P-POSSUM and NELA risk scores in a retrospective multicentre study in Singapore. The NELA model showed slightly superior discrimination (AUC = 0.86 vs. 0.84 for P-POSSUM). Although both models overpredicted mortality, the NELA model demonstrated better overall performance (Lai et al., 2021).

Thahir et al. (2021) performed a single-centre retrospective analysis in the UK, evaluating the predictive performance of the P-POSSUM and NELA models. The NELA model exhibited superior discrimination (AUC = 0.81 vs. 0.77). While P-POSSUM overpredicted mortality and the NELA model slightly underpredicted it, both showed good calibration (Hosmer-Lemeshow $p = 0.06$) (Thahir et al., 2021).

Barghash and colleagues (2022) conducted a single-centre retrospective study in the UK, analysing 681 patients to compare the NELA and P-POSSUM models. The NELA model demonstrated slightly better discrimination (AUC = 0.79 vs. 0.78). However, both models substantially underestimated mortality, with observed-to-expected mortality ratios of 2.81 for P-POSSUM and 2.25 for NELA (Barghash et al., 2022).

Darbyshire et al. (2022) conducted a registry-based multicentre analysis in the UK, assessing the discrimination and calibration of the NELA and P-POSSUM

models. Among 116,396 patients with a completed P-POSSUM score and 46,935 with a NELA score, both models demonstrated excellent discrimination, with NELA outperforming P-POSSUM (AUC = 0.86 vs. 0.80). While P-POSSUM was well-calibrated for predicted mortalities up to 20%, it increasingly overestimated mortality at higher risk levels. The NELA model exhibited good calibration across all risk deciles but overpredicted mortality in laparoscopic procedures.

Kokkinakis et al. (2023) conducted a prospective multicentre cohort study in Greece, externally validating the P-POSSUM, NELA, and ACS-NSQIP models. All models demonstrated good discrimination, with the NELA model achieving the highest AUC (0.85). However, only the surgeon-adjusted ACS-NSQIP model was well-calibrated ($p = 0.742$) and exhibited minimal between-hospital heterogeneity (Kokkinakis et al., 2023).

Hansted et al. (2023) performed a registry-based multicentre study in Denmark, providing external validation for the NELA and P-POSSUM models. The updated NELA model demonstrated the best discrimination (AUC = 0.85); however, both models significantly underpredicted mortality. These authors identified an optimal cut-off point of 9%, but the model's accuracy remained insufficient for high-risk patients (Hansted et al., 2023).

2.12 Frailty in Emergency General Surgery

Research on the impact of patient frailty in the context of EGS and EL has gained increasing attention over the past decade. Earlier studies in EGS primarily focused on advanced age as a predictor of adverse postoperative outcomes. However, a consensus document by Vaughan et al. (2022) identified frailty as one of the priorities in future research in EGS (Vaughan et al., 2022).

The CFS has been recommended as the one of the most appropriate tool for frailty assessment in EL patients (Tian et al., 2023). Initially validated for individuals over 65, the CFS has also been shown to correlate with mortality and other adverse outcomes in younger adults (Partridge et al., 2022; Tian et al., 2023). While establishing and enforcing perioperative pathways for frail patients requires substantial resources, emerging evidence suggests these pathways are cost-effective (Partridge et al., 2022).

Prevalence of Frailty in the Emergency General Surgery Settings

The prevalence of frailty among patients undergoing EGS procedures varies across studies, influenced by the assessment tool and cut-off thresholds used. A meta-analysis by Kennedy et al. (2022) reported a frailty prevalence of 30.8% among patients aged 65 or older, with estimates ranging from 16% to 61.6% depending on the assessment method (Kennedy et al., 2022). Park et al. (2024) conducted a meta-analysis including only studies that utilised the CFS. However, frailty was not uniformly defined between studies with cut-offs ranging from CFS ≥4 or ≥6. The pooled prevalence of frailty across all age groups was 25.0% (95%

CI: 0.17–0.36), with estimates ranging from 10.6% to 47.1%. Among patients aged 55 or older, frailty prevalence was 32% (95% CI: 0.20–0.48), with a range of 14.6% to 47.1%. The NELA project estimated frailty in 11% of patients over 65, increasing to 50% in those over 85 (NELA project team, 2018).

Impact of Frailty on Mortality and Morbidity following Emergency Laparotomy

Multiple studies and meta-analyses have examined the impact of frailty on mortality following EGS, with most focusing on in-hospital or 30-day mortality. However, variability in frailty assessment tools and differences in cut-off values across studies may contribute to inconsistencies in reported outcomes.

One of the earliest studies on frailty in EGS was a multi-centre prospective study by Hewitt et al. (2015), which included all patients aged 65 or older admitted to an EGS unit, irrespective diagnosis whether they had an operation. Among 325 patients, frail individuals had significantly higher 30-day (OR = 4.04) and 90-day (OR = 3.04) mortality rates, along with prolonged hospital stays (mean length of stay (LOS): 11.1 vs. 7.6 days). Frailty was assessed using the CFS (Hewitt et al., 2015).

Joseph et al. (2016) conducted a prospective single-centre cohort study analysing 220 EGS patients using the Rockwood Frailty Index. Frailty was independently associated with higher complication rates, increased intensive care unit (ICU) LOS, and prolonged overall hospitalisation. In contrast, age and the American Society of Anesthesiologists (ASA) score were not identified as independent predictors of these outcomes (Joseph et al., 2016).

Ward et al. (2019) performed a meta-analysis of four studies using various frailty assessment tools to evaluate 30-day mortality in frail versus non-frail patients. The analysis demonstrated a significantly increased mortality risk among frail patients (risk ratio [RR] = 3.04, 95% CI: 2.67–3.46). Furthermore, three of the four studies reporting on complications found that frailty was associated with an increased postoperative complication rate (Congiusta et al., 2017; Farhat et al., 2012; Orouji Jokar et al., 2016). Two studies indicated that frail patients were more likely to be discharged to a long-term care facility or rehabilitation centre rather than home (McIsaac et al., 2020; Orouji Jokar et al., 2016). Frailty was also associated with a longer LOS in four of five studies (Hewitt et al., 2015; Lorenzon et al., 2017; McIsaac et al., 2020; Orouji Jokar et al., 2016), nevertheless one study found no significant difference (Goeteyn et al., 2017). ICU admission was independently associated with frailty in one study (McIsaac et al., 2020), while another found an association only in univariable analysis (Lorenzon et al., 2017), and a third study reported no association (Orouji Jokar et al., 2016).

Similarly, Kennedy et al. (2022) conducted a meta-analysis incorporating six studies utilising various frailty assessment tools. Their findings indicated an OR of 4.3 (95% CI: 2.25–8.19) for 30-day mortality among frail compared to non-frail patients. Additionally, frail patients were more likely to be discharged to a

rehabilitation centre or nursing home (OR = 1.89) and had a significantly longer LOS, as confirmed by a separate meta-analysis of three studies (Kennedy et al., 2022).

The mid- and long-term mortality of frail patients following EL has only recently gained more attention. Parmar et al. (2021) conducted a prospective multicentre observational study including 937 older adults across 49 centres in the UK. Frailty was significantly associated with 90-day mortality, with ORs of 3.18 for patients with a CFS score of 5, and OR of 6.10 for those with a CFS score of ≥6. Frailty was also independently associated with increased postoperative complications (adjusted OR = 4.56 for CFS 5 and 3.92 for CFS ≥6), as well as longer hospital and ICU stays. However, no association was found between frailty and 30-day readmission (Parmar et al., 2021).

Vilches-Moraga et al. conducted a single-centre observational study on 113 elderly adults undergoing EL in the UK. Multivariable analysis revealed that frailty and the absence of input from a specialised perioperative care-of-the-elderly team were both associated with higher 12-month mortality (Vilches-Moraga et al., 2020).

A more recent meta-analysis by Park et al. (2024) included 12 studies involving 5,704 patients, all of which used the CFS for frailty assessment in EL patients. While seven studies focused on older adults, the remainder assessed frailty across all adult patients. All except one study defined frailty as CFS ≥4 or ≥5. The meta-analysis demonstrated significantly higher mortality rates among frail patients at 30 days (OR = 3.84), 90 days (OR = 2.71), 6 months (OR = 5.90), and 1 year (OR = 3.03). A subgroup analysis showed similar associations with 30-day mortality between studies that included only older adults and those that assessed all adult patients. Additionally, three studies reported a correlation between increasing CFS scores and a higher risk of 30-day mortality (Park, Alani, et al., 2024).

Loss of Independence after Emergency Laparotomy

Patients who are older and more frail are at risk of becoming even less independent when undergoing EL.

Zattoni et al. (2021) conducted a single-centre prospective cohort study of 78 patients over 70 undergoing EL and found that one in four surviving patients experienced a severe decline in functional status. Both frailty and advanced age were identified as independent risk factors for loss of independence (Zattoni et al., 2021). Similarly, according to a Norwegian study, 65% of patients over 80 were discharged to a nursing home postoperatively, compared to only 16% who had been living in a nursing home before surgery (Aakre et al., 2020).

Tan et al. (2019) conducted a prospective cohort study of 90 patients over 65 undergoing emergency abdominal surgery and found that 6.9% of previously independent patients had lost their independence one year postoperatively, with frailty being a significant risk factor for functional decline (Tan et al., 2019).

Decision-making and Patient Preferences

In certain cases, undergoing EL may be futile, with death being inevitable. A retrospective NSQIP-based study by Al-Temimi et al. (2012) involving 37553 patients found that individuals over 90 years old with ASA class V, septic shock, dependent functional status, and an abnormal white blood cell count had a survival probability of less than 10% (Al-Temimi et al., 2012). However, in most cases, the futility of care is not as clear-cut, and a high risk of mortality alone should not be the sole determinant in decision-making.

While clinicians often base their decision-making in EGS on mortality risk or LOS, patients tend to prioritise postoperative quality of life over the risk of mortality when considering emergency surgery (Law et al., 2020). Using the Delphi process, Law et al. (2020) attempted to establish consensus between elderly patients and clinicians but achieved only 50% agreement. Patients did not concur with clinicians that mortality, return to theatre, alternative treatments to EL, symptom control, or input from other specialties would significantly influence their decision-making. Mortality risks that clinicians perceived as exceptionally high were often considered acceptable by elderly patients. However, the patient group unanimously agreed that maintaining independence and returning home were key factors in their decision-making. They also strongly valued postoperative quality of life over mortality risk when deciding to undergo emergency surgery.

Given these findings, shared decision-making between clinicians and patients, including setting realistic expectations and defining the ceiling of care, is equally important in EGS as in elective surgery (Partridge et al., 2022; Tian et al., 2023).

Multidisciplinary Approach

The perioperative management of frail patients should be multidisciplinary, incorporating proactive co-management by geriatric specialists (Partridge et al., 2022; Tian et al., 2023). While most evidence on the effectiveness of prehabilitation and frailty pathways comes from elective surgery, emergency medical and orthopaedic settings, emerging research suggests promising outcomes in EGS.

Engelhardt et al. (2018) conducted a single-centre prospective before-after study of 239 older trauma and EGS patients, demonstrating that routine frailty screening and implementation of a frailty pathway significantly reduced 30-day readmission rates (from 36.4% to 10.2%) and loss of independence by 40% (Engelhardt et al., 2018).

Shipway et al. (2018) reported that implementing an embedded geriatric surgical liaison service reduced the LOS of both elective and EGS patients, highlighting the broad range of postoperative medical complications that prompted medical review (Shipway et al., 2018).

Khadaroo et al. (2020) performed a controlled before-after study of 684 patients over 65 undergoing EGS procedures. Integrating a geriatric team and optimising evidence-based, elderly-friendly care resulted in a 19% reduction in

the combined outcome of major complications or death within the intervention group. The study also demonstrated reductions in minor complications, LOS, and the proportion of patients requiring a higher level of care after discharge.

A cross-sectional population-based study from the UK found that only 25% of EGS admissions resulted in an operation, with this proportion decreasing to 15% in patients over 75 years (Ramsay et al., 2018). Furthermore, a large proportion of postoperative complications in frail patients are medical rather than surgical in nature, raising concerns about whether the traditional model – where surgeons manage both nonoperatively treated multimorbid patients and operatively managed frail patients at risk of severe medical complications – is optimal. Despite this, the ninth NELA audit revealed that only 33.2% of EL patients over 80 or over 65 and frail received input from a geriatrician, although a steady increase in geriatric involvement has been observed over time (NELA Project Team, 2024).

Meanwhile, in 2018 only 18% of acute hospitals in Australia and New Zealand provided a proactive surgical-geriatric medicine service while 87% of hospitals provided an orthogeriatric service (Thillainadesan et al., 2019). Lack of funding and a shortage of geriatricians were perceived to be the major barriers to developing these services.

2.13 Summary of the Literature

Population ageing is accelerating globally, increasing the proportion of older adults requiring acute surgical care. Frailty – defined as a state of increased vulnerability due to reduced physiological reserve – is common in older individuals and associated with adverse outcomes across multiple healthcare settings. While over 70 frailty assessment tools exist, the CFS stands out for its practicality, validity, and applicability in emergency settings, including retrospective use.

Prevalence of frailty varies by setting and assessment method but is consistently higher in hospitalised and surgical populations than in the community. Studies show frailty is strongly associated with increased short-term mortality, complications, prolonged hospital stay, institutionalisation, and functional decline. Despite this, frailty is often under-recognised in clinical practice and is not routinely included in established surgical risk models.

EGS, particularly EL, carries high morbidity and mortality. Existing risk prediction tools such as P-POSSUM, NELA, and ACS-NSQIP have demonstrated good discriminatory ability, particularly the NELA model. However, their calibration is variable, and none explicitly incorporate frailty, despite growing evidence of its independent prognostic significance.

Furthermore, differences in surgical indication and presentation between frail and non-frail patients may partly explain outcome disparities. While frailty is potentially reversible, lack of targeted management can lead to long-term deterioration. Evidence supports the integration of frailty screening, multi-

disciplinary care, and advance care planning to improve outcomes. However, these practices remain inconsistently applied.

Overall, the literature highlights the prognostic importance of frailty in EL, the strengths and limitations of current risk prediction tools, and the need for better data on long-term outcomes and context-specific surgical risk in frail populations.

3. AIMS OF THE STUDY

The main purpose is to investigate the role of frailty in predicting outcomes after EL, with a focus on how the incorporation of frailty assessment – specifically using the CFS – can enhance existing risk prediction tools, and to explore the short- and long-term outcomes of frail patients undergoing EL in various clinical settings.

The specific aims were:

1. The primary aim of Study I was to evaluate whether incorporating frailty, as measured by the Clinical Frailty Scale, would enhance the discriminatory performance of the P-POSSUM and NELA prognostic models in predicting mortality following emergency laparotomy. Additionally, the study aimed to assess the impact of frailty on 30-day mortality among patients aged over and under 65 years undergoing emergency laparotomy.
2. The primary aim of Study II was to examine the impact of frailty on 180-day mortality following emergency laparotomy, and to determine whether this association could be explained by differences in indications for surgery, the presence of sepsis, intra-abdominal contamination, or the presence of malignancy compared to non-frail patients. The secondary aim was to assess the impact of frailty on preoperative waiting time and the length of postoperative hospital stay.
3. The primary aim of Study III was to investigate the prevalence of frailty among patients over the age of 50 undergoing emergency laparotomy in two referral hospitals in Estonia, as well as the impact of frailty on short- and long-term mortality. The secondary aim was to assess the effect of frailty on postoperative complications, length of postoperative hospital stay, and the progression of frailty and decline of functional independence in both the short and long term.

4. MATERIALS AND METHODS

4.1 Ethics

This research was conducted in accordance with the principles of the Declaration of Helsinki and approved by the relevant institutional review boards. Ethical approval for studies I and II was granted by the Oxford University Hospitals NHS Trust (Approved Local Audit no. 7023). For study III, ethical approval was obtained from the Research Ethics Committee of the University of Tartu (approval number – 365/M-13) and the participating hospitals.

4.2 Inclusion and Exclusion Criteria

Studies I and II

For studies I and II, all adult patients entered into the NELA database at Oxford University Hospitals NHS Foundation Trust between 1 January 2018 and 15 June 2021 were eligible for inclusion. Eligibility criteria followed those defined by NELA during the study period, including patients who underwent an emergency laparotomy for gastrointestinal pathology such as obstruction, perforation, ischaemia, sepsis, or intra-abdominal bleeding.

For study I patients whose NELA database entry or EPR notes did not have sufficient information to assess the CFS or to calculate the P-POSSUM and NELA-RPT were excluded from the analysis.

For study II patients without sufficient information in either the NELA database entry or EPR notes to assess CFS were excluded from the analysis.

Study III

For study III, all consecutive patients aged ≥50 years who underwent emergency laparotomy between March 2022 and April 2023 at the North Estonia Medical Centre and between June 2022 and July 2023 at the East Tallinn Central Hospital were included. The procedures were classified as emergency surgeries if they were necessitated by conditions directly related to the emergency admission.

Patients were included if they underwent any of the following major emergency abdominal surgeries:

- Surgeries involving the stomach, small intestine, large intestine, or rectum due to perforation, ischemia, intra-abdominal abscess, haemorrhage, or bowel obstruction.
- Opening and/or drainage of intra-abdominal abscesses or hematomas (excluding those opened and drained during appendectomy or cholecystectomy).
- Bowel resection or suturing due to strangulated umbilical, inguinal, femoral, or incisional hernias (including parastomal hernias).
- Laparoscopic or open adhesiolysis.

- Stoma creation surgeries performed through a midline laparotomy.
- Reoperations due to major postoperative complications of planned gastrointestinal surgeries if they met the above criteria.
- Surgeries following complications of endoscopy if they met the above criteria (including complications following non-general surgical procedures).
- Surgeries due to extensive abdominal wound dehiscence.
- Surgeries for removal of ingested foreign bodies from the gastrointestinal tract.
- Laparotomies/laparoscopies for unresolved pathology where a definitive surgery was initially planned (excluding primarily diagnostic surgeries).
- In the case of simultaneous surgeries, the primary surgery had to meet the above criteria to be included in the study.
- Emergency surgeries on the bile ducts or liver for perforation, abscess, haemorrhage, or bile leak.
- Drainage and/or opening of abscesses following appendectomy or cholecystectomy.
- Reoperations following non-gastrointestinal surgeries if they met the above criteria (e.g., bowel injury following gynaecological surgery or bowel ischemia following vascular surgery).
- Mesenteric artery thromboembolectomy with accompanying bowel resection due to ischemia.

