



Frailty and emergency surgery in the elderly: protocol of a prospective, multicenter study in Italy for evaluating perioperative outcome (The FRAILESEL Study)

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Abstract

Improvements in living conditions and progress in medical management have resulted in better quality of life and longer life expectancy. Therefore, the number of older people undergoing surgery is increasing. Frailty is often described as a syndrome in aged patients where there is augmented vulnerability due to progressive loss of functional reserves. Studies suggest that frailty predisposes elderly to worsening outcome after surgery. Since emergency surgery is associated with higher mortality rates, it is paramount to have an accurate stratification of surgical risk in such patients. The aim of our study is to characterize the clinicopathological findings, management, and short-term outcome of elderly patients undergoing emergency surgery. The secondary objectives are to evaluate the presence and influence of frailty and analyze the prognostic role of existing risk-scores. The final FRAILESEL protocol was approved by the Ethical Committee of “Sapienza” University of Rome, Italy. The FRAILESEL study is a nationwide, Italian, multicenter, observational study conducted through a resident-led model. Patients over 65 years of age who require emergency surgical procedures will be included in this study. The primary outcome measures are 30-day postoperative mortality and morbidity rates. The Clavien-Dindo classification system is used to categorize complications. The secondary outcome measures include length of hospital stay, length of stay in intensive care unit, and predictive value for morbidity and mortality of several frailty and surgical risk-scores. The results of the FRAILESEL study will be disseminated through national and international conference presentations and peer-reviewed journals. The study is also registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02825082).

Keywords Emergency surgery · Frailty · Elderly patient · Geriatric · Scores · Risk assessment

Abbreviations

FRAILESEL	Frailty and Emergency Surgery in the Elderly	SICG	Società Italiana di Chirurgia Geriatrica SICE Società Italiana Chirurgia Endoscopica
ERASO	Elderly Risk Assessment and Surgical Outcome	WSES	World Society of Emergency Surgery
SICUT	Società Italiana di Chirurgia d’Urgenza e del Trauma	DCC	Data Coordination Center
ACOI	Associazione dei Chirurghi Ospedalieri Italiani	PI	Principal Investigator
		ICD-9-CM	Ninth revision of international classification of disease clinical modification
		P-POSSUM	Portsmouth-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
		CR-POSSUM	ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity
		SAPS II	Simplified Acute Physiology Score II
		mFI	Modified Frailty Index
		CACI	Charlson Age-Comorbidity Index

Members of ERASO (Elderly Risk Assessment for Surgical Outcome) Collaborative Study Group are listed in the Appendix list.

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Introduction

Improvements in living conditions and progress in medical and surgical management have resulted in an increase in life-expectancy. According to the United Nations (2015), there has been a substantial increase in the number of people over 60 years of age, and this growth is projected to accelerate in the coming decades. Between 2015 and 2030, the number of elderly people in the world will grow by 56%, from 900 million to 1.4 billion [1]. In Italy, the same rate of growth is expected. According to the Italian National Institute for Statistics (Istituto Nazionale di Statistica, ISTAT), there were about 13.5 million people aged 65 and older in Italy in 2016, representing 22.3% of the inhabitants [2].

With this aging population, the number of elderly patients requiring emergency surgical intervention has risen dramatically [3–8]. Moreover, there is usually less time to make decisions during emergency interventions, and less information about the patient's condition is available. Hence, the outcome is usually worse than after elective surgery [6]. The surgeons must combine medical expertise with surgical skill and delays in management must be minimized.

Elderly patients also have a higher risk of developing postoperative complications, with an increased risk of mortality due to their poor physical and neurological condition [9–14]. Ideally, surgical risk should be estimated before surgery, and for this purpose many scoring systems have been developed [15–25]. However, not all elderly patients should automatically be considered at risk of complications and higher mortality due to their age.

Protocol

Objectives

The main objective of this Italian nationwide study is to characterize the clinicopathological findings, management strategies and short-term outcome of elderly patients undergoing emergency surgery. The secondary objectives are to evaluate the presence and influence of frailty, and to analyze the prognostic role of existing risk-scores to define the most suitable scoring system to classify the elderly. We will conduct an epidemiological investigation to gather information about the number of elderly patients operated on yearly, and the prevalence of various pathological conditions leading elderly patients to need emergency surgery. Furthermore, we aim to develop and validate a new simplified modified Frailty Index suitable for emergency surgery. The study was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02825082).