Patients were excluded from the study if they met any of the following criteria:
- Preoperative frailty was not assessed during hospitalization.
- Elective laparoscopies and laparotomies.
- Surgeries performed due to blunt or penetrating trauma.
- Surgeries for removal of foreign bodies from the large intestine or rectum (considered as trauma).
- Primarily diagnostic laparoscopies and laparotomies (surgeries initially planned as definitive but found to be unfeasible were included).
- Appendectomies and cholecystectomies, including those with local abscess drainage (unless performed as part of a larger simultaneous operation).
- Elective hernia surgeries without bowel resection.
- Stomas created laparoscopically or through a “small incision.”
- Minor abdominal wall dehiscences not causing bowel strangulation.
- Surgeries involving the oesophagus, pancreas, spleen, kidneys, and urinary tract.
- Rectal surgeries that did not involve opening the abdominal cavity.
- Vascular surgeries (including aortic aneurysm surgeries and mesenteric artery thromboembolectomies without bowel resection).
- Gynaecological and obstetric surgeries (emergency surgeries for bowel obstruction due to gynaecological cancer were included).
- Surgeries for ectopic pregnancies or gynaecological abscesses (PID).
- Transplant-related surgeries and their complications.

- Surgeries for the removal of dialysis catheters.
- Surgeries involving the spleen, kidneys, urinary tract (including bladder), liver, gallbladder, bile ducts, or pancreas.
- In the case of simultaneous surgeries, those where the primary surgery did not meet the inclusion criteria were excluded.

4.3 Data Collection

Study I and II

For Studies I and II, patient data including pre-morbid frailty measured using the CFS, age, and sex were extracted from the NELA database. In instances where the CFS grade was unavailable from NELA, frailty assessment was conducted retrospectively through a comprehensive review of electronic patient records (EPR), including clinical notes from doctors, nurses, occupational therapists, physiotherapists, and other relevant healthcare professionals.

For Study I, additional data necessary for calculating the P-POSSUM and NELA risk scores were directly obtained from the NELA database. For Study II, data collected included the indication for surgery, presence of sepsis, intra-peritoneal contamination, and malignancy status. Additionally, the time from admission to surgery, referred to as delay to surgery (DTS), and the hospital LOS in days were obtained. Any missing data points in the NELA database were supplemented through review of the patients' EPR when available.

Dates of death were identified using EPR data, which is integrated with the national death register. All patients included were followed for a minimum duration of 180 days.

Study III

For study III, data was prospectively collected on patients' demographics (age, sex, and living situation before hospitalization), preoperative CFS grade (reflecting the patients' level of frailty two weeks before EL), surgical parameters (operation date, clinical and laboratory metrics), postoperative outcomes and complications (need for invasive interventions due to complications, LOS in the surgical emergency unit and in rehabilitation, discharge information), and follow-up information (rehospitalisation, CFS and living situation six months after surgery, and date of death). The date of death was obtained from the National Electronic Health Information System. The six-month living situation and CFS were assessed via telephone interviews with the patient or, if unavailable, family or nursing home staff.

4.4 Statistical Methods

Data analysis for all studies was performed using RStudio electronic software, Version 2023.03.0 (250 Northern Ave, Boston, MA 02210, USA).

Normality of distribution for continuous variables was assessed with the Shapiro-Wilk test. Continuous variables with non-normal distribution were summarised as median and interquartile range (IQR), whereas categorical variables were expressed as total numbers and percentages. Kaplan-Meier curves were utilised to represent survival data, and Cox regression models provided hazard ratios (HR) with 95% CI. Logistic regression models were employed to calculate OR and 95% CI. The validity of assumptions for all regression models was verified. The statistical significance level (α) was consistently set at 0.05 across all analyses.

Study I

Univariate logistic regression models assessed 30-day mortality odds, with frailty as an independent variable, for the entire cohort and age-specific subgroups (<65 and ≥ 65 years). The discriminative ability of the P-POSSUM and NELA RPT models was evaluated using area under the receiver operating characteristic curve (AUC), and the DeLong test assessed differences in AUC between models. Calibration of predictive models was analysed by comparing observed versus predicted mortality, employing the chi-square test to assess significance.

Study II

The Wilcoxon rank-sum test assessed differences in non-normally distributed continuous variables, while the chi-squared or Fisher's exact tests evaluated categorical data distributions. Multivariable analyses included Cox regression for survival outcomes, and linear regression for duration to surgery (DTS) and postoperative LOS. Due to skewed DTS and LOS data distributions, logarithmic transformations were applied, with results expressed as proportional increases and 95% CI. Regression models utilised bi-directional stepwise elimination based on Akaike Information Criteria (AIC). The assumption of proportional hazards for Cox regression was verified using Schoenfeld's residuals.

Study III

Univariable logistic regression calculated ORs with 95% CI for invasive interventions and of being admitted to rehabilitation or nursing home. Univariable Poisson regression estimated incidence rate ratios (IRR) and 95% CI for combined LOS in active care and rehabilitation. Functional status changes were analysed using the Wilcoxon signed-rank test, comparing preoperative and six-month postoperative CFS. The McNemar test assessed changes in patient living situations six months postoperatively, categorised as independent or institutionalised.

5. RESULTS

5.1 Study I

Study Population

Overall, 823 patients were entered into the NELA database between 01.01.2018 and 15.06.2021 in the Surgical Emergency Unit at the Oxford University Hospitals NHS Trust. CFS was provided in the NELA database in 571 cases but was reassessed according to the patient's notes in 95 cases where an evident misclassification was noted. An attempt was made to assess the CFS based on patient notes for all patients who did not have this information provided in the NELA database. In total, thirty patients were excluded. Twenty patients were excluded because they were duplicates or did not have sufficient data to retrospectively assess CFS. Of the remaining 803 patients, 8 did not have enough information to calculate the P-POSSUM score, and 10 did not have enough information to calculate the NELA score and were excluded from the analysis.

Baseline Characteristics

Of the included 793 patients, 411 (51.8%) were aged 65 years or older. The overall 30-day mortality was 60 patients (7.6%). The mortality rate in the 65 years or older group was 46 patients (11.2%). Table 1 shows the baseline characteristics of the study population.

There was a statistically significant correlation between patient frailty and 30-day mortality. The OR for each CFS grade in different age groups is represented in Table 2.

Table 1. Descriptive statistics of study I

Characteristic	All included patients n=793	Patients under 65 years n=382	Patients 65 years or older n=411
Mean age (years) (SD[a])	63.1 (17.5)	48.2 (12.4)	76.9 (7.3)
Median age (years) (range)	66 (18–94)	51 (18–64)	77 (65–94)
Sex			
Male n(%)	392 (49.4)	198 (51.8)	194 (47.2)
Female n(%)	401 (50.6)	184 (48.2)	217 (52.8)
ASA[b] score n(%)			
1	137 (17.3)	97 (25.4)	40 (9.7)
2	328 (41.4)	176 (46.1)	152 (37.0)
3	265 (33.4)	91 (23.8)	174 (42.3)
4	58 (7.3)	15 (3.9)	43 (10.5)
5	5 (0.6)	3 (0.8)	2 (0.5)

Characteristic	All included patients n=793	Patients under 65 years n=382	Patients 65 years or older n=411
CFS grade[c] n(%)			
1…3	460 (58.0%)	290 (75.9%)	170 (41.4%)
4	129 (16.3%)	48 (12.6%)	81 (19.7%)
5	109 (13.7%)	23 (6.0%)	86 (20.9%)
6	73 (9.2%)	14 (3.7%)	59 (14.4%)
7	18 (2.3%)	6 (1.6%)	12 (2.9%)
8	4 (0.5%)	1 (0.3%)	3 (0.7%)
9	0	0	0

[a]SD – Standard Deviation, [b]ASA – American Society of Anesthesiologists, [c]CFS – Clinical Frailty Scale: 1…3 – fit/not frail, 4 – living with very mild frailty, 5 – living with mild frailty, 6 – living with moderate frailty, 7 – living with severe frailty, 8 – living with very severe frailty, 9 – terminally ill.

Table 2. Odds ratios of 30-day mortality by CFSa in different age groups

CFS	All included patients		Patients under 65 years		Patients 65 years or older	
grade	OR[b] (95% CI[c])	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
1…3	1		1		1	
4	3.4 (1.4–8.2)	<0.01	3.8 (0.9–16.6)	0.07	2.6 (0.9–7.9)	0.10
5	5.0 (2.2–11.7)	<0.01	5.5 (1.0–30.0)	0.05	3.6 (1.3–10.2)	<0.05
6	13.5 (6.1–30.1)	<0.01	9.6 (1.7–54.6)	0.01	10.4 (3.8–28.0)	<0.01
7…8	34.5 (12.3–96.6)	<0.01	23.0 (3.6–148.4)	<0.01	31.8 (8.7–116.8)	<0.01

[a]CFS – Clinical Frailty Scale: 1…3 – fit/not frail, 4 – living with very mild frailty, 5 – living with mild frailty, 6 – living with moderate frailty, 7…8 – living with severe or very severe frailty. [b]OR – Odds Ratio. [c]CI – Confidence Interval.

Discrimination for 30-day Mortality

When compared to the P-POSSUM and NELA RPT, CFS alone had lower discrimination across the whole cohort (AUC=0.777) as well as in the subgroup aged 65 years or older (AUC=0.756). The P-POSSUM score had reasonably good discrimination (AUC=0.840) when applied to all age groups. However, reduced discrimination was observed in the subgroup aged 65 years or older (AUC = 0.775). Compared with P-POSSUM, the NELA RPT demonstrated superior discrimination across the entire cohort (AUC = 0.875), although discrimination was similarly reduced in patients aged 65 years or older (AUC = 0.814). Interestingly, the DeLong test to compare the discrimination of P-POSSUM and NELA RPT showed that the NELA RPT's higher discrimination was not statistically significant in either the whole study population (p=0.06) or the ≥ 65 group (p=0.13).

Table 3. Discrimination of CFS[a] alone, original and modified risk prediction tools for both 30- and 180-day mortality

	Area Under the Curve			
	30-day mortality		180-day mortality	
	All patients	65 years or older	All patients	65 years or older
CFS alone	0.777	0.756	0.777	0.734
P-POSSUM[b]	0.839	0.774	0.807	0.751
Modified P-POSSUM	0.881	0.846	0.865	0.813
p-value modified vs non-modified	p<0.05	p<0.05	<0.01	<0.05
NELA RPT[c]	0.875	0.814	0.849	0.793
Modified NELA RPT	0.887	0.864	0.872	0.822
p-value modified vs non-modified	p=0.37	p<0.05	p=0.09	0.13

[a]CFS – Clinical Frailty Scale, [b]P-POSSUM – Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality, [c]NELA RPT – National Emergency Laparotomy Audit Risk Prediction Tool

When modified with the CFS, both the P-POSSUM and the NELA RPT showed improved discrimination for the whole study population as well as the 65 or older age group (figure 1) (Table 3). This improvement was statistically significant in the DeLong test, except for the NELA RPT when younger patients were included.

Calibration

The observed 30-mortality was 7.6% across all age groups and 11.2% among patients 65 years or older.

The NELA RPT showed excellent calibration for the whole study population as well as for patients aged 65 years or older. P-POSSUM overpredicted mortality in both age groups; however, the difference between observed and expected mortality was not statistically significant (Table 4).

Table 4. Calibration of risk prediction tools in all age groups and in patients 65 years or older for 30-day mortality

	Risk prediction tool	
	P-POSSUM[a]	NELA RPT[b]
All age groups		
Predicted mean 30-d mortality % (95% CI[c])	13.0 (11.6–14.4)	6.9 (6.1–7.6)
p-value, observed vs expected	0.34	1.0
Patients 65 years or older		
Predicted mean 30-d mortality % (95% CI)	16.0 (14.0–18.1)	10.4 (9.2–11.6)
p-value, observed vs expected	0.47	1.0

[a]P-POSSUM – Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality, [b]NELA RPT – National Emergency Laparotomy Audit Risk Prediction Tool , [c]CI – Confidence Interval

Impact of Frailty at Six Months

At six months after the initial operation the observed mortality was 12.8% across all age groups and 18.4% among patients 65 years or older.

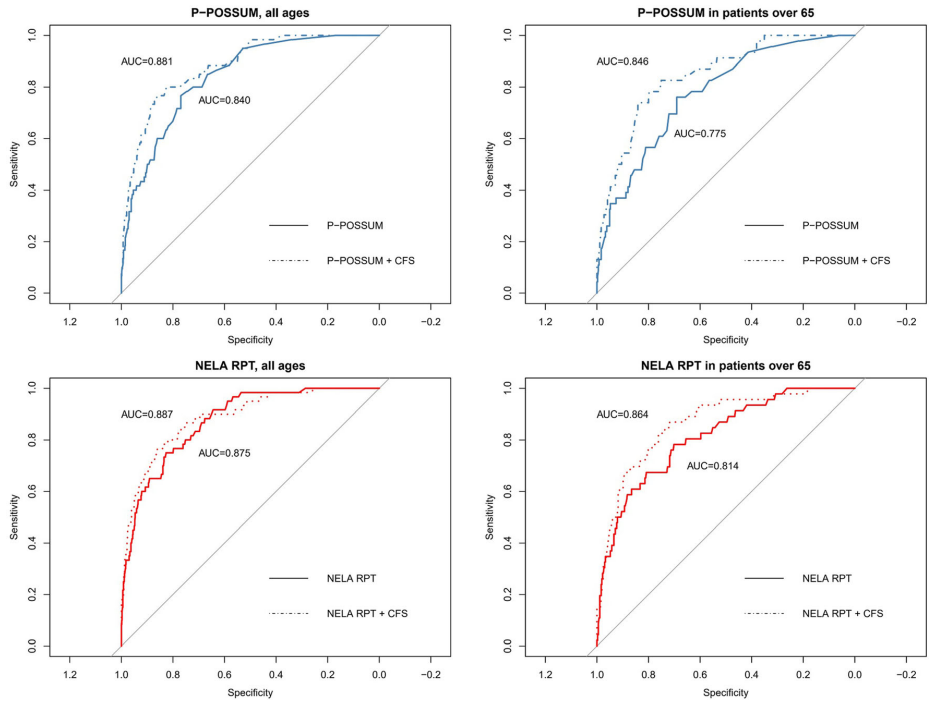

Figure 2. Receiver operating characteristic curve for original and modified risk prediction tools

Table 5. 30- and 180-day mortality by CFS[a] grade.

CFS grade	1–3	4	5	6	7	8
30-day mortality n(%)	11 (2.4)	10 (7.6)	12 (10.8)	18 (24.7)	7 (38.9)	3 (75.0)
180-day mortality n(%)	19 (4.1)	19 (14.5)	24 (21.6)	29 (39.7)	8 (44.4)	4 (100)

[a]CFS – Clinical Frailty Scale: 1–3 – fit/not frail, 4 – living with very mild frailty, 5 – living with mild frailty, 6 – living with moderate frailty, 7 – living with severe frailty, 8 – living with very severe frailty

On univariate analysis there was a statistically significant ($p<0.01$) association between higher CFS grades and both 30- and 180-day mortality (Table 5). On univariate analysis NELA RPT and age were also predictive of 180-day mortality ($p<0.01$). Patient sex was not associated with 180-day mortality ($p=0.19$). CFS remained an independent predictor of 180-day mortality on multivariate analysis adjusted for NELA RPT predicted mortality and age. However, on this multivariate analysis patient age was not an independent predictor of 180-day mortality (Table 6).

Although P-POSSUM and NELA RPT were originally designed to predict 30-day mortality, AUC for CFS alone and both original and modified P-POSSUM and NELA RPT were calculated for 180-day mortality (Table 3). All prediction tools showed a slightly worse performance for 180-day mortality when compared to 30-day mortality. However, even for 180-day mortality, modified P-POSSUM and NELA RPT had higher AUC than the original prediction tools.

Table 6. Predictors of 180-day mortality (Logistic Regression).

	Odds ratio (95% CI[c])	p-value
CFS[a] grade		
1–3	1	<0.01
4	3.3 (1.6–7.2)	<0.01
5	5.3 (2.5–11.2)	<0.01
6	11.1 (5.2–24.1)	<0.01
7–8	16.6 (5.6–48.7)	<0.01
NELA RPT[b] predicted mortality	1.07 (1.05–1.09)	<0.01
Age	1.00 (0.98–1.02)	0.99

[a]CFS – Clinical Frailty Scale: 1–3 – fit/not frail, 4 – living with very mild frailty, 5 – living with mild frailty, 6 – living with moderate frailty, 7–8 – living with severe or very severe frailty. [b]NELA RPT – National Emergency Laparotomy Audit Risk Prediction Tool. [c]CI – Confidence Interval

5.2 Study II

Study Population

Following Institutional Review Board approval, data analysis was conducted on 823 patients entered into the NELA database between January 1, 2018, and June 15, 2021, at the Surgical Emergency Unit of the Oxford University Hospitals NHS Foundation Trust.

CFS was available for 571 cases within the NELA database. However, in 95 instances where more than one clinicians' EPR notes significantly contradicted the CFS assessment in the NELA database, the CFS was reassessed based on the patient's notes. Additionally, efforts were made to assess the CFS from the patient notes for 247 cases where this information was not recorded on the NELA database. Five patients were excluded due to being duplicates, and 15 were excluded because their frailty status could not be evaluated, leaving 803 cases for further statistical analysis.

Baseline Characteristics

Descriptive baseline characteristics are presented in Table 7. Of the 803 included patients, 407 (50.7%) were female and 396 (49.3%) were male. The mean age was 63.2 years (range 18–94 years) with a median of 66.0 years (IQR 52–77 years). The distribution of age was not normal and was moderately left skewed. A total of 418 patients (52.1%) were aged 65 years or older.

Table 7. Descriptive statistics of study II

	CFS[a] 1…3	CFS 4	CFS 5	CFS 6	CFS 7
Number of patients (% of total)	466 (58.0)	131 (16.3)	111 (13.8)	73 (9.1)	22 (2.7)
Median age in years (IQR[b])	59 (46–71)	70 (57–80)	77 (67–93)	77 (68–82)	76 (62–87)
Sex ratio (M:F)	1.16	0.90	0.63	0.70	1.00
Presence of sepsis clinically	199 (44.1)	53 (41.7)	47 (43.1)	36 (50.7)	11 (52.4)
Indication for operation					
Obstruction	254 (56.1)	69 (53.9)	65 (59.1)	46 (63)	12 (54.5)
Other	8 (1.8)	4 (3.1)	0 (0)	0 (0)	0 (0)
Sepsis	146 (32.2)	44 (34.4)	33 (30)	21 (28.8)	8 (36.4)
Haemorrhage	6 (1.3)	4 (3.1)	2 (1.8)	3 (4.1)	0 (0)
Ischaemia	39 (8.6)	7 (5.5)	10 (9.1)	3 (4.1)	2 (9.1)
Intraperitoneal soiling					
No contamination	313 (69.1)	84 (65.6)	80 (72.7)	50 (68.5)	13 (59.1)
Pus	53 (11.7)	17 (13.3)	8 (7.3)	5 (6.8)	3 (13.6)
Gastroduodenal or bile	23 (5.1)	7 (5.5)	5 (4.5)	0 (0)	0 (0)
Small bowel	17 (3.8)	4 (3.1)	7 (6.4)	4 (5.5)	3 (13.6)
Faeces or feculent fluid	37 (8.2)	13 (10.2)	9 (8.2)	10 (13.7)	3 (13.6)
Blood	10 (2.2)	3 (2.3)	1 (0.9)	4 (5.5)	0 (0)
Malignancy status at operation					
No malignancy	342 (74)	98 (75.4)	73 (66.4)	52 (71.2)	19 (86.4)
Primary or locally spread	72 (15.6)	17 (13.1)	19 (17.3)	11 (15.1)	1 (4.5)
Disseminated malignancy	48 (10.4)	15 (11.5)	18 (16.4)	10 (13.7)	2 (9.1)
Median DTS[c] hours (IQR)	27 (11–67)	45 (16–100)	54 (18–112)	33 (14–76)	32 (10–177)
Median LOS[d] days (IQR)	7.0 (4.0–13.8)	8.0 (5.0–16.0)	10.0 (5.0–16.0)	13.0 (6.0–23.0)	12.0 (6.0–17.0)
In-hospital mortality	12 (2.6)	11 (8.4)	14 (12.6)	18 (24.7)	10 (45.5)
30-day mortality	11 (2.4)	10 (7.6)	12 (10.8)	18 (24.7)	10 (45.5)
90-day mortality	15 (3.2)	13 (9.9)	18 (16.2)	24 (32.9)	11 (50)
180-day mortality	19 (4.1)	19 (14.5)	24 (21.6)	29 (39.7)	12 (54.5)

Values are reported as n (% within CFS grade), unless otherwise specified. [a]CFS – Clinical Frailty Scale, [b]IQR – interquartile range, [c]DTS – delay to surgery, [d]LOS – postoperative length of hospital stay.

346 (42%) patients were assessed to be living with at least very mild frailty (CFS ≥ 4), while only 22 patients were assessed to be living with severe frailty (CFS=7).

The median age was 64 years for men and 67 years for women, but this difference was not found to be statistically significant (p = 0.059). The prevalence of frailty (CFS ≥ 4) was higher in female patients compared to men (46.9% vs 36.9%, p < 0.001).

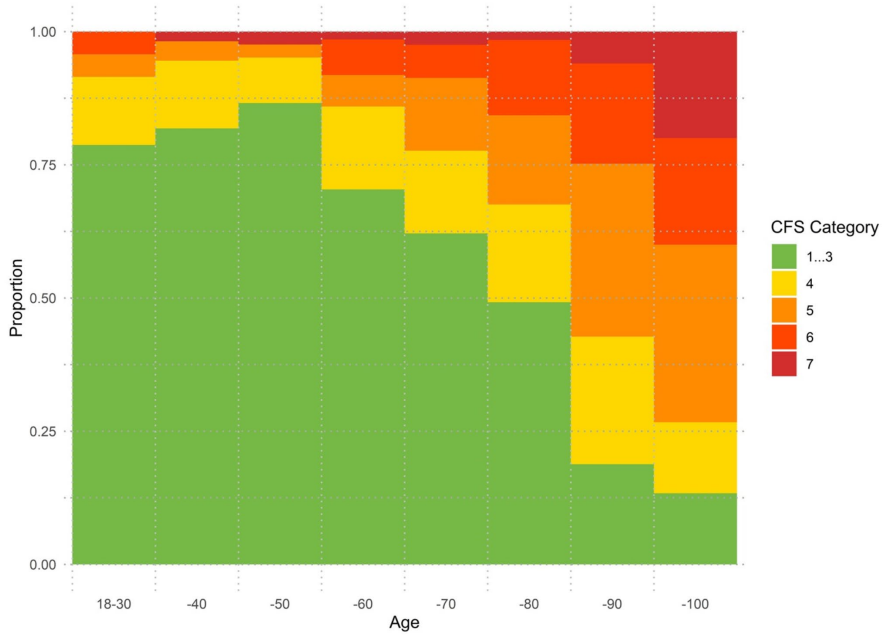

Figure 3. Proportion of Clinical Frailty Scale (CFS) Categories by Age Groups.

The prevalence of frailty increased with age (Figure 2). 17.1% of patients under 50 were living with at least very mild frailty. For patients aged between 70 and 80, the prevalence of frailty was 48.9%, and for patients aged 80 years or older, the prevalence was 79.3%. However, it is important to note that 20.6% of patients over 80 were considered fit for their age.

Sepsis was clinically present in 346 (44.4%) cases, and the status was unknown in 24 cases. In 17 cases data on both, indication and intraperitoneal soiling was missing. The most common indication was obstruction in 446 (56.7%) cases, followed by sepsis in 252 (32.1%) cases. Other indications were less common: ischaemia 61 (7.8%), haemorrhage 15 (1.9%), and other in 12 (1.5%) cases. In 540 (68.7%) cases, no peritoneal soiling was found during the operation. Pus, small bowel content, gastroduodenal content or bile, faeces or feculent fluid, or blood were present in 86 (10.9%), 35 (4.5%), 35 (4.5%), 72 (9.2%), and 18 (2.3)

cases, respectively. In 584 (73.3%) cases, no malignancy was diagnosed before or in association with the operation. Information on malignancy status was unavailable for 6 cases. Malignancy was locally spread in 120 (15.1%) cases and disseminated in 93 (11.7%) cases.

The exact time from admission to surgery was available for 621 patients. The median DTS was 33 hours (IQR 13–77 hours), with a mean of 67.6 hours.

The median postoperative LOS was 8 days (IQR 5–15 days), with a mean of 13.2 days. The distributions of postoperative LOS and DTS were markedly right-skewed.

The overall 30-day mortality was 61 patients (7.6%), and the 180-day mortality was 103 patients (12.8%).

The odds of re-operation or return to the intensive treatment unit, whether planned or unplanned, were not statistically significantly different for patients across different CFS grades in our cohort.

Indication, Sepsis, Intraperitoneal Soiling and Malignancy Status across Different CFS Grades

Due to the limited number of patients living with severe frailty (CFS=7), they were grouped together with those on CFS grade 6. For the same reason, intraperitoneal soiling with small bowel content was grouped together with contamination with gastroduodenal content or bile. The 'other' category within indication was merged with 'obstruction' in accordance with the NELA risk calculator guidelines. Additionally, due to the low incidence, surgical procedures indicated for bleeding were incorporated into this same category (Table 8). We found no statistically significant differences in the distribution of indication, sepsis, intraperitoneal soiling, and malignancy status across different CFS grades.

Table 8. Distribution of operation parameters and clinical risk factors by Clinical Frailty Scale (CFS) grade.

	CFS 1…3	CFS 4	CFS 5	CFS 6...7	p-value
Indication for operation					
Obstruction OR Other OR					
Bleeding	268 (59.2)	77 (60.2)	67 (60.9)	61 (64.2)	
Sepsis	146 (32.2)	44 (34.4)	33 (30)	29 (30.5)	
Ischaemia	39 (8.6)	7 (5.5)	10 (9.1)	5 (5.3)	0.799
Presence of sepsis clinically	199 (44.1)	53 (41.7)	47 (43.1)	47 (51.1)	0.548
Intraperitoneal soiling					
No contamination or blood	323 (71.3)	87 (68)	81 (73.6)	67 (70.5)	
Pus	53 (11.7)	17 (13.3)	8 (7.3)	8 (8.4)	
Free bowel content	77 (17)	24 (18.8)	21 (19.1)	20 (21.1)	0.688
Malignancy status					
No malignancy	342 (74)	98 (75.4)	73 (66.4)	71 (74.7)	
Primary or locally spread	72 (15.6)	17 (13.1)	19 (17.3)	12 (12.6)	
Disseminated	48 (10.4)	15 (11.5)	18 (16.4)	12 (12.6)	0.568

Values are reported as n (% within CFS grade).

Survival after Operation

Figure 3 depicts Kaplan-Meier curves stratified by CFS grade. A significant association between CFS grade and both 30-day and 180-day mortality was identified in univariable analysis ($p < 0.001$ for each grade). By 180 days post-operation, mortality reached 54.5% in CFS grade 7 patients, while it was only 4.1% in patients considered fit for their age. The HR for mortality for CFS grades 4, 5, and 6–7 were 3.73 (95% CI 1.98–7.06), 5.84 (95% CI 3.20–10.67), and 13.66 (95% CI 7.92–23.56), respectively, in univariable Cox regression analysis.

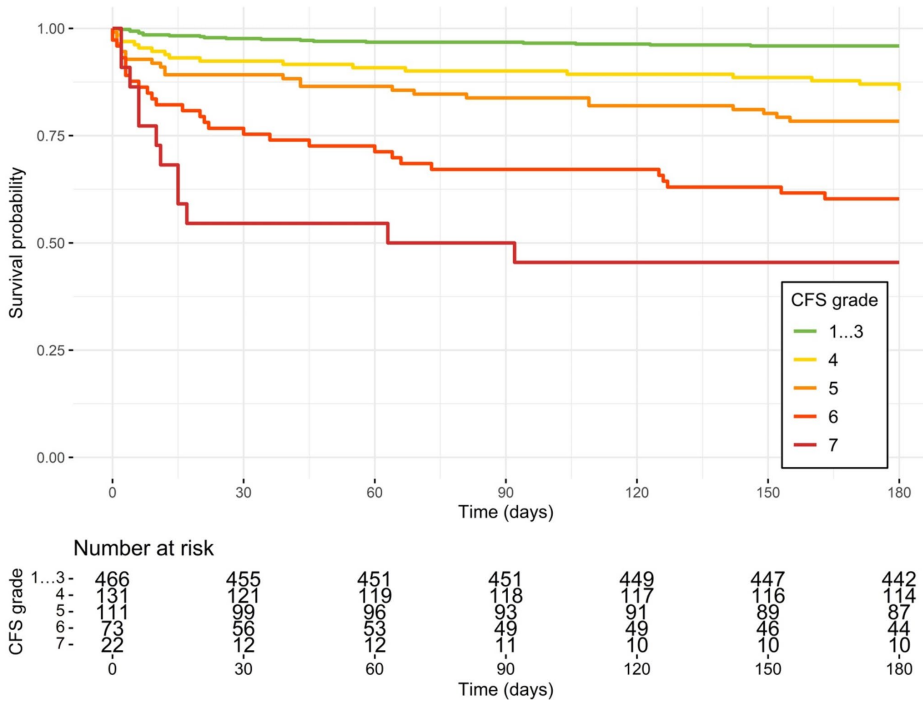

Figure 4. Kaplan-Meier curves for different Clinical Frailty Scale (CFS) grades.

Age was significantly correlated with both 30-day and 180-day mortality ($p < 0.001$). Only one patient under 50 died within 30 days after the operation (30-day mortality of 0.6%). For patients aged 50 and above, 30-day mortality rate was 60 patients (9.5%). The overall 180-day mortality was 5 patients (2.9%) for those under 50, and 98 (15.5%) for patients aged 50 and above. Figure 4 illustrates the distribution of 180-day mortality by age and CFS grade.

Additional factors significantly affecting survival in univariable analysis included intraperitoneal soiling with free bowel content (HR 2.22, 95% CI 1.42–3.45), indication categories of sepsis or ischaemia (HR 1.87, 95% CI 1.22–2.86 and HR 2.27, 95% CI 1.20–4.31, respectively), disseminated malignancy at the time of operation (HR 1.73, 95% CI 1.03–2.91), and sepsis clinically (HR 2.42,

95% CI 1.60–3.68). The effect of intraperitoneal soiling with pus (HR 1.39, 95% CI 0.75–2.60), sex (HR 0.77 for female sex, 95% CI 0.52–1.14), and locally spread malignancy (HR 1.26, 95% CI 0.74–2.16) on survival was not statistically significant on univariable analysis.

For multivariable analysis, CFS categories 6–7 were combined due to the small sample sizes. The indication category 'other' (n=12) was grouped with operations performed for obstruction according to the updated NELA risk calculator. Due to the small number of patients in whom the indication was haemorrhage (n=15), these cases were excluded from the final model to prevent overfitting. Local and disseminated malignancy were grouped together. A good model fit was achieved, with a concordance index of 0.838. After adjusting for age, sex, indication, sepsis, intraperitoneal soiling, and malignancy, patient frailty was found to be independently associated with poorer 180-day survival (Table 3). The HR for CFS grades 4, 5, and 6–7 were 3.93 (95% CI 1.89–8.20), 5.86 (95% CI 2.87–11.97), and 14.17 (95% CI 7.33–27.40), respectively.

Delay to Surgery

The median DTS was 27 hours for fit patients and 43.5 hours for patients living with at least very mild frailty (CFS ≥ 4) (p = 0.003).

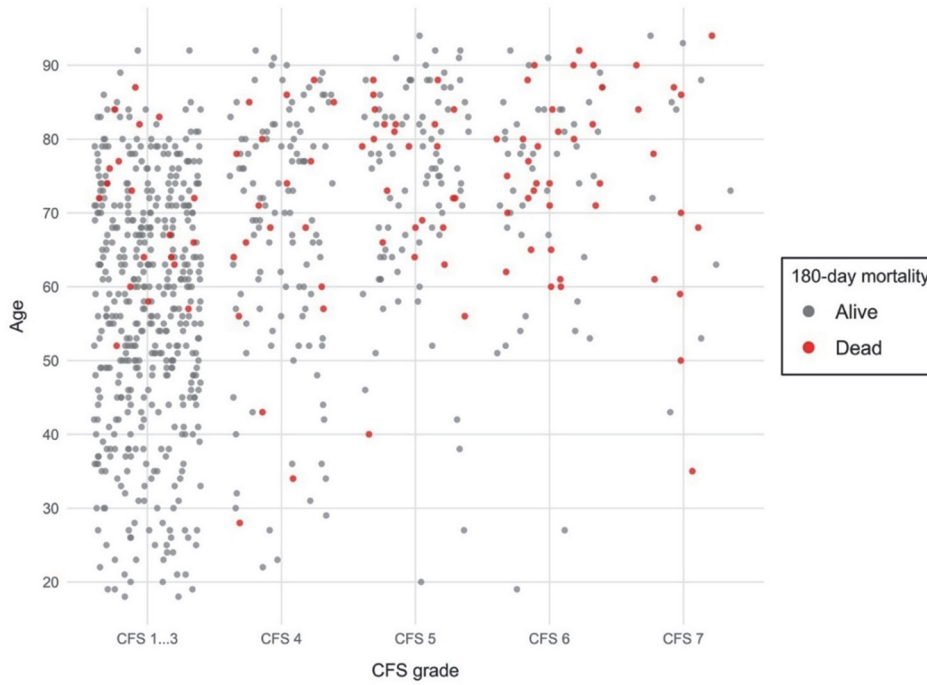

Figure 5. Distribution of 180-day mortality by age and Clinical Frailty Scale (CFS) grade.

We used logarithmically transformed linear regression for the multivariable analysis of DTS due to the positive skew in DTS distribution. Stepwise bi-directional elimination was used, with patient frailty, age, sex, intraperitoneal soiling, indication, and sepsis as input variables. The best model fit was achieved with patient frailty, intraperitoneal soiling, and sepsis included as independent variables (Table 9). In the adjusted model, patient frailty (CFS ≥ 4) was associated with a 1.38-fold increase of DTS.

DTS was not associated with 30-day or 180-day mortality across our cohort ($p = 0.981$ and $p = 0.632$, respectively). Although there was a statistically significant difference in DTS across different intraperitoneal soiling categories, as well as between patients who had sepsis and those who did not, DTS did not significantly affect 30-day mortality within those subgroups. The correlation between DTS and postoperative LOS was negligible, with Pearson's correlation coefficient of 0.10.

Table 9. Risk factors of prolonged delay to surgery after emergency laparotomy.

Risk factor	Delay to surgery multiplier (95% CI[b])	
	Univariable regression	Multivariable regression
CFS[a] grade		
1…3	1	1
≥ 4	1.37 (1.12–1.67)	1.38 (1.14–1.67)
Age	1.001 (0.995–1.006)	n/a
Male sex	0.87 (0.72–1.06)	n/a
Intraperitoneal soiling		
No intraperitoneal soiling	1	1
Pus	1.41 (1.02–1.96)	2.06 (1.41–2.89)
Free bowel content	0.53 (0.41–0.68)	0.72 (0.54–0.96)
Indication for operation		
Obstruction or "other"	1	
Sepsis	0.76 (0.61–0.94)	n/a
Ischaemia	0.92 (0.64–1.33)	n/a
Presence of sepsis	0.65 (0.54–0.79)	0.63 (0.49–0.80)

[a]CFS – Clinical Frailty Scale, [b]CI – Confidence Interval.

Length of Hospital Stay after Operation

The median postoperative LOS was 7 days for fit patients and 10 days for patients living with at least very mild frailty (CFS ≥ 4) ($p < 0.001$).

Overall, death during hospitalization was not associated with postoperative LOS ($p = 0.093$). However, death during hospitalization affected postoperative LOS differently in fit compared to frail patients (Figure 5). Among fit patients, postoperative LOS tended to be slightly longer in those who died in hospital, although this difference was not statistically significant ($p = 0.552$). In frail

patients, postoperative LOS was significantly shorter in patients who died in hospital (median of 6 vs. 10 days, p = 0.003).