Study design and participating sites

The ERASO (Elderly Risk Assessment And Surgical Outcome) Collaborative Study Group, on behalf of the Italian surgical societies 'Italian Society for Emergency and Trauma Surgery' (Società Italiana di Chirurgia d'Urgenza e del Trauma, SICUT), 'Italian Hospital Surgeons Association' (Associazione dei Chirurghi Ospedalieri Italiani, ACOI), 'Italian Society for Geriatric Surgery' (Società Italiana di Chirurgia Geriatrica, SICG), 'Italian Society for Endoscopic Surgery' (Società Italiana di Chirurgia Endoscopica) and the Italian Chapter of the 'World Society of Emergency Surgery' (WSES), designed the FRAILESEL study. The prospective, observational study will be conducted following a resident-led model, similar to what has been described by Banghu et al. [26] and van Rossem et al. [27]. Briefly, teams of medical students and surgical residents with senior staff surgeon oversight collect data on patients across Italy for 18 months. The Data Coordination Center (DCC) is the Emergency Surgery Unit of Sant'Andrea Hospital, one of the teaching hospitals of "Sapienza" University of Rome, and the Study Director is responsible for the selection of the study sites. Any center performing emergency surgery can participate in this trial. Twenty-eight centers initially participate in the study and have started enrolment. The centers include academic medical centers, teaching hospitals, tertiary referral centers and community hospitals. Investigators involved in the study were trained in clinical score calculation prior to initiation of the study. Furthermore, all centers and participants have been specifically instructed in searching for frailty criteria and in data collection methodologies. Frailty is assessed by considering the frailty phenotypes as described by Fried et al [28]. To ensure that there is a uniform protocol of data acquisition in place for the main study, a 3-month pilot study was performed, that collected data retrospectively. Such data are not yet published, and are stored separately for further analyses. No modifications to the study protocol or database were necessary after the pilot phase. All patients are treated according to the local hospital protocol, and receive routine care as standard therapy. The duration of the recruitment phase of patients is expected to be 18 months. The main strength of this project is the multicenter, prospective, contemporary methodology, with independent validation of data. This will produce high quality data on the emergency procedures carried out in the elderly, and on outcomes throughout Italy from a wide range of hospital types. Limitations include the inability to assess the postoperative visits to the general practitioner. Moreover, a minority of patients may present to other hospitals with complications following surgery, or because they need medical assessment. Despite this, teams will try to document the number of patients that were readmitted to other facilities.

Our study uses the standard 30 day follow-up period, as this is the international standard and allows comparison to other studies. However, complications which may occur after 30 days will be reported.

Trial population recruitment and eligibility criteria

Inclusion criteria

All patients at the age of 65 years or over who are undergoing emergency surgery can be entered into this study. Emergency procedures are defined as unforeseen, non-elective operations according to the NCEPOD Classification of Interventions [29]. The type of surgical approach takes into account open abdominal or laparoscopic procedures, including laparoscopic procedures that are converted to open abdominal procedures. Surgical procedures will be sorted on the basis of the 9th revision of International Classification of Disease Clinical Modification (ICD-9-CM). All abdominal procedures with ICD-9-CM code numbers ranging from 42.0 to 54.99 are considered eligible. Thoracic procedures (ICD-9-CM code 32.0–34.99), vascular procedures (ICD-9-CM code 38.0–39.99), gynecological procedures (ICD-9-CM code 55.0–59.99), and urological procedures (ICD-9-CM code 60.0–64.99) are considered eligible for the study if performed by general or emergency surgeon in a general or trauma surgery setting.

Exclusion criteria

Exclusion criteria include patients aged under 65 at the day of surgery; lack of informed consent; patients already hospitalized and scheduled for the same procedure; participation in another trial.

Outcome measures

The primary outcomes are 30-day overall postoperative morbidity and mortality rates. Secondary outcomes are 30-day postoperative morbidity and mortality rates, stratified for each procedure or cause of intervention, length of hospital stay, admission and length of stay in ICU, and place of discharge (home or rehabilitation or care facility). Other secondary outcomes include the number of elderly subjects undergoing yearly emergency surgery, reported as the elderly to non elderly patient ratio, emergency surgery in the elderly per 100,000 inhabitants, sensitivity, specificity, and the overall predictive value for morbidity and mortality of P-POSSUM, CR-POSSUM, SAPS II, mFI and CACI. The postoperative complications are reported and categorized according to the Clavien-Dindo classification system.

Data collection, validation, and management

In each participating hospital, one local investigator (usually a surgical resident) is responsible for data collection and for entering data into a password-protected electronic spreadsheet (Excel 2010; Microsoft, Redmond, Washington, USA) specifically constructed with predefined data fields. There are six categories, namely “patient demographics”, “comorbidities”, “clinicopathological data”, “surgical intervention”, “score”, and “follow-ups” (Table 1). Patient details will be recorded and anonymized using the code center, an ID number and a unique alphanumeric code for any further integration. The anonymization procedure is provided by the enrolling center. Patient data will be collected, if possible, on a daily basis; preoperative and intraoperative data will be processed after surgery, and the postoperative outcomes will be noted at the time of discharge and at the end of follow-ups. Data will be obtained from the electronic patient database, from admission charts, and operative reports, or directly from the surgeon who performed the operation when details were unclear or missing. Consent to participate in the study and to collect data for scientific purpose will be obtained from the patient at admission. The standardized data collection protocol has been approved by the Central Ethical Committee. There is no minimum number of patients per center. Following data collection, only datasets with > 95% data completeness will be accepted for pooled national analysis. The principal investigator (PI) at the selected site will identify an independent assessor to validate all data, with a target of > 98% accuracy. Overall, at least 5% of the datasets will be independently validated. Outcome data will not be analyzed specific to each individual center. Data will be submitted monthly via e-mail. Once in the Data Coordination Center (DCC) pooled warehouse, records are reviewed and edited and, whenever necessary, transformed to comply with the FRAILESEL data dictionary (see Table 1 for further information). The Study Director and the Study Coordinator will then identify unacceptable data entries using custom Excel queries to detect missing, impossible and improbable values and logical inconsistencies between data fields and across the forms. The DCC will then ask the sites to check for the incomplete data, and once the sites have resolved the data queries, the DCC will update the patient records. To identify complications during follow-ups, each center will check their database to monitor visits to the emergency department, postoperative imaging or intervention, outpatient visits or hospital readmissions. Additional checking of admission diagnosis and surgical procedures in the study months will identify any missing patients. The data will be collected from each individual center according to the current Italian Law regarding privacy policy (Legislative Decree no. 196/2003 “RIGHT TO PERSONAL DATA PROTECTION CODE”). It will be the responsibility of the local