For multivariable analysis of postoperative LOS, we utilized logarithmically transformed linear regression. Stepwise bi-directional elimination was employed with patient frailty, age, sex, intraperitoneal soiling, indication, sepsis, and death during hospitalization as input variables. The best model fit was achieved with patient frailty, age, intraperitoneal soiling, sepsis, and death during hospitalization included as independent variables (Table 10). In the adjusted model, patient frailty (CFS ≥ 4) was associated with 1.24 times increase in postoperative LOS.

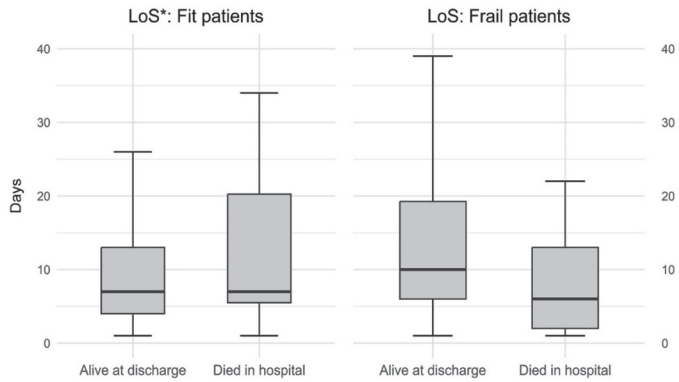

Figure 6. Boxplots of Postoperative Length of Stay for Fit and Frail Patients. *LOS – postoperative length of stay. Boxes represent interquartile ranges (IQR), whiskers extend 1.5 times IQR.

Table 10. Risk factors of prolonged postoperative length of hospital stay after emergency laparotomy.

	Postoperative length of stay multiplier (95% CI[b])	
Risk factor	Univariable regression	Multivariable regression
CFS[a] grade		
1…3	1	1
≥ 4	1.26 (1.10–1.43)	1.24 (1.08–1.42)
Age (per one year)	1.007 (1.003–1.010)	1.006 (1.003–1.011)
Male sex	0.99 (0.87–1.12)	n/a
Indication for operation		
Obstruction or "other"	1	n/a
Sepsis	1.50 (1.30–1.72)	n/a
Ischaemia	1.09 (0.86–1.39)	n/a
Presence of sepsis	1.59 (1.40–1.81)	1.43 (1.22–1.67)
Intraperitoneal soiling with pus or free bowel content	1.52 (1.32–1.75)	1.27 (1.07–1.51)
Died in hospital	0.77 (0.60–0.98)	0.55 (0.43–0.71)

[a]CFS – Clinical Frailty Scale, [b]CI – Confidence Interval.

5.3 Study III

Baseline Characteristics

In total, 251 patients were enrolled. The baseline characteristics are summarised in Table 11. The median age was 73 years. Approximately one-fifth of the patients were included from the East Tallinn Central Hospital, with the remainder from the North Estonia Medical Centre Foundation. 30.7% of the patients were non-frail (CFS 1–3), 27.1% had a CFS of 4, and 42.2% were considered frail to varying degrees (CFS 5–9). Complications necessitating re-laparotomy or other invasive interventions were observed in 55 individuals (21.9%). The median LOS in the surgical emergency unit was 8 days, while the combined median LOS in active care and rehabilitation was 10 days.

30-day, 90-day, and 180-day mortality rates were 37 (14.7%), 61 (24.3%), and 71 (28.3%), respectively. The preoperative living situation was documented for all patients. The postoperative living situation at six months was available for 168 patients, including all surviving patients with CFS ≥ 5. The information on living situation at six months was unavailable for 12 patients whose preoperative CFS was less than 5.

Table 11. Descriptive Statistics of study III.

Total number of patients	251
M:F ratio	0.9
Median age (IQR[a])	73 (65–81)
Centre	
NEMC[b]	199 (79.3)
ETCH[c]	52 (20.7)
CFS[d] grade	
1	17 (6.8)
2	25 (10)
3	35 (13.9)
4	68 (27.1)
5	54 (21.5)
6	28 (11.2)
7	5 (2)
8	8 (3.2)
9	11 (4.4)
Patients requiring reoperations or other invasive interventions for complications.	55 (21.9)
Median length of active care in days (IQR)	8 (5–16)
Median length of active care + rehabilitation in days (iqr)	10 (5–23)
30-day mortality	37 (14.7)
90-day mortality	61 (24.3)
180-day mortality	71 (28.3)
Place of living before operation	
Independently or at home with relatives	246 (98)
Institutionalised at hospital or nursing home	5 (2)

Total number of patients	251
Place of living six months after operation	
Independently or at home with relatives	159 (94.6)
Institutionalised at hospital or care home	9 (5.4)
Median NELA[e] predicted 30-day mortality in % (IQR)	7.7 (3.6–16.2)

Numbers are n(%), unless otherwise specified. [a]IQR – interquartile range, [b]NEMC – North Estonia Medical Centre, [c]ETCH – East Tallinn Central Hospital, [d]CFS – Clinical Frailty Scale, [e]NELA – National Emergency Laparotomy Audit.

Postoperative Course

The postoperative course of patients across different CFS grades is described in Table 12. Among frail patients, the proportion requiring re-laparotomy or other invasive interventions in all, except CFS 4 cohort, was significantly higher compared to patients with a CFS 1–3. The OR (95% CI) was 2.3 (0.9–5.7) for CFS 4, 2.6 (1.1–5.7) for CFS 5, 3.1 (1.2–8.2) for CFS 6–8, and 4.3 (1.1–17.7) for CFS 9. Combined, the OR (95% CI) of frail patients (CFS 5–9) developing major complications was 1.89 (1.0–3.5) when compared to patients with a CFS ≤ 4.

Nearly one-third of frail patients were admitted to the ICU postoperatively; however, the difference in ICU admission rates across different CFS categories was not statistically significant. Notably, only two terminally ill patients (CFS 9) were admitted to the ICU after the operation.

The LOS in the surgical emergency unit for patients who survived active care did not differ significantly between CFS categories. However, the combined LOS in active care and rehabilitation was significantly longer for patients with higher frailty levels. The IRR (95% CI) was 1.1 (1.0–1.2) for CFS 4, 1.3 (1.2–1.5) for CFS 5, 1.7 (1.6–1.9) for CFS 6–8, and 2.1 (1.8–2.5) for CFS 9. Patients with higher levels of frailty were less likely to be discharged home or to the care of relatives, and more likely to be admitted to rehabilitation or nursing home. The OR (95% CI) for being admitted to rehabilitation or a nursing home was 2.6 (1.0–4.6) for CFS 4, 6.1 (2.7–13.4) for CFS 5, and 12.3 (5.0–30) for CFS 6–8. Notably, only one patient with a CFS of 9 was discharged home from the surgical emergency unit.

There were no statistically significant differences between CFS categories in the rate of patients requiring emergency re-hospitalisation (p=0.755). A trend was observed indicating that patients with higher levels of frailty experienced more emergency readmissions due to medical issues and fewer for surgical problems. However, the number of readmitted patients in these groups was relatively small, and these differences did not reach statistical significance (p=0.236 and p=0.596, respectively).

Table 12. Postoperative Course by CFS Grade.

	CFS 1–3	CFS 4	CFS 5	CFS 6–8	CFS 9
Number of patients (% of total)	77 (30.7)	68 (27.1)	54 (21.5)	41 (16.3)	11 (4.4)
M:F ratio	0.9	1.0	0.59	1.1	1.8
Median age (IQR[b])	67 (60–75)	75 (68–81)	76 (71–84)	77 (69–83)	72 (64–74)
Patients requiring reoperations or other invasive interventions for complications.	9 (11.7)	16 (23.5)	14 (25.9)	12 (29.3)	4 (36.4)
Patients admitted to the intensive care unit after operation	15 (19.5)	17 (25)	18 (33.3)	13 (31.7)	2 (18.2)
Mean length of intensive care stay (standard deviation)	1.5 (5.6)	2.2 (5.8)	2.6 (8.2)	2.5 (5.6)	0.3 (0.7)
Discharged home or to the care of relatives after active care	63 (81.8)	46 (67.6)	23 (42.6)	11 (26.8)	1 (9.1)
Survived active care	77 (100)	65 (95.6)	45 (83.3)	27 (65.9)	7 (63.6)
Median length of active care in days (IQR[b]) of surviving patients	7 (5–13)	8 (5–13)	13 (7–18)	9 (8–21)	7 (5–11)
Median length of active care + aftercare in days (IQR) of surviving patients	8 (5–15)	9 (6–24)	15 (8–28)	20 (8–37)	24 (15–32)
Surviving patients readmitted as emergency (any)	11 (14.5)	13 (20)	7 (15.9)	5 (19.2)	2 (28.6)
Surviving patients readmitted as emergency (medical)	4 (5.3)	8 (12.3)	5 (11.4)	4 (15.4)	2 (28.6)
Surviving patients readmitted as emergency (surgical)	8 (10.5)	6 (9.2)	2 (4.5)	1 (3.8)	0 (0)
30-day mortality					
Total	0	6 (8.8)	10 (18.5)	16 (39)	5 (45.5)
Age 50–65	0	0 (0)	2 (28.6)	2 (33.3)	2 (50)
Age 65–80	0	1 (2.6)	4 (15.4)	8 (42.1)	3 (42.9)
Age 80+	0	5 (29.4)	4 (19.0)	6 (37.5)	NA
90-day mortality					
Total	3 (3.9)	9 (13.2)	18 (33.3)	23 (56.1)	8 (72.7)
Age 50–65	0 (0)	2 (15.4)	3 (42.9)	2 (33.3)	3 (75)
Age 65–80	2 (5.4)	2 (5.3)	8 (30.8)	11 (57.9)	5 (71.4)
Age 80+	1 (10)	5 (29.4)	7 (33.3)	10 (62.5)	NA
180-day mortality					
Total	5 (6.5)	10 (14.7)	21 (38.9)	25 (61.0)	10 (90.9)
Age 50–65	0 (0)	3 (23.1)	3 (42.9)	2 (33.3)	4 (100)
Age 65–80	4 (10.8)	2 (5.3)	11 (42.3)	12 (63.2)	6 (85.7)
Age 80+	1 (10)	5 (29.4)	7 (33.3)	11 (68.8)	NA

Numbers are n (% within specified category), unless otherwise specified. [a]CFS – Clinical Frailty Scale [b]IQR – Interquartile Range.

Mortality

No patients with a CFS 1–3 in any age group died within 30 days post-operation, whereas significant mortality was observed among frail patients, with increasing mortality rates correlating with higher levels of frailty (Table 12). Figure 2 displays Kaplan-Meier curves of postoperative survival stratified by CFS category. In Cox regression, the HR (95% CI) were 2.4 (0.8–7.1) for CFS 4, 7.5 (2.8–20.0) for CFS 5, 14.4 (5.5–37.8) for CFS 6–8, and 28.7 (9.7–84.6) for CFS 9, compared to non-frail patients. The sole patient classified as CFS 9, who survived beyond 180 days, subsequently died 198 days post-surgery, consistent with the definition of terminally ill patients in the CFS.

Although mortality rates tended to be lower for younger patients compared to older patients, CFS independently influenced mortality within each age group (Table 12). In a multivariable Cox regression model adjusted for age and sex, the HR and 95% CI were 2.3 (0.8–6.5) for CFS 4, 6.7 (2.5–18.3) for CFS 5, 12.7 (4.7–33.9) for CFS 6–8, and 28.6 (9.7–84.4) for CFS 9. In the adjusted model, neither age nor sex had a statistically significant effect, with 95% CI of 0.99–1.04 for age and 0.8–2.2 for sex.

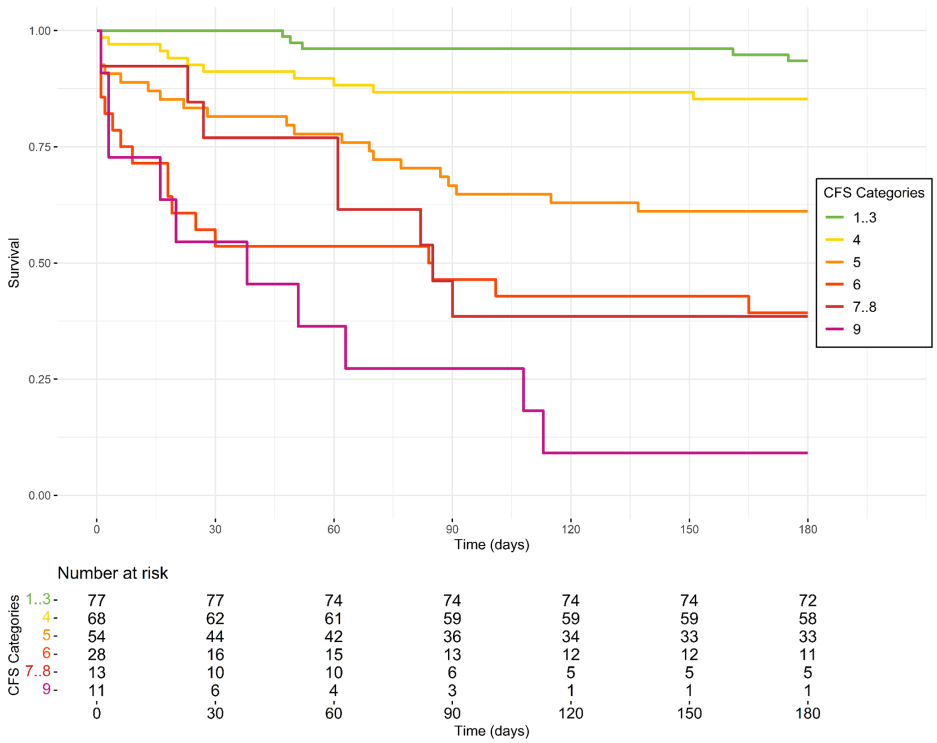

Figure 7. Survival after Emergency Laparotomy by Clinical Frailty Scale (CFS) Grade.

Permanent Change in the Patient's Functional Status

At six months post-EL, surviving patients demonstrated an increased level of frailty compared to their preoperative CFS grade. CFS 8 and CFS 9 were discarded from this analysis because of the definitions of those grades. Among patients aged 80 years or younger, the mean increase in CFS was 0.31 points ($p = 0.008$), while for those older than 80 years, the mean increase was 0.44 points ($p = 0.035$).

Table 13. The Place of Living Preoperatively and Six Months after the Operation.

	CFS[a] < 5	CFS ≥ 5
Number of patients at six months	118	50
Patients institutionalised preoperatively	0	1 (2.0%)
Patients institutionalised at six months after operation	2 (1.7%)	7 (14.0%)

[a]CFS – Clinical Frailty Scale

This persistent decline in functional status is further corroborated by the change in the living arrangements at six months post-EL in patients who were notably frail (CFS ≥ 5) preoperatively. Table 13 details the living situation preoperatively and six months after the operation. Living arrangement data at six months was available for 118 patients with a preoperative CFS < 5, and for 50 patients with a preoperative CFS ≥ 5. Preoperatively, only one patient (with a CFS of 7) was residing in a care home. At six months post-EL, 2 (1.7%) patients with a preoperative CFS < 5 and 7 (14.0%) patients with a preoperative CFS ≥ 5 were institutionalised. The change in living arrangements was not statistically significant for patients with a preoperative CFS < 5 ($p = 0.480$), but it was significant for those with a preoperative CFS ≥ 5 ($p = 0.041$).

6. DISCUSSION

The findings of these studies underline the crucial role of frailty in the outcomes following EL. Across different institutions and different settings, frailty measured by the CFS consistently emerged as a significant predictor of both short-term and long-term adverse outcomes. Frailty independently correlated with elevated postoperative mortality, increased incidence of complications, prolonged hospital stay, and heightened requirements for postoperative care and rehabilitation services. Furthermore, frail and elderly patients demonstrated considerable deterioration in functional status, affecting their independence postoperatively. Incorporating frailty assessments would significantly enhance the prognostic capabilities of existing clinical risk prediction tools such as the P-POSSUM and the NELA RPT. These studies collectively underscore the necessity of routine preoperative frailty evaluation, not only to optimise clinical decision-making but also to enhance resource allocation efficiency and develop patient-centred care pathways that address both immediate and long-term health outcomes.

Study I

Study I evaluated the performance of two commonly used risk prediction tools, P-POSSUM and NELA RPT, and demonstrated that their discrimination improves with the addition of CFS.

Discrimination was assessed using the area under the ROC curve, reflecting each model's ability to accurately stratify patients by risk. Both tools showed good overall discrimination; however, performance declined in the elderly subgroup, consistent with findings from other studies (Ah et al., 2019; Sharrock et al., 2017; Simpson et al., 2022). A possible explanation is that while both P-POSSUM and NELA RPT incorporate age, neither accounts for frailty, which is more prevalent among older adults. Prior studies have shown frailty alone to be predictive of mortality, with discriminatory performance comparable to that observed in our cohort (Palaniappan et al., 2022; Parmar et al., 2021). While the AUC for CFS alone remains lower than that of specialised tools, we showed that combining CFS with either P-POSSUM or NELA RPT significantly improved model discrimination. Notably, the modified P-POSSUM outperformed the unmodified NELA RPT. The improvement in both tools was particularly marked in patients aged ≥ 65 years. Previous attempts to improve the NELA RPT with frailty measures have not demonstrated improved discrimination. Barazanchi et al. (2020) reported that combining the mFI with P-POSSUM and ACS-NSQIP improved predictive performance, but no benefit was seen with NELA RPT; however, they did not perform a subgroup analysis for the elderly. In our cohort, combining CFS with NELA RPT did not yield a statistically significant improvement across all age groups; however, a significant improvement was observed in patients aged ≥ 65 years. Reliable risk stratification is fundamental to clinical decision making. There is clear benefit in routinely admitting high-risk patients

to an intensive care unit postoperatively, as this has been shown to reduce adverse events after the operation (Kokkinakis et al., 2023; NELA project team, 2018).

While previous reports have consistently shown that the NELA RPT has significantly better calibration than P-POSSUM (Barazanchi et al., 2020; Darbyshire et al., 2022; Lai et al., 2021), While previous reports have consistently shown that the NELA RPT has significantly better calibration than P-POSSUM (Hansted et al., 2023; Kokkinakis et al., 2023). In our cohort, the NELA RPT demonstrated excellent calibration, with only slight underprediction across all age groups. In contrast, the P-POSSUM exhibited poor goodness of fit and overpredicted mortality by nearly two-fold; however, the difference between observed and expected mortality was not statistically significant. Such overestimation may contribute to unnecessary allocation of healthcare resources. Conversely, there are instances where surgical intervention is deemed futile. This unsuitability typically results from a combination of patient frailty, physiological deterioration, and the severity of the surgical procedure. Accurate and reliable risk prediction can support patients, their families, and caregivers in setting realistic goals and avoiding the considerable burden of treatment in situations where active care is unlikely to be beneficial.

We demonstrated that frailty influenced mortality not only in patients aged ≥ 65 but also in younger individuals. However, among younger patients with less severe frailty, the association with mortality was statistically less significant, and even in those with higher frailty scores, the odds ratios were lower than those observed in the elderly. Additionally, the proportion of frail individuals was significantly lower among patients under 65 years of age in our cohort. This may partly explain why the improvement in discrimination for the NELA RPT was not significant across the entire study population but reached significance in patients aged 65 and over.

There is evidence that a multidisciplinary approach involving co-management between geriatricians and surgeons improves outcomes in elderly frail patients (Engelhardt et al., 2018; Khadaroo et al., 2020; Shipway et al., 2018). It is highly likely that high-risk and frail younger patients would also benefit from a similar approach.

Furthermore, current risk prediction models are primarily designed to estimate 30-day mortality. While mortality is highest within the first month postoperatively, a substantial proportion of deaths occur beyond this conventional timeframe. In addition, mortality represents only the most visible and readily measurable adverse outcome among a broader spectrum of postoperative complications. Further research is needed not only to improve the prediction of long-term mortality but also to assess and predict outcomes such as postoperative quality of health and return to independent functioning following EL.

Study II

Study II confirmed that patient frailty is associated with increased short- and long-term mortality following EL. We found no evidence that this association is explained by differences in indication, intraperitoneal soiling, or malignancy status. the mortality hazard was 14-fold higher in moderately and severely frail patients, this effect did not appear to be significantly confounded by indication, sepsis, intraperitoneal soiling, or malignancy.

Although reports often focus on prevalence of frailty in the elderly, it is crucial for clinicians to recognize that there are also fit people within this age group. In our cohort a fifth of patients over 80 were considered fit for their age and the outcome of their operation was more favourable accordingly.

The longer LOS observed in frail patients likely reflects postoperative complications and functional decline. (Carter et al., 2020; Tan et al., 2019). Notably, our study revealed that death during hospitalization impacts postoperative LOS differently in fit versus frail patients. Previous studies have reported conflicting findings on LOS, with some identifying prolonged stays in frail patients and others finding no difference compared to fit individuals (Ward et al., 2019). Considering that mortality is higher among frail patients, and that LOS is shorter for those frail patients who die in hospital – unlike their non-frail counterparts – it is essential to adjust for in-hospital death when investigating meaningful differences in LOS between frail and non-frail patients. As with mortality, the effect of frailty on postoperative LOS remained significant even adjusting for the other mentioned risk factors.

The finding of a longer DTS for frail patients is consistent with previous research. However, the clinical implication of such delay is less clear. We found no evidence that a longer DTS correlates with worse survival or an extended postoperative LOS in our cohort. It is conceivable that this additional waiting period allowed for the involvement of more senior staff in the decision-making process, as well as elderly care specialists to achieve better physiological optimization before surgery. While it could be hypothesized that such efficient use of time could offset the intrinsic risks associated with frailty, our study lacked specific data on this aspect. Further research is needed to explore and substantiate this hypothesis.

Study III

Study III demonstrated that frailty, as assessed by the CFS, significantly impacts both short- and long-term outcomes in patients undergoing EL. Our findings highlighted that frail patients (CFS $\geq$ 5) experience markedly higher 180-day mortality rates, increased odds of major complications, prolonged hospital stays, and substantial declines in functional status and independence six months post-surgery. Additionally, frailty was independently associated with mortality across all age groups, while neither age nor sex had a statistically significant effect in the adjusted multivariable model. These results underscore the importance of

preoperative frailty assessment in predicting adverse outcomes and guiding peri-operative care strategies.

This study represents the first effort to employ the CFS in research within Estonia, building upon similar prospective studies conducted in the UK (Parmar et al., 2021) and New Zealand (Park et al., 2024). The proportion of frail patients in our cohort was considerably higher compared to the ELF study in the UK. In the ELF study, 59% of patients were classified within CFS grades 1–3, and only 20% were considered frail (CFS ≥ 5). Conversely, our cohort comprised only 30.7% of patients within CFS grades 1–3, with 42.2% assessed as frail (CFS ≥ 5). Notably, the ELF study included patients aged 65 years or older, whereas our cohort included patients aged 50 and above. The multicentre study from New Zealand by Park et al. (2024) identified only 14.6% of patients over 55 undergoing EL as frail (CFS ≥ 5). Higher levels of frailty and comorbidity in the Eastern compared to the Western Europe are well documented through different papers based on the Survey of Health, Ageing and Retirement in Europe (SHARE) (Ahrenfeldt et al., 2019; Pitter et al., 2024; Romero-Ortuno et al., 2014). The reasons for this are complex and multifaceted, but one significant factor is likely the negative impact of the Soviet regime (Zatonski, 2007).

Table 14 compares the 90-day mortality by age group and CFS between our study and the ELF study. Although our cohort had a lower 90-day mortality rate among patients with CFS < 5, the mortality among frail patients (CFS ≥ 5) was higher compared to the ELF study.

Table 14. 90-day Mortality Rates in Our Cohort and in the Emergency Laparotomy and Frailty (ELF) Study (Parmar et al., 2021).

90-day mortality (%)	CFS[a] 1–3	CFS 4	CFS 5	CFS 6–7
Total (age 65 or more)				
Our study	6.4	12.7	31.9	60.0
The ELF Study	12.2	27.8	27.8	42.9
Age 65–80				
Our study	5.4	5.3	30.8	57.9
The ELF Study	12.0	25.2	24.6	49.1
Age 80+				
Our study	10	29.4	33.3	62.5
The ELF Study	11.2	30.5	25.5	41.9

[a]CFS – Clinical Frailty Scale

Table 15 outlines the differences in 180-day mortality between our study and the prospective multicentre study by Park et al. (2024) from New Zealand. While frail patients in both studies had higher mortality rates compared to non-frail patients, the 180-day mortality of frail patients in our study was noticeably higher compared to the same CFS grade in the New Zealand cohort.

Table 15. 90-day Mortality Rates in Our Cohort and in New Zealand by Park et al. (2024).

180-day mortality (%)	CFS[a] 1–3	CFS 4	CFS 5	CFS 6–8	CFS 9
Total					
Our study	6.5	14.7	38.9	61.0	90.9
Park *et al*	7.8	23.4	29.3	37.5	33.3
Age < 65					
Our study	0	23.1	42.9	33.3	100
Park *et al*	7.9	14.8	33.3	40.0	NA
Age 65–80					
Our study	10.8	5.3	42.3	63.2	85.7
Park *et al*	7.0	26.8	35.3	26.7	33.3
Age 80+					
Our study	10.0	29.4	33.3	68.8	NA
Park *et al*	9.4	24.1	23.8	46.2	NA

[a]CFS – Clinical Frailty Scale

Variations between studies may stem from several factors, such as differences in perioperative care pathways, the extent of geriatricians' and other specialists' involvement in patient care, and variations in the criteria used to select patients for surgery. Further research is needed to determine whether postoperative involvement of geriatricians following emergency laparotomy, both after surgery and during critical care, effectively improves quality of life and extends independent living.

Contributing to the increased mortality of frail patients is the fact that health care professionals often disproportionately focus their efforts on issues related to the acute illness that lead to the hospitalisation (Krumholz, 2013). However, especially in the frail patients, numerous other issues can arise that can cumulatively be detrimental to the patient's outcome. This highlights the critical need for internal medicine or geriatrics specialists in emergency surgery units.

In addition to the observed association with increased mortality, the postoperative course appears considerably more exhausting and challenging in frail patients, both in terms of healthcare resources and the burden on the patients themselves. This study demonstrated that frail patients had higher odds of experiencing complications necessitating re-laparotomy or other invasive re-interventions. Additionally, the LOS in acute care and rehabilitation was significantly longer for frail patients. Nearly one-third of frail patients were admitted to the ICU postoperatively. Although there were no statistically significant differences in ICU admissions compared to fit patients, this remains an important consideration in understanding the burden of care. It is important to acknowledge that these associations may be influenced by confounding factors not accounted for in this analysis.

Frail patients were significantly less likely to be discharged home or to the care of family members indicating a postoperative functional decline that has

been previously described. A novel finding in our study was the long-term deterioration of independence and increase in frailty apparent even six months after EL. This increase in CFS, compared to the preoperative score, was slightly more pronounced in elderly patients in our cohort. Another indication of reduced independence at six months was the significantly higher rate of nursing home residents among surviving frail patients compared to those with a CFS < 5 preoperatively.

The immense burden of care and loss of independence among surviving frail patients are critical aspects that should be clearly communicated to patients before they consider undergoing the high-risk path of EL. It has been repeatedly shown that frail patients are more likely to prefer reduced treatment and interventions, and often prioritise independence and quality of life over extending life (Etkind et al., 2020; T. R. Fried et al., 2002; Heyland et al., 2013). Moreover, there are cases where surgical care would be futile. The acute care setting is not optimal for a patient to make complex decisions such as limiting treatment. Therefore, it is prudent to engage in advance care planning for frail patients beforehand to facilitate decision-making during emergencies. These advance care plans should be well-documented, discussed with patient's family, and communicated to healthcare professionals to mitigate the risk of administering high-burden invasive care to patients who do not want it (Heyland et al., 2013).

Limitations

The retrospective nature of studies I and II introduces inherent limitations. The CFS is a robust tool with substantial inter-rater reliability and can be reliably used retrospectively based on chart reviews. We found that in cases where CFS data were missing from the NELA database, occupational and physiotherapy records were invaluable. However, the absence of detailed records may lead to misclassification, skewing patients towards a "not frail" designation and potentially introducing information bias, especially for patients on CFS grade 4. In both studies the CFS needed to be reclassified in 95 cases. Unfortunately, we were unable to determine the reasons behind this initial misclassification.

Although the number of patients included in studies I and II was relatively large, the lower proportion of patients with higher CFS grades and the number of categories analysed in our regression model necessitated the grouping of certain variables to prevent overfitting. Consequently, a larger cohort could yield more precise estimates of effect sizes.

Additionally, as studies I and II were conducted at a single institution, the generalizability of the results may be limited.

Study III relied on accurate and consistent data collection when assessing the CFS, which could introduce observer bias. While we observed significant postoperative functional decline, the long-term impact of these changes and their implications on patients' quality of life and healthcare resource utilization require further investigation. Larger, multi-centre studies would be beneficial to confirm the finding of diminished functional status six months after surgery for frail patients.

7. CONCLUSIONS

The addition of frailty, as measured by the Clinical Frailty Scale, can improve the discriminatory ability of the P-POSSUM and NELA risk models. Although the prevalence of frailty is higher among patients over the age of 65, it is significantly associated with increased 30-day mortality in patients undergoing emergency laparotomy both over and under the age of 65.

Higher levels of frailty are associated with increased 180-day mortality following emergency laparotomy. Frailty has an independent negative impact on mortality, preoperative waiting time, and length of hospital stay, which is not explained by differences in indication for surgery, presence of sepsis, intraperitoneal soiling, or the presence of malignancy when compared to non-frail patients.

The prevalence of frailty among patients over the age of 50 undergoing emergency laparotomy in Estonian referral hospitals is high. Higher levels of frailty are associated with increased short- and long-term mortality; and when frailty is taken into account, age and sex do not independently influence mortality in this patient group. Frail patients experience more postoperative complications requiring invasive intervention, have longer hospital stays, a lower likelihood of being discharged home, and demonstrate a noticeable decline in functional independence even six months after surgery compared to their preoperative status.

8. SUMMARY IN ESTONIAN

Hapruse mõju erakorralise laparotoomia ravitulemustele: prognostiliste mudelite ja otsustusprotsessi täiustamisest

8.1 Sissejuhatus

Maailma rahvastik vananeb ning prognooside kohaselt on arenenud riikides aastaks 2050 peaaegu iga kolmas inimene üle 65-aastane (European Comission, 2023; Pérez-Zepeda et al., 2022). Selline demograafiline kriis seab suure väljakutse riikide meditsiinisüsteemidele. Ometi ei ole kõik vanemaealised oma tervise seisundi poolest eakaaslastega võrdsed ning teisest küljest on ka alla 65-aastaste hulgas nõrgema tervisega inimesi. Selleks, et iseloomustada inimese tervise üldist tugevust ja vastupidavust on paarkümmend aastat tagasi välja töötatud hapruse kontseptsioon. Haprus on seisund, mille puhul organismi kehvem toimimine ning füsioloogilise reservi vähenemine põhjustavad suurema haavatavuse väliste mõjurite suhtes. Habraste inimeste puhul võib ka küllalt väikestel teguritel (nagu kukkumine või raviskeemi uue ravimi lisamine) olla suur negatiivne mõju, millest taastumine on hapruse tõttu raske ning aeganõudev ja endise olukorra täielik saavutamine ei pruugi alati võimalik olla. Haprus on objektiivselt mõõdetav ning selle raskusastme hindamiseks on välja töötatud mitmeid mõõdikuid (Fried et al., 2001; Rockwood et al., 2005). Üks kõige laialdasemalt kasutatav selline mõõdik on 9-astmeline Kliiniline Hapruse Skaala ehk *Clinical Frailty Scale*, kus kõrgem aste vastab raskemale hapruse tasemele. Kliiniline Hapruse Skaala on tõendatud, praktikas kergesti kasutatav ning sobib hapruse hindamiseks väga erinevatel erialadel, sealhulgas ka erakorralistes olukordades, kus hapruse määramiseks on oluline hinnata just patsiendi seisundit enne ägeda haiguse teket. Erakorralise kirurgia raames on hapruse mõju uuritud ainult viimased kümmekond aastat.

8.2 Eesmärgid

Käesoleva uurimistöö eesmärk oli hinnata hapruse mõju erakorralise laparotoomia (EL) ravitulemustele nii pikas- kui lühiperspektiivis ning uurida hapruse levimust EL läbi teinud patsientide hulgas. Lisaks oli eesmärk uurida, kas olemasolevaid prognostilisi mudeleid on võimalik muuta täpsemaks lisades neisse CFS abil mõõdetud hapruse taseme.

Konkreetsed eesmärgid olid järgnevad:

I uuringu põhieesmärgiks oli hinnata, kas Kliinilise Hapruse Skaala (Clinical Frailty Scale) abil mõõdetud hapruse lisamine parandaks P-POSSUM ja NELA prognostiliste mudelite eristusvõimet (ingl.k. discrimination) erakorralise laparotoomia järgse suremuse prognoosimisel. Lisaks oli eesmärgiks analüüsida hapruse

mõju nii üle kui alla 65-aastaste erakorralise laparotoomia läbi teinud patsientide 30-päeva suremusele.

II uuringu põhieesmärgiks oli analüüsida hapruse mõju 180-päeva suremusele pärast erakorralist laparotoomiat ning uurida, kas see seos võiks olla seletatav erinevustega operatsiooni näidustustes, sepsise esinemises, kõhuõõne saastatuses või pahaloomuliste haiguste esinemises võrreldes mitte-habraste patsientidega. Teisene eesmärk oli hinnata hapruse mõju erakorralise laparotoomia ooteaja pikkusele ning operatsioonijärgse haiglaravi kestusele.

III uuringu põhieesmärgiks oli uurida hapruse levimust üle 50-aastaste erakorralise laparotoomia läbi teinud patsientide hulgas kahes Eesti suurhaiglas ning hapruse mõju lühi- ja pikaajalisele suremusele. Teisene eesmärk oli hinnata hapruse mõju operatsioonijärgsetele tüsistustele, operatsioonijärgse haiglaravi kestusele ning hapruse süvenemisele ja iseseisva toimetuleku vähenemisele nii pikas- kui lühiperspektiivis.

8.3 Uuritavad ja meetodid

I ja II uuringusse kaasati retrospektiivselt kõik täisealised patsiendid, kellele oli Oxfordi Ülikooli haiglas tehtud üldkirurgilise patoloogia tõttu EL ja kelle andmed olid sisestatud prospektiivsesse NELA andmebaasi vahemikus 2018 jaanuar kuni 2021 juuni.

III uuringusse kaasati prospektiivselt kõik üle 50-aastased patsiendid, kellele oli Põhja-Eesti Regionaalhaiglas (vahemikus 2022 märts kuni 2023 aprill) või Ida-Tallinna Keskhaiglas (vahemikus 2022 juuni kuni 2023 juuli) teostatud EL üldkirurgilise patoloogia tõttu.

Kõigis uuringutes kasutati patsientide hapruse taseme määramiseks Kliinilist Hapruse Skaalat (CFS). Lisaks koguti andmeid patsiendi vanuse ja soo kohta, operatsiooni käigu ja patsiendi operatsiooniaegse seisundi kohta ning andmeid haiglas viibitud aja ja operatsiooni ooteaja kohta. Eesti haiglates läbi viidud uuringu jaoks koguti lisaks andmeid haiglast väljakirjutamise sihtkoha, operatsioonijärgsete tüsistuste ning rehospitaliseerimiste ning hapruse ja iseseisva toimetuleku kohta kuni pool aastat peale operatsiooni.

8.4 Tulemused

I uuringusse kaasati 793 täisealist haiget, kellest 52.1% olid üle 65-aastased ja 25.7% olid märgatavalt haprad (CFS $\geq$ 5). Nii NELA kui P-POSSUM riskimudeli eristusvõime oli parem, kui CFS-l üksi (AUC vastavalt 0.875, 0.839 ja 0.777). Üle-65 aastaste alagrupis oli kõigi kolme eristusvõime madalam, kusjuures vahe oli kõige suurem P-POSSUM puhul (kõik vanused AUC = 0.839 *vs* üle 65-aastastel AUC = 0.774). Lisades riskimudelitesse CFS, paranes nii P-POSSUM kui NELA eristusvõime, kusjuures paranemine oli eriti märgatav just üle 65-aastaste grupis (AUC paranemine P-POSSUM puhul 0.775-lt 0.846-le ja NELA

puhul 0.814-lt 0.864-le). Lisaks esines statistiliselt oluline seos CFS ja 30-päeva suremuse vahel nii üle- kui alla 65-aastaste hulgas.

II uuringusse kaasati 803 täisealist patsienti mediaan vanusega 66.0 aastat. Hapruse levimus oli suurem vanuse kasvades, kuid ka 17.1% alla 50-aastastest olid vähemalt väga kergelt haprad (CFS ≥ 4) samas, kui 20.6% üle 80-aastastest ei olnud üldse haprad (CFS = 1–3). Hapruse erinevate tasemete vahel ei esinenud erinevusi operatsiooni näidustuse, sepsise esinemise, kõhuõõne saastatuse ega pahaloomulise haiguse olemasolu kategooriate jaotuses. Samadele teguritele ning vanusele ja soole kohandatud mitmeses Cox regressioonimudelis jäi haprus 30-päeva suremuse iseseisvaks riskifaktoriks. Hapruse tasemete CFS 4, 5 ja 6–7 kaupa oli HR vastavalt 3.93 (95% CI 1.89–8.20), 5.86 (95% CI 2.87–11.97) ja 14.17 (95% CI 7.33–27.40) võrreldes mitte-habrastega. Samadele teguritele kohandatud mitmeses regressioonanalüüsis oli haprus seotud pikema operatsiooni ooteajaga ning pikema operatsiooni järgselt haiglas veedetud ajaga.

III uuringusse kaasati 251 üle 50-aastast patsienti mediaan vanusega 73 aastat, kellest ainult 30.7% olid mitte-haprad (CFS = 1–3). Kõrgem hapruse tase oli seotud kõrgema 180-päeva suremusega, suurema hulga tüsistustega, mis vajasid invasiivset sekkumist või korduvat operatsiooni ning pikema haiglas- ja järelravil viibitud ajaga. Vanusele ja soole kohaldatud mitmeses Cox regressioonianalüüsis oli 180-päeva suremuse HR (95% CI) 2.3 (0.8–6.5) CFS 4 puhul, 6.7 (2.5–18.3) CFS 5 puhul, 12.7 (4.7–33.9) CFS 6–8 puhul ja 28.6 (9.7–84.4) CFS 9 puhul. Samas analüüsis ei olnud vanusel ega sool statistiliselt olulist mõju 180-päeva suremusele.

Lisaks mõjutas haprus oluliselt iseseisvat toimetulekut nii lühi- kui pikas perspektiivis. Hapramate patsientide tõenäosus haiglast koju pääseda oli oluliselt madalam. Patsientidest, kes varasemalt elasid üksi või koos lähedastega kodus, oli habrastel suurem tõenäosus pool aastat pärast operatsiooni elada hooldusasutuses. Patsientide hapruse tase oli isegi pool aastat peale operatsiooni kõrgem võrreldes operatsioonieelsega (CFS keskmine suurenemine 0.31 punkti p = 0.008) ning see muutus oli eriti märgatav üle 80-aastaste hulgas (CFS keskmine suuremine 0.44 punkti p = 0.035).

8.5 Järeldused

Kliinilise Hapruse Skaala (*Clinical Frailty Scale*) abil mõõdetud hapruse lisamisega on võimalik parandada P-POSSUM ja NELA riskimudelite eristusvõimet. Kuigi haprus on sagedasem üle 65-aastaste hulgas, on sellel oluline negatiivne mõju erakorralise laparotoomia järgsele 30-päeva suremusele nii üle kui alla 65-aastaste vanuserühmas.

Kõrgem hapruse tase on seotud suurema 180-päeva suremusega pärast erakorralist laparotoomiat. Haprusel on iseseisev negatiivne mõju suremusele, operatsiooni ooteajale ja operatsioonijärgse haiglaravi kestusele, mida ei selgita

erinevused operatsiooni näidustustes, sepsise esinemises, kõhuõõne saastatuses ega pahaloomulise haiguse esinemises võrreldes mitte-habraste patsientidega.

Hapruse levimus üle 50-aastaste erakorralise laparotoomia läbi teinud patsientide hulgas Eesti suurhaiglates on kõrge. Kõrgem hapruse tase on seotud suurema lühi- ja pikaajalise suremusega ning haprust arvesse võttes ei ole vanusel ega sool selles patsientide grupis iseseisvat mõju suremusele. Erakorralise laparotoomia läbi teinud habraste patsientide hulgas esineb rohkem invasiivset sekkumist vajavaid tüsistusi, nende operatsioonijärgse haiglaravi kestus on pikem, haiglast koju pääsemise tõenäosus on väiksem ning isegi pool aastat pärast operatsiooni on märgata iseseisva toimetuleku halvenemist võrreldes operatsioonieelse seisundiga.

REFERENCES

Aakre, E. K., Ulvik, A., Hufthammer, K. O., & Jammer, I. (2020). Mortality and complications after emergency laparotomy in patients above 80 years. *Acta Anaesthesiologica Scandinavica*, *64*(7), 913–919. https://doi.org/10.1111/aas.13594

Ah, R., BChir, M., Cao, Y., Geijer, H., Taha, K., Pourhossein-Sarmeh, S., Talving, P., Ljungqvist, O., & Mohseni, S. (2019). Prognostic Value of P-POSSUM and Osteopenia for Predicting Mortality After Emergency Laparotomy in Geriatric Patients. *Bulletin of Emergency & Trauma*, *7*(3), 223–231. https://doi.org/10.29252/beat-070303

Ahmed, A., Sorajja, P., Pai, A., Plimpton, N., Bae, R., Pedersen, W. A., Tindell, L., Farivar, R. S., Harris, K., & Gössl, M. (2016). Prospective Evaluation of the Eyeball Test for Assessing Frailty in Patients With Valvular Heart Disease. *Journal of the American College of Cardiology*, *68*(25), 2911–2912. https://doi.org/10.1016/j.jacc.2016.10.016

Ahrenfeldt, L. J., Möller, S., Thinggaard, M., Christensen, K., & Lindahl-Jacobsen, R. (2019). Sex Differences in Comorbidity and Frailty in Europe. *International Journal of Public Health*, *64*(7), 1025–1036. https://doi.org/10.1007/s00038-019-01270-9

Al-Temimi, M. H., Griffee, M., Enniss, T. M., Preston, R., Vargo, D., Overton, S., Kimball, E., Barton, R., & Nirula, R. (2012). When Is Death Inevitable after Emergency Laparotomy? Analysis of the American College of Surgeons National Surgical Quality Improvement Program Database. *Journal of the American College of Surgeons*, *215*(4), 503. https://doi.org/10.1016/j.jamcollsurg.2012.06.004

Andreasen, J., Lund, H., Aadahl, M., & Sørensen, E. E. (2015). The experience of daily life of acutely admitted frail elderly patients one week after discharge from the hospital. *International Journal of Qualitative Studies on Health and Well-Being*, *10*(1), 27370. https://doi.org/10.3402/qhw.v10.27370

Apóstolo, J., Cooke, R., Bobrowicz-Campos, E., Santana, S., Marcucci, M., Cano, A., Vollenbroek-Hutten, M., Germini, F., D'Avanzo, B., Gwyther, H., & Holland, C. (2018). Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: A systematic review. *JBI Evidence Synthesis*, *16*(1), 140. https://doi.org/10.11124/JBISRIR-2017-003382

Barazanchi, A., Bhat, S., Palmer-Neels, K., Macfater, W. S., Xia, W., Zeng, I., Taneja, A., MacCormick, A. D., & Hill, A. G. (2020). Evaluating and improving current risk prediction tools in emergency laparotomy. *The Journal of Trauma and Acute Care Surgery*, *89*(2), 382–387. https://doi.org/10.1097/TA.0000000000002745

Barghash, M., Iskandar, A., Fawzy, S. I., Effiom, D., Huck, C., Hajibandeh, S., Hajibandeh, S., & Mansour, M. (2022). Predictive Performance of NELA Versus P-POSSUM Mortality Scores: Are We Underestimating the Risk of Mortality Following Emergency Laparotomy? *Cureus*, *14*(12), e32859. https://doi.org/10.7759/cureus.32859

Bilimoria, K. Y., Liu, Y., Paruch, J. L., Zhou, L., Kmiecik, T. E., Ko, C. Y., & Cohen, M. E. (2013). Development and Evaluation of the Universal ACS NSQIP Surgical Risk Calculator: A Decision Aide and Informed Consent Tool for Patients and Surgeons. *Journal of the American College of Surgeons*, *217*(5), 833–842.e3. https://doi.org/10.1016/j.jamcollsurg.2013.07.385

Buta, B. J., Walston, J. D., Godino, J. G., Park, M., Kalyani, R. R., Xue, Q.-L., Bandeen-Roche, K., & Varadhan, R. (2016). Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Research Reviews*, *26*, 53–61. https://doi.org/10.1016/j.arr.2015.12.003

Carter, B., Law, J., Hewitt, J., Parmar, K. L., Boyle, J. M., Casey, P., Maitra, I., Pearce, L., Moug, S. J., & ELF Study Group. (2020). Association between preadmission frailty and care level at discharge in older adults undergoing emergency laparotomy. *The British Journal of Surgery*, *107*(3), 218–226. https://doi.org/10.1002/bjs.11392

Church, S., Rogers, E., Rockwood, K., & Theou, O. (2020). A scoping review of the Clinical Frailty Scale. *BMC Geriatrics*, *20*(1), 393. https://doi.org/10.1186/s12877-020-01801-7

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *The Lancet*, *381*(9868), 752–762. https://doi.org/10.1016/S0140-6736(12)62167-9

Collard, R. M., Boter, H., Schoevers, R. A., & Oude Voshaar, R. C. (2012). Prevalence of frailty in community-dwelling older persons: A systematic review. *Journal of the American Geriatrics Society*, *60*(8), 1487–1492. https://doi.org/10.1111/j.1532-5415.2012.04054.x

Congiusta, D. V., Palvannan, P., & Merchant, A. M. (2017). The Impact of Frailty on Morbidity and Mortality following Open Emergent Colectomies. *BioMed Research International*, *2017*, 5126452. https://doi.org/10.1155/2017/5126452

Copeland, G. P., Jones, D., & Walters, M. (1991). POSSUM: A scoring system for surgical audit. *The British Journal of Surgery*, *78*(3), 355–360. https://doi.org/10.1002/bjs.1800780327

Dam, C. S. van, Trappenburg, M. C., Wee, M. M. ter, Hoogendijk, E. O., Vet, R. de, Smulders, Y. M., Nanayakkara, P. B., Muller, M., & Peters, M. L. (2022). The Prognostic Accuracy of Clinical Judgment Versus a Validated Frailty Screening Instrument in Older Patients at the Emergency Department: Findings of the AmsterGEM Study. *Annals of Emergency Medicine*, *80*(5), 422–431. https://doi.org/10.1016/j.annemergmed.2022.04.039

Darbyshire, A. R., Kostakis, I., Pucher, P. H., Prytherch, D., & Mercer, S. J. (2022). P-POSSUM and the NELA Score Overpredict Mortality for Laparoscopic Emergency Bowel Surgery: An Analysis of the NELA Database. *World Journal of Surgery*, *46*(3), 1. https://doi.org/10.1007/s00268-021-06404-w

Dent, E., Hanlon, P., Sim, M., Jylhävä, J., Liu, Z., Vetrano, D. L., Stolz, E., Pérez-Zepeda, M. U., Crabtree, D. R., Nicholson, C., Job, J., Ambagtsheer, R. C., Ward, P. R., Shi, S. M., Huynh, Q., & Hoogendijk, E. O. (2023). Recent developments in frailty identification, management, risk factors and prevention: A narrative review of leading journals in geriatrics and gerontology. *Ageing Research Reviews*, *91*, 102082. https://doi.org/10.1016/j.arr.2023.102082

Dent, E., Morley, J. E., Cruz-Jentoft, A. J., Woodhouse, L., Rodríguez-Mañas, L., Fried, L. P., Woo, J., Aprahamian, I., Sanford, A., Lundy, J., Landi, F., Beilby, J., Martin, F. C., Bauer, J. M., Ferrucci, L., Merchant, R. A., Dong, B., Arai, H., Hoogendijk, E. O., … Vellas, B. (2019). Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. *The Journal of Nutrition, Health and Aging*, *23*(9), 771–787. https://doi.org/10.1007/s12603-019-1273-z

Eliezer, D. D. (2020). High-Risk Emergency Laparotomy in Australia: Comparing NELA, P-POSSUM, and ACS-NSQIP Calculators. *Journal of Surgical Research*, *246*, 300–304. https://doi.org/10.1016/j.jss.2019.09.024

Engelhardt, K. E., Reuter, Q., Liu, J., Bean, J. F., Barnum, J., Shapiro, M. B., Ambre, A., Dunbar, A., Markzon, M., Reddy, T. N., Schilling, C., & Posluszny, J. A. J. (2018). Frailty screening and a frailty pathway decrease length of stay, loss of independence,

and 30-day readmission rates in frail geriatric trauma and emergency general surgery patients. *Journal of Trauma and Acute Care Surgery*, *85*(1), 167. https://doi.org/ 10.1097/TA.0000000000001931

Etkind, S. N., Lovell, N., Bone, A. E., Guo, P., Nicholson, C., Murtagh, F. E. M., & Higginson, I. J. (2020). The stability of care preferences following acute illness: A mixed methods prospective cohort study of frail older people. *BMC Geriatrics*, *20*. https://doi.org/10.1186/s12877-020-01725-2

Eugene, N., Oliver, C. M., Bassett, M. G., Poulton, T. E., Kuryba, A., Johnston, C., Anderson, I. D., Moonesinghe, S. R., Grocott, M. P., Murray, D. M., Cromwell, D. A., Walker, K., & NELA collaboration. (2018). Development and internal validation of a novel risk adjustment model for adult patients undergoing emergency laparotomy surgery: The National Emergency Laparotomy Audit risk model. *British Journal of Anaesthesia*, *121*(4), 739–748. https://doi.org/10.1016/j.bja.2018.06.026

European Comission. (2023). *The Impact of Demographic Change in a Changing Environment*. https://commission.europa.eu/system/files/2023-01/Demography_ report_2022_0.pdf

Farhat, J. S., Velanovich, V., Falvo, A. J., Horst, H. M., Swartz, A., Patton, J. H., & Rubinfeld, I. S. (2012). Are the frail destined to fail? Frailty index as predictor of surgical morbidity and mortality in the elderly. *The Journal of Trauma and Acute Care Surgery*, *72*(6), 1526–1530; discussion 1530–1531. https://doi.org/10.1097/TA.0b013e3182542fab

Fehlmann, C. A., Nickel, C. H., Cino, E., Al-Najjar, Z., Langlois, N., & Eagles, D. (2022). Frailty assessment in emergency medicine using the Clinical Frailty Scale: A scoping review. *Internal and Emergency Medicine*, *17*(8), 2407–2418. https://doi.org/10.1007/s11739-022-03042-5

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*(3), 255–263. https://doi.org/10.1093/gerona/59.3.m255

Fried, T. R., Bradley, E. H., Towle, V. R., & Allore, H. (2002). Understanding the treatment preferences of seriously ill patients. *The New England Journal of Medicine*, *346*(14), 1061–1066. https://doi.org/10.1056/NEJMsa012528

Fried, T. R., Van Ness, P. H., Byers, A. L., Towle, V. R., O'Leary, J. R., & Dubin, J. A. (2007). Changes in preferences for life-sustaining treatment among older persons with advanced illness. *Journal of General Internal Medicine*, *22*(4), 495–501. https://doi.org/10.1007/s11606-007-0104-9

Fried, Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., Burke, G., & McBurnie, M. A. (2001). Frailty in Older Adults: Evidence for a Phenotype. *The Journals of Gerontology: Series A*, *56*(3), M146–M157. https://doi.org/10.1093/gerona/56.3.M146

Gale, S. C., Shafi, S., Dombrovskiy, V. Y., Arumugam, D., & Crystal, J. S. (2014). The public health burden of emergency general surgery in the United States: A 10-year analysis of the Nationwide Inpatient Sample – 2001 to 2010. *The Journal of Trauma and Acute Care Surgery*, *77*(2), 202–208. https://doi.org/10.1097/TA.0000000000000362

Geriatric Emergency Department Guidelines Task Force. (2014). Geriatric Emergency Department Guidelines. *Annals of Emergency Medicine*, *63*(5), e7–e25. https://doi.org/10.1016/j.annemergmed.2014.02.008

Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, M. T., & Schols, J. M. (2010). Toward a conceptual definition of frail community dwelling older people. *Nursing Outlook*, *58*(2), 76–86. https://doi.org/10.1016/j.outlook.2009.09.005

Goeteyn, J., Evans, L. A., De Cleyn, S., Fauconnier, S., Damen, C., Hewitt, J., Ceelen, W., & Older Persons Surgical Outomes Collaborative. (2017). Frailty as a predictor of mortality in the elderly emergency general surgery patient. *Acta Chirurgica Belgica*, *117*(6), 370–375. https://doi.org/10.1080/00015458.2017.1337339

Handforth, C., Clegg, A., Young, C., Simpkins, S., Seymour, M. T., Selby, P. J., & Young, J. (2015). The prevalence and outcomes of frailty in older cancer patients: A systematic review. *Annals of Oncology*, *26*(6), 1091–1101. https://doi.org/10.1093/annonc/mdu540

Hansted, A. K., Storm, N., Burcharth, J., Diasso, P. D. K., Ninh, M., Møller, M., & Vester-Andersen, M. (2023). Validation of the NELA risk prediction model in emergency abdominal surgery. *Acta Anaesthesiologica Scandinavica*, *67*, 1194–1201. https://doi.org/10.1111/aas.14294

Havens, J. M., Peetz, A. B., Do, W. S., Cooper, Z., Kelly, E., Askari, R., Reznor, G., & Salim, A. (2015). The excess morbidity and mortality of emergency general surgery. *Journal of Trauma and Acute Care Surgery*, *78*(2), 306. https://doi.org/10.1097/TA.0000000000000517

He, W., Goodkind, D., & Kowal, P. (2015). *An Aging World*.

Hewitt, Carter, B., McCarthy, K., Pearce, L., Law, J., Wilson, F. V., Tay, H. S., McCormack, C., Stechman, M. J., Moug, S. J., & Myint, P. K. (2019). Frailty predicts mortality in all emergency surgical admissions regardless of age. An observational study. *Age and Ageing*, *48*(3), 388–394. https://doi.org/10.1093/ageing/afy217

Hewitt, Long, S., Carter, B., Bach, S., McCarthy, K., & Clegg, A. (2018). The prevalence of frailty and its association with clinical outcomes in general surgery: A systematic review and meta-analysis. *Age and Ageing*, *47*(6), 793–800. https://doi.org/10.1093/ageing/afy110

Hewitt, Milton, T. J., Jeanes, J., Murshed, I., Nann, S., Wells, S., Gupta, A. K., Ovenden, C. D., Kovoor, J. G., Bacchi, S., Dobbins, C., & Trochsler, M. I. (2024). Emergency laparotomy preoperative risk assessment tool performance: A systematic review. *Surgery in Practice and Science*, *19*, 100264. https://doi.org/10.1016/j.sipas.2024.100264

Hewitt, Moug, S. J., Middleton, M., Chakrabarti, M., Stechman, M. J., & McCarthy, K. (2015). Prevalence of frailty and its association with mortality in general surgery. *The American Journal of Surgery*, *209*(2), 254–259. https://doi.org/10.1016/j.amjsurg.2014.05.022

Heyland, D. K., Barwich, D., Pichora, D., Dodek, P., Lamontagne, F., You, J. J., Tayler, C., Porterfield, P., Sinuff, T., Simon, J., ACCEPT (Advance Care Planning Evaluation in Elderly Patients) Study Team, & Canadian Researchers at the End of Life Network (CARENET). (2013). Failure to engage hospitalized elderly patients and their families in advance care planning. *JAMA Internal Medicine*, *173*(9), 778–787. https://doi.org/10.1001/jamainternmed.2013.180

Hii, T. B. K., Lainchbury, J. G., & Bridgman, P. G. (2015). Frailty in acute cardiology: Comparison of a quick clinical assessment against a validated frailty assessment tool. *Heart, Lung & Circulation*, *24*(6), 551–556. https://doi.org/10.1016/j.hlc.2014.11.024

Hoogendijk, E. O., Afilalo, J., Ensrud, K. E., Kowal, P., Onder, G., & Fried, L. P. (2019). Frailty: Implications for clinical practice and public health. *The Lancet*, *394*(10206), 1365–1375. https://doi.org/10.1016/S0140-6736(19)31786-6

Hopkins, S. A., Bentley, A., Phillips, V., & Barclay, S. (2020). Advance care plans and hospitalized frail older adults: A systematic review. *BMJ Supportive & Palliative Care*, *10*(2), 164–174. https://doi.org/10.1136/bmjspcare-2019-002093

Hwang, A.-C., Chen, L.-Y., Tang, T.-C., Peng, L.-N., Lin, M.-H., Chou, Y.-J., Hsiao, F.-Y., & Chen, L.-K. (2023). Transitions in Frailty and 4-Year Mortality Risk in Taiwan Longitudinal Study on Aging. *Journal of the American Medical Directors Association*, *24*(1), 48–56.e5. https://doi.org/10.1016/j.jamda.2022.10.005

Ingraham, A., Schumacher, J., Fernandes-Taylor, S., Yang, D.-Y., Godat, L., Smith, A., Barbosa, R., Cribari, C., Salim, A., Schroeppel, T., Staudenmayer, K., Crandall, M., & Utter, G. H. (2022). General surgeon involvement in the care of patients designated with an American Association for the Surgery of Trauma-endorsed ICD-10-CM emergency general surgery diagnosis code in Wisconsin. *The Journal of Trauma and Acute Care Surgery*, *92*(1), 117–125. https://doi.org/10.1097/TA.0000000000003387

Jackwert, K., Holmér, M., Hallongren, M., Asmar, T., Wretenberg, P., & Andersson, Å. G. (2024). Agreement between Clinical Frailty Scale-scores based on information from patient interviews and Clinical Frailty Scale-scores based on information from medical records – A cross sectional study. *BMC Geriatrics*, *24*(1), 570. https://doi.org/10.1186/s12877-024-05160-5

Joseph, B., Zangbar, B., Pandit, V., Fain, M., Mohler, M. J., Kulvatunyou, N., Jokar, T. O., O'Keeffe, T., Friese, R. S., & Rhee, P. (2016). Emergency General Surgery in the Elderly: Too Old or Too Frail? *Journal of the American College of Surgeons*, *222*(5), 805–813. https://doi.org/10.1016/j.jamcollsurg.2016.01.063

Kay, R. S., Hughes, M., Williamson, T. R., Hall, A. J., Duckworth, A. D., & Clement, N. D. (2022). The Clinical Frailty Scale can be used retrospectively to assess the frailty of patients with hip fracture: A validation study. *European Geriatric Medicine*, *13*(5), 1101–1107. https://doi.org/10.1007/s41999-022-00686-6

Kennedy, C. A., Shipway, D., & Barry, K. (2022). Frailty and emergency abdominal surgery: A systematic review and meta-analysis. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*, *20*(6), e307–e314. https://doi.org/10.1016/j.surge.2021.11.009

Khadaroo, R., Warkentin, L., Wagg, A., Padwal, R., Clement, F., & Wang, X. (2020). Clinical effectiveness of the elder-friendly approaches to the surgical environment initiative in emergency general surgery. *JAMA Surgery*. https://doi.org/155(4):e196021

Kocher, E. T. (1903). *Chirurgische Operationslehre*.

Kojima, G. (2015). Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. *Journal of the American Medical Directors Association*, *16*(11), 940–945. https://doi.org/10.1016/j.jamda.2015.06.025

Kojima, G., Iliffe, S., & Walters, K. (2018). Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age and Ageing*, *47*(2), 193–200. https://doi.org/10.1093/ageing/afx162

Kojima, G., Taniguchi, Y., Iliffe, S., Jivraj, S., & Walters, K. (2019). Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis. *Ageing Research Reviews*, *50*, 81–88. https://doi.org/10.1016/j.arr.2019.01.010

Kokkinakis, S., Kritsotakis, E. I., Paterakis, K., Karali, G.-A., Malikides, V., Kyprianou, A., Papalexandraki, M., Anastasiadis, C. S., Zoras, O., Drakos, N., Kehagias, I., Kehagias, D., Gouvas, N., Kokkinos, G., Pozotou, I., Papatheodorou, P., Frantzeskou, K., Schizas, D., Syllaios, A., … Lasithiotakis, K. (2023). Prospective multicenter

external validation of postoperative mortality prediction tools in patients undergoing emergency laparotomy. *Journal of Trauma and Acute Care Surgery*, *94*(6), 847. https://doi.org/10.1097/TA.0000000000003904

Krumholz, H. M. (2013). Post-Hospital Syndrome – A Condition of Generalized Risk. *The New England Journal of Medicine*, *368*(2), 100–102. https://doi.org/10.1056/NEJMp1212324

Lai, C. P. T., Goo, T. T., Ong, M. W., Prakash, P. S., Lim, W. W., & Drakeford, P. A. (2021). A Comparison of the P-POSSUM and NELA Risk Score for Patients Undergoing Emergency Laparotomy in Singapore. *World Journal of Surgery*, *45*(8), 2439–2446. https://doi.org/10.1007/s00268-021-06120-5

Law, J., Welch, C., Javanmard-Emamghissi, H., Clark, M., Bisset, C. N., O'Neil, P., Moug, S. J., & Group, the E. study. (2020). Decision-making for older patients undergoing emergency laparotomy: Defining patient and clinician values and priorities. *Colorectal Disease*, *22*(11), 1694–1703. https://doi.org/10.1111/codi.15165

Lee, K. C., Sturgeon, D., Lipsitz, S., Weissman, J. S., Mitchell, S., & Cooper, Z. (2020). Mortality and Health Care Utilization Among Medicare Patients Undergoing Emergency General Surgery vs Those With Acute Medical Conditions. *JAMA Surgery*, *155*(3), 216–223. https://doi.org/10.1001/jamasurg.2019.5087

Lewis, D. (1978). *Public Policy and the Frail Elderly: A Staff Report*. https://eric.ed.gov/?id=ED216300

Lewis, Dent, E., Alkhouri, H., Kellett, J., Williamson, M., Asha, S., Holdgate, A., Mackenzie, J., Winoto, L., Fajardo-Pulido, D., Ticehurst, M., Hillman, K., McCarthy, S., Elcombe, E., Rogers, K., & Cardona, M. (2019). Which frailty scale for patients admitted via Emergency Department? A cohort study. *Archives of Gerontology and Geriatrics*, *80*, 104–114. https://doi.org/10.1016/j.archger.2018.11.002

Liau, S. J., Lalic, S., Sluggett, J. K., Cesari, M., Onder, G., Vetrano, D. L., Morin, L., Hartikainen, S., Hamina, A., Johnell, K., Tan, E. C. K., Visvanathan, R., & Bell, J. S. (2021). Medication Management in Frail Older People: Consensus Principles for Clinical Practice, Research, and Education. *Journal of the American Medical Directors Association*, *22*(1), 43–49. https://doi.org/10.1016/j.jamda.2020.05.004

Lipping, E., Saar, S., Reinsoo, A., Bahhir, A., Kirsimägi, Ü., Lepner, U., & Talving, P. (2024). Short Postoperative Intravenous Versus Oral Antibacterial Therapy in Complicated Acute Appendicitis: A Pilot Noninferiority Randomized Trial. *Annals of Surgery*, *279*(2), 191–195. https://doi.org/10.1097/SLA.0000000000006103

Lo, A. X., Heinemann, A. W., Gray, E., Lindquist, L. A., Kocherginsky, M., Post, L. A., & Dresden, S. M. (2021). Inter-rater Reliability of Clinical Frailty Scores for Older Patients in the Emergency Department. *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine*, *28*(1), 110–113. https://doi.org/10.1111/acem.13953

Lorenzon, L., Costa, G., Massa, G., Frezza, B., Stella, F., & Balducci, G. (2017). The impact of frailty syndrome and risk scores on emergency cholecystectomy patients. *Surgery Today*, *47*(1), 74–83. https://doi.org/10.1007/s00595-016-1361-1

Manfredi, G., Midão, L., Paúl, C., Cena, C., Duarte, M., & Costa, E. (2019). Prevalence of frailty status among the European elderly population: Findings from the Survey of Health, Aging and Retirement in Europe. *Geriatrics & Gerontology International*, *19*(8), 723–729. https://doi.org/10.1111/ggi.13689

Martínez-Velilla, N., Casas-Herrero, A., Zambom-Ferraresi, F., Sáez de Asteasu, M. L., Lucia, A., Galbete, A., García-Baztán, A., Alonso-Renedo, J., González-Glaría, B., Gonzalo-Lázaro, M., Apezteguía Iráizoz, I., Gutiérrez-Valencia, M., Rodríguez-

Mañas, L., & Izquierdo, M. (2019). Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. *JAMA Internal Medicine*, *179*(1), 28–36. https://doi.org/10.1001/jamainternmed.2018.4869

Martínez-Velilla, N., Valenzuela, P. L., Zambom-Ferraresi, F., Asteasu, M. L. S. de, Ramírez-Vélez, R., García-Hermoso, A., Lucia, A., & Izquierdo, M. (2020). Tailored exercise is safe and beneficial for acutely hospitalised older adults with COPD. *European Respiratory Journal*, *56*(6). https://doi.org/10.1183/13993003.01048-2020

McIsaac, D. I., MacDonald, D. B., & Aucoin, S. D. (2020). Frailty for Perioperative Clinicians: A Narrative Review. *Anesthesia and Analgesia*, *130*(6), 1450–1460. https://doi.org/10.1213/ANE.0000000000004602

Mitnitski, A. B., Song, X., & Rockwood, K. (2004). The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*(6), M627–632. https://doi.org/10.1093/gerona/59.6.m627

Moloney, E., O'Donovan, M. R., Sezgin, D., Flanagan, E., McGrath, K., Timmons, S., & O'Caoimh, R. (2023). Diagnostic Accuracy of Frailty Screening Instruments Validated for Use among Older Adults Attending Emergency Departments: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, *20*(13), 6280. https://doi.org/10.3390/ijerph20136280

Morley, J. E., Vellas, B., van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., Cesari, M., Chumlea, W. C., Doehner, W., Evans, J., Fried, L. P., Guralnik, J. M., Katz, P. R., Malmstrom, T. K., McCarter, R. J., Gutierrez Robledo, L. M., Rockwood, K., von Haehling, S., Vandewoude, M. F., & Walston, J. (2013). Frailty Consensus: A Call to Action. *Journal of the American Medical Directors Association*, *14*(6), 392–397. https://doi.org/10.1016/j.jamda.2013.03.022

Nally, D. M., Sorensen, J., & Kavanagh, D. O. (2020). Emergency laparotomy research methodology: A systematic review. *The Surgeon*, *18*(2), 80–90. https://doi.org/10.1016/j.surge.2019.06.003

Negm, A. M., Kennedy, C. C., Thabane, L., Veroniki, A.-A., Adachi, J. D., Richardson, J., Cameron, I. D., Giangregorio, A., Petropoulou, M., Alsaad, S. M., Alzahrani, J., Maaz, M., Ahmed, M. M., Kim, E., Tehfe, H., Dima, R., Sabanayagam, K., Hewston, P., Abu Alrob, H., & Papaioannou, A. (2019). Management of Frailty: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. *Journal of the American Medical Directors Association*, *20*(10), 1190–1198. https://doi.org/10.1016/j.jamda.2019.08.009

NELA project team. (2015). *First patient report of the National Emergency Laparotomy Audit*.

NELA project team. (2018). *Fourth patient report of the National Emergency Laparotomy Audit*.

NELA Project Team. (2024). *Ninth Patient Report of the National Emergency Laparotomy Audit*.

Ng, Z. Q., & Weber, D. (2022). One-Year Outcomes Following Emergency Laparotomy: A Systematic Review. *World Journal of Surgery*, *46*(3), 512–523. https://doi.org/10.1007/s00268-021-06385-w

O'Caoimh, R., Sezgin, D., O'Donovan, M. R., Molloy, D. W., Clegg, A., Rockwood, K., & Liew, A. (2021). Prevalence of frailty in 62 countries across the world: A systematic review and meta-analysis of population-level studies. *Age and Ageing*, *50*(1), 96–104. https://doi.org/10.1093/ageing/afaa219

Oliver, C. M., Walker, E., Giannaris, S., Grocott, M. P. W., & Moonesinghe, S. R. (2015). Risk assessment tools validated for patients undergoing emergency laparotomy: A systematic review. *British Journal of Anaesthesia*, *115*(6), 849–860. https://doi.org/10.1093/bja/aev350

Orouji Jokar, T., Ibraheem, K., Rhee, P., Kulavatunyou, N., Haider, A., Phelan, H. A., Fain, M., Mohler, M. J., & Joseph, B. (2016). Emergency general surgery specific frailty index: A validation study. *The Journal of Trauma and Acute Care Surgery*, *81*(2), 254–260. https://doi.org/10.1097/TA.0000000000001120

Palaniappan, S., Soiza, R. L., Duffy, S., Moug, S. J., Myint, P. K., & Older People's Surgical Outcomes Collaborative (OPSOC), The Emergency Laparoscopic, Laparotomy Scottish Audit (ELLSA). (2022). Comparison of the clinical frailty score (CFS) to the National Emergency Laparotomy Audit (NELA) risk calculator in all patients undergoing emergency laparotomy. *Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland*, *24*(6), 782–789. https://doi.org/10.1111/codi.16089

Park, B., Alani, Z., Sulistio, E., Barazanchi, A. W. H., Koea, J., Vandal, A., Hill, A. G., & MacCormick, A. D. (2024). Frailty using the Clinical Frailty Scale to predict short- and long-term adverse outcomes following emergency laparotomy: Meta-analysis. *BJS Open*, *8*(4), zrae078. https://doi.org/10.1093/bjsopen/zrae078

Park, B., Vandal, A., Sulistio, E., Bhat, S., Welsh, F., Eglinton, T., Koea, J., Taneja, A., Hill, A. G., Barazanchi, A. W. H., & MacCormick, A. D. (2024). Association between frailty, long-term mortality and functional outcomes for older adults undergoing emergency laparotomy. *World Journal of Surgery*, *48*(5), 1111–1122. https://doi.org/10.1002/wjs.12141

Parkin, C. J., Moritz, P., Kirkland, O., & Glover, A. (2021). What is the Accuracy of the ACS-NSQIP Surgical Risk Calculator in Emergency Abdominal Surgery? A Meta-Analysis. *The Journal of Surgical Research*, *268*, 300–307. https://doi.org/10.1016/j.jss.2021.07.009

Parmar, K. L., Law, J., Carter, B., Hewitt, J., Boyle, J. M., Casey, P., Maitra, I., Farrell, I. S., Pearce, L., Moug, S. J., & ELF Study Group. (2021). Frailty in Older Patients Undergoing Emergency Laparotomy: Results From the UK Observational Emergency Laparotomy and Frailty (ELF) Study. *Annals of Surgery*, *273*(4), 709–718. https://doi.org/10.1097/SLA.0000000000003402

Partridge, J. S. L., Ryan, J., Dhesi, J. K., & The CPOC-BGS perioperative frailty guideline group. (2022). New guidelines for the perioperative care of people living with frailty undergoing elective and emergency surgery – A commentary. *Age and Ageing*, *51*(11), afac237. https://doi.org/10.1093/ageing/afac237

Party, T. A.-Q. W., James Aitken, R., Griffiths, B., Van Acker, J., O'Loughlin, E., Fletcher, D., Treacy, J. P., Watters, D., & Babidge, W. J. (2021). Two-year outcomes from the Australian and New Zealand Emergency Laparotomy Audit-Quality Improvement pilot study. *ANZ Journal of Surgery*, *91*(12), 2575–2582. https://doi.org/10.1111/ans.17037

Pérez-Zepeda, M. U., Godin, J., Armstrong, J. J., Andrew, M. K., Mitnitski, A., Kirkland, S., Rockwood, K., & Theou, O. (2021). Frailty among middle-aged and older Canadians: Population norms for the frailty index using the Canadian Longitudinal Study on Aging. *Age and Ageing*, *50*(2), 447–456. https://doi.org/10.1093/ageing/afaa144

Pérez-Zepeda, M. U., Martínez-Velilla, N., Kehler, D. S., Izquierdo, M., Rockwood, K., & Theou, O. (2022). The impact of an exercise intervention on frailty levels in

hospitalised older adults: Secondary analysis of a randomised controlled trial. *Age and Ageing*, *51*(2), afac028. https://doi.org/10.1093/ageing/afac028

Pfannenstiel, H. J. (1900). Ueber die Vortheile des suprasymphysären Fascienquerschnitts für die gynäkologischen Koeliotomien. *Sammlung Klinischer Vorträge, Gynaekologie*.

Pitter, J. G., Zemplényi, A., Babarczy, B., Németh, B., Kaló, Z., & Vokó, Z. (2024). Frailty prevalence in 42 European countries by age and gender: Development of the SHARE Frailty Atlas for Europe. *GeroScience*, *46*(2), 1807–1824. https://doi.org/10.1007/s11357-023-00975-3

Prytherch, D. R., Whiteley, M. S., Higgins, B., Weaver, P. C., Prout, W. G., & Powell, S. J. (1998). POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. *The British Journal of Surgery*, *85*(9), 1217–1220. https://doi.org/10.1046/j.1365-2168.1998.00840.x

Rajaretnam, N., Okoye, E., & Burns, B. (2025). Laparotomy. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK525961/

Ramsay, G., Wohlgemut, J. M., & Jansen, J. O. (2018). Emergency general surgery in the United Kingdom: A lot of general, not many emergencies, and not much surgery. *The Journal of Trauma and Acute Care Surgery*, *85*(3), 500–506. https://doi.org/10.1097/TA.0000000000002010

Ringer, T., Thompson, C., McLeod, S., & Melady, D. (2020). Inter-rater Agreement Between Self-rated and Staff-rated Clinical Frailty Scale Scores in Older Emergency Department Patients: A Prospective Observational Study. *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine*, *27*(5), 419–422. https://doi.org/10.1111/acem.13907

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A Comparison of Two Approaches to Measuring Frailty in Elderly People. *The Journals of Gerontology: Series A*, *62*(7), 738–743. https://doi.org/10.1093/gerona/62.7.738

Rockwood, K., Mogilner, A., & Mitnitski, A. (2004). Changes with age in the distribution of a frailty index. *Mechanisms of Ageing and Development*, *125*(7), 517–519. https://doi.org/10.1016/j.mad.2004.05.003

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *CMAJ*, *173*(5), 489–495. https://doi.org/10.1503/cmaj.050051

Rockwood, K., & Theou, O. (2020). Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. *Canadian Geriatrics Journal: CGJ*, *23*(3), 210–215. https://doi.org/10.5770/cgj.23.463

Rodríguez-Mañas, L., Féart, C., Mann, G., Viña, J., Chatterji, S., Chodzko-Zajko, W., Gonzalez-Colaço Harmand, M., Bergman, H., Carcaillon, L., Nicholson, C., Scuteri, A., Sinclair, A., Pelaez, M., Van der Cammen, T., Beland, F., Bickenbach, J., Delamarche, P., Ferrucci, L., Fried, L. P., … Vega, E. (2013). Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *68*(1), 62–67. https://doi.org/10.1093/gerona/gls119

Roller-Wirnsberger, R., Lindner, S., Liew, A., O'Caoimh, R., Koula, M.-L., Moody, D., Espinosa, J. M., van Durme, T., Dimitrov, P., Benjak, T., Nicolaidou, E., Hammar, T., Vanhecke, E., Junius-Walker, U., Csizmadia, P., Galluzzo, L., Macijauskienė, J., Salem, M., Rietman, L., … Rodriguez-Mañas, L. (2020). European Collaborative and Interprofessional Capability Framework for Prevention and Management of Frailty –

A consensus process supported by the Joint Action for Frailty Prevention (ADVANTAGE) and the European Geriatric Medicine Society (EuGMS). *Aging Clinical and Experimental Research*, *32*(4), 561–570. https://doi.org/10.1007/s40520-019-01455-5

Romero-Ortuno, R., Fouweather, T., & Jagger, C. (2014). Cross-national disparities in sex differences in life expectancy with and without frailty. *Age and Ageing*, *43*(2), 222–228. https://doi.org/10.1093/ageing/aft115

Sáez de Asteasu, M. L., Martínez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, Á., Lucía, A., Galbete, A., & Izquierdo, M. (2019). Physical Exercise Improves Function in Acutely Hospitalized Older Patients: Secondary Analysis of a Randomized Clinical Trial. *Journal of the American Medical Directors Association*, *20*(7), 866–873. https://doi.org/10.1016/j.jamda.2019.04.001

Scott, J. W., Olufajo, O. A., Brat, G. A., Rose, J. A., Zogg, C. K., Haider, A. H., Salim, A., & Havens, J. M. (2016). Use of National Burden to Define Operative Emergency General Surgery. *JAMA Surgery*, *151*(6), e160480. https://doi.org/10.1001/jamasurg.2016.0480

Shafi, S., Aboutanos, M. B., Agarwal, S. J., Brown, C. V. R., Crandall, M., Feliciano, D. V., Guillamondegui, O., Haider, A., Inaba, K., Osler, T. M., Ross, S., Rozycki, G. S., & Tominaga, G. T. (2013). Emergency general surgery: Definition and estimated burden of disease. *Journal of Trauma and Acute Care Surgery*, *74*(4), 1092. https://doi.org/10.1097/TA.0b013e31827e1bc7

Sharp, T., Moran, E., Kuhn, I., & Barclay, S. (2013). Do the elderly have a voice? Advance care planning discussions with frail and older individuals: a systematic literature review and narrative synthesis. *The British Journal of General Practice*, *63*(615), e657–e668. https://doi.org/10.3399/bjgp13X673667

Sharrock, A. E., McLachlan, J., Chambers, R., Bailey, I. S., & Kirkby-Bott, J. (2017). Emergency Abdominal Surgery in the Elderly: Can We Predict Mortality? *World Journal of Surgery*, *41*(2), 402–409. https://doi.org/10.1007/s00268-016-3751-3

Shears, M., Takaoka, A., Rochwerg, B., Bagshaw, S. M., Johnstone, J., Holding, A., Tharmalingam, S., Millen, T., Clarke, F., Rockwood, K., Li, G., Thabane, L., Muscedere, J., Stelfox, H. T., Cook, D. J., & Canadian Critical Care Trials Group. (2018). Assessing frailty in the intensive care unit: A reliability and validity study. *Journal of Critical Care*, *45*, 197–203. https://doi.org/10.1016/j.jcrc.2018.02.004

Shipway, L, K., N, W., M, F., P, Z., & K, M. (2018). Embedded geriatric surgical liaison is associated with reduced inpatient length of stay in older patients admitted for gastrointestinal surgery. *Future Healthcare Journal*, *5*(2). https://doi.org/10.7861/futurehosp.5-2-108

Simpson, G., Wilson, J., Vimalachandran, D., McNicol, F., & Magee, C. (2022). Sarcopenia estimation using psoas major enhances P-POSSUM mortality prediction in older patients undergoing emergency laparotomy: Cross-sectional study. *European Journal of Trauma and Emergency Surgery: Official Publication of the European Trauma Society*, *48*(3), 2003–2012. https://doi.org/10.1007/s00068-021-01669-1

Sobhani, A., Fadayevatan, R., Sharifi, F., Kamrani, A. A., Ejtahed, H.-S., Hosseini, R. S., Mohamadi, S., Fadayevatan, A., & Mortazavi, S. (2021). The conceptual and practical definitions of frailty in older adults: A systematic review. *Journal of Diabetes and Metabolic Disorders*, *20*(2), 1975–2013. https://doi.org/10.1007/s40200-021-00897-x

Stewart, B., Khanduri, P., McCord, C., Ohene-Yeboah, M., Uranues, S., Vega Rivera, F., & Mock, C. (2014). Global disease burden of conditions requiring emergency surgery. *British Journal of Surgery*, *101*(1), e9–e22. https://doi.org/10.1002/bjs.9329

Stiffler, K. A., Finley, A., Midha, S., & Wilber, S. T. (2013). Frailty Assessment in the Emergency Department. *The Journal of Emergency Medicine*, *45*(2), 291–298. https:// doi.org/10.1016/j.jemermed.2012.11.047

Stille, K., Temmel, N., Hepp, J., & Herget-Rosenthal, S. (2020). Validation of the Clinical Frailty Scale for retrospective use in acute care. *European Geriatric Medicine*, *11*(6), 1009–1015. https://doi.org/10.1007/s41999-020-00370-7

Stolz, E., Mayerl, H., & Hoogendijk, E. O. (2022). Frailty in the oldest old: Is the current level or the rate of change more predictive of mortality? *Age and Ageing*, *51*(2), afac020. https://doi.org/10.1093/ageing/afac020

Tan, H. L., Chia, S. T. X., Nadkarni, N. V., Ang, S. Y., Seow, D. C. C., & Wong, T. H. (2019). Frailty and functional decline after emergency abdominal surgery in the elderly: A prospective cohort study. *World Journal of Emergency Surgery*, *14*(1), 62. https://doi.org/10.1186/s13017-019-0280-z

Thahir, A., Pinto-Lopes, R., Madenlidou, S., Daby, L., & Halahakoon, C. (2021). Mortality risk scoring in emergency general surgery: Are we using the best tool? *Journal of Perioperative Practice*, *31*(4), 153–158. https://doi.org/10.1177/1750458920920133

Theou, O., Pérez-Zepeda, M. U., van der Valk, A. M., Searle, S. D., Howlett, S. E., & Rockwood, K. (2021). A classification tree to assist with routine scoring of the Clinical Frailty Scale. *Age and Ageing*, *50*(4), 1406–1411. https://doi.org/10.1093/ageing/afab006

Thillainadesan, J., Hilmer, S., Close, J., Kearney, L., & Naganathan, V. (2019). Geriatric medicine services for older surgical patients in acute hospitals: Results from a binational survey. *Australasian Journal on Ageing*, *38*(4), 278–283. https://doi.org/10.1111/ajag.12675

Tian, B. W. C. A., Stahel, P. F., Picetti, E., Campanelli, G., Di Saverio, S., Moore, E., Bensard, D., Sakakushev, B., Galante, J., Fraga, G. P., Koike, K., Di Carlo, I., Tebala, G. D., Leppaniemi, A., Tan, E., Damaskos, D., De'Angelis, N., Hecker, A., Pisano, M., … Catena, F. (2023). Assessing and managing frailty in emergency laparotomy: A WSES position paper. *World Journal of Emergency Surgery*, *18*(1), 38. https://doi.org/10.1186/s13017-023-00506-7

Veronese, N., Custodero, C., Cella, A., Demurtas, J., Zora, S., Maggi, S., Barbagallo, M., Sabbà, C., Ferrucci, L., & Pilotto, A. (2021). Prevalence of multidimensional frailty and pre-frailty in older people in different settings: A systematic review and meta-analysis. *Ageing Research Reviews*, *72*, 101498. https://doi.org/10.1016/j.arr.2021.101498

Vilches-Moraga, A., Rowley, M., Fox, J., Khan, H., Paracha, A., Price, A., & Pearce, L. (2020). Emergency laparotomy in the older patient: Factors predictive of 12-month mortality – Salford-POPS-GS. An observational study. *Aging Clinical and Experimental Research*, *32*(11), 2367–2373. https://doi.org/10.1007/s40520-020-01578-0

Walree, I. C. van, Scheepers, E. R. M., Bos, F. van den, Huis-Tanja, L. H. van, Emmelot-Vonk, M. H., & Hamaker, M. E. (2020). Clinical judgment versus geriatric assessment for frailty in older patients with cancer. *Journal of Geriatric Oncology*, *11*(7), 1138–1144. https://doi.org/10.1016/j.jgo.2020.05.011

Ward, Alenazi, A., Delisle, M., & Logsetty, S. (2019). The impact of frailty on acute care general surgery patients: A systematic review. *Journal of Trauma and Acute Care Surgery*, *86*(1), 148. https://doi.org/10.1097/TA.0000000000002084

Ward, R. E., Orkaby, A. R., Dumontier, C., Charest, B., Hawley, C. E., Yaksic, E., Quach, L., Kim, D. H., Gagnon, D. R., Gaziano, J. M., Cho, K., Djousse, L., & Driver, J. A. (2021). Trajectories of Frailty in the 5 Years Prior to Death Among U.S. Veterans

Born 1927–1934. *The Journals of Gerontology: Series A*, *76*(11), e347–e353. https://doi.org/10.1093/gerona/glab196

Wohlgemut, J. M., Ramsay, G., & Jansen, J. O. (2020). The Changing Face of Emergency General Surgery: A 20-year Analysis of Secular Trends in Demographics, Diagnoses, Operations, and Outcomes. *Annals of Surgery*, *271*(3), 581. https://doi.org/10.1097/SLA.0000000000003066

Young, R. L., & Smithard, D. G. (2020). The Clinical Frailty Scale: Do Staff Agree? *Geriatrics*, *5*(2), 40. https://doi.org/10.3390/geriatrics5020040

Zatonski, W. (2007). The East-West Health Gap in Europe – What are the causes? *European Journal of Public Health*, *17*(2), 121. https://doi.org/10.1093/eurpub/ckm006

Zattoni, D., Montroni, I., Saur, N. M., Garutti, A., Bacchi Reggiani, M. L., Ghignone, F., Taffurelli, G., & Ugolini, G. (2021). Prediction of functional loss in emergency surgery is possible with a simple frailty screening tool. *World Journal of Emergency Surgery: WJES*, *16*, 12. https://doi.org/10.1186/s13017-021-00356-1

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Isand KG, Hussain S, Sadiqi M, Kirsimägi Ü, Bond-Smith G, Kolk H, Saar S, Lepner U, Talving P. Impact of frailty on outcomes following emergency laparotomy: a retrospective analysis across diverse clinical conditions. European Journal of Trauma Emergency Surgery 2024;50(6):3299–3309. doi:10.1007/s00068-024-02632-6

Isand KG, Hussain S, Sadiqi M, Kirsimägi Ü, Bond-Smith G, Kolk H, Saar S, Lepner U, Talving P. Frailty Assessment Can Enhance Current Risk Predic-

tion Tools in Emergency Laparotomy: A Retrospective Cohort Study. World Journal of Surgery 2023;47(11):2688–2697. doi:10.1007/s00268-023-07140-z

PANC Study Collaborative (2023). PANC Study (Pancreatitis: A National Cohort Study): national cohort study examining the first 30 days from presentation of acute pancreatitis in the UK. BJS open, 7(3), zrad008. https://doi.org/10.1093/bjsopen/zrad008

Saar S, Mihnovitš V, Lustenberger T, Rauk ML, Noor EH, Lipping E, **Isand KG**, Lepp J, Lomp A, Lepner U, Talving P. Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis: A randomized controlled trial. Journal of Trauma and Acute Care Surgery 2019; 86(1):36–42. doi:10.1097/TA.0000000000002086

Mohseni S, Ivarsson J, Ahl R, Dogan S, Saar S, Reinsoo A, Sepp T, **Isand KG**, Garder E, Kaur I, Ruus H, Talving P. Simultaneous common bile duct clearance and laparoscopic cholecystectomy: experience of a one-stage approach. European Journal of Trauma Emergency Surgery 2019;45(2):337–342. doi:10.1007/s00068-018-0921-z

Talving P, Rauk ML, Vipp L, **Isand KG**, Šamarin A, Põder K, Rätsep I, Saar S, Necrosis of the tail of pancreas following proximal splenic artery embolization. Journal of surgical case reports 2016;2016(5):rjw087. Published 2016 May 13. doi:10.1093/jscr/rjw087

Talving P, Ilmoja ML, Taal G, **Isand KG**, Teppo S, Noor EH, Kruusat R, Remmelgas A, Saar S, Blunt Cardiac Rupture in a Toddler. Journal of Pediatric Surgery Case Reports. 2016;11:1–3. doi:10.1016/j.epsc.2016.05.001

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Isand KG, Aim A, Bahhir A, Uuetoa M, Kolk H, Saar S, Lepner U, Talving P. Impact of preoperative frailty on outcomes in patients subjected to emergency laparotomy: a prospective study. European Journal of Trauma Emergency Surgery 2025;51(1):34. doi:10.1007/s00068-024-02752-z

Isand KG, Hussain S, Sadiqi M, Kirsimägi Ü, Bond-Smith G, Kolk H, Saar S, Lepner U, Talving P. Impact of frailty on outcomes following emergency laparotomy: a retrospective analysis across diverse clinical conditions. European Journal of Trauma Emergency Surgery 2024;50(6):3299–3309. doi:10.1007/s00068-024-02632-6

Isand KG, Hussain S, Sadiqi M, Kirsimägi Ü, Bond-Smith G, Kolk H, Saar S, Lepner U, Talving P. Frailty Assessment Can Enhance Current Risk Prediction Tools in Emergency Laparotomy: A Retrospective Cohort Study. World

Journal of Surgery 2023;47(11):2688–2697. doi:10.1007/s00268-023-07140-z

PANC Study Collaborative (2023). PANC Study (Pancreatitis: A National Cohort Study): national cohort study examining the first 30 days from presentation of acute pancreatitis in the UK. BJS open, 7(3), zrad008. https://doi.org/10.1093/bjsopen/zrad008

Saar S, Mihnovitš V, Lustenberger T, Rauk ML, Noor EH, Lipping E, **Isand KG**, Lepp J, Lomp A, Lepner U, Talving P. Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis: A randomized controlled trial. Journal of Trauma and Acute Care Surgery 2019; 86(1):36–42. doi:10.1097/TA.0000000000002086

Mohseni S, Ivarsson J, Ahl R, Dogan S, Saar S, Reinsoo A, Sepp T, **Isand KG**, Garder E, Kaur I, Ruus H, Talving P. Simultaneous common bile duct clearance and laparoscopic cholecystectomy: experience of a one-stage approach. European Journal of Trauma Emergency Surgery 2019;45(2):337–342. doi:10.1007/s00068-018-0921-z

Talving P, Rauk ML, Vipp L, **Isand KG**, Šamarin A, Põder K, Rätsep I, Saar S, Necrosis of the tail of pancreas following proximal splenic artery embolization. Journal of surgical case reports 2016;2016(5):rjw087. Published 2016 May 13. doi:10.1093/jscr/rjw087

Talving P, Ilmoja ML, Taal G, **Isand KG**, Teppo S, Noor EH, Kruusat R, Remmelgas A, Saar S, Blunt Cardiac Rupture in a Toddler. Journal of Pediatric Surgery Case Reports. 2016;11:1–3. doi:10.1016/j.epsc.2016.05.001

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