Table 1 Data spreadsheet fields

Form	Field	Options (definitions)
Demographics	ID	Progressive number
	ID center	Number
	ID code	Alphanumeric (3 characters)
	Age	In years
	Gender	Male/Female
	BMI	BMI in kg/m ²
	Admission date	Day/month/year
	Operation date	Day/month/year
Clinicopathological data	Timing of surgery	Emergency/urgency
	Vital parameters	Systolic blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, urine output, mechanical ventilation or CPAP, FiO ₂ , GCS
	Laboratory analysis	Arterial blood gas analysis (PaO ₂ , PaCO ₂ bicarbonate, lactates), chemistry (sodium, potassium, bilirubin, glycemia, CRP), renal function (BUN, creatinine), hemoglobin, WBC, PLT, INR
Comorbidities	Tumor	Site, TNM classification, Dukes staging system, grading, radicality of surgery, vascular invasion
	Associated diseases	Cardiovascular disease (ECG-report, hypertension, MI < 6 months, heart failure < 30 days, chronic heart disease, Previous cardiac surgery or PCI, peripheral vasculopathy), cerebrovascular disease, respiratory disease (chronic lung diseases, respiratory failure), smoke, renal disease (acute/chronic), diabetes, liver disease (acute/chronic), solid tumor (localized/metastatic) leukemia, lymphoma, AIDS, drugs (oral anticoagulants, immunosuppressants or steroids, oral hypoglycemic agents or insulin), peptic ulcer
Surgical intervention	Performance status	Hemiplegia, dementia, weight loss, physical activity, walk time, grip strength, exhaustion
	Organ/body-district categories	Abdominal wall, appendicitis, biliary tract and pancreas, esophagus, large bowel, small bowel, solid organs, stomach and duodenum, thorax, Others
	Onset symptoms	Obstruction, acute abdomen (peritonitis—abscess and/or overt perforations), Vascular disorders, Trauma
	Primary operative indication	Benign/malignant/delayed elective
	Surgical approach	Open/Laparoscopic/Laparoscopic converted/Laparoscopic assisted
	Primary surgical procedure	ICD-9-CM code
	Associated procedures	Numbers
	List of associated procedures	ICD-9-CM code
	Intraoperative reliefs	Blood loss (ml), peritoneal contamination (yes/no)
	Operative time	Minutes
Follow-ups	ICU admission	Yes/no
	ICU length of stay	Days
	Date of discharge	Day/month/year
	Total length of stay	Days
	Type of discharge	Home, short-term rehabilitation facility, caregiver residential facility
	Complications 30-day postoperatively	Yes/no
	Complication type	Free text
Score	Complication grade (Clavien-Dindo classification)	None/I/II/III/IV/V
	30-day mortality	Yes/no
		ASA, P-POSSUM, CR-POSSUM, SAPS II, CACI, mFI

ASA American Society of Anaesthesiologists, BMI body mass index, BUN blood urea nitrogen, CPAP continuous positive airway pressure, CRP C-reactive protein, GCS Glasgow Coma Scale, ICD-9-CM 9th revision of International Classification of Disease Clinical Modification, ID identifier, INR International Normalized Ratio, MI myocardial infarction, mFI Modified Frailty Index, PCI Percutaneous Coronary Intervention, PLT platelet, WBC white blood cell, P-POSSUM Portsmouth-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, CR-POSSUM ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, SAPS II Simplified Acute Physiology Score II, CACI Charlson Age-Comorbidity Index

investigators to ensure that the local data will be protected and held according to such privacy policy and in line with what has been approved by the ethics board.

No patients are involved in setting the research question or the outcome measures; nor are they involved in the design and implementation of the study. There are no plans to involve patients in dissemination of results.

Study timeline

The following timeline has been outlined, to define specific stages of the study.

- 1 June 2016–30 September 2016: call for participants.
- 1 October 2016–31 December 2016: pilot study.
- 1 January 2017–30 December 2017: main study data collection.
- 1 January 2018–1 March 2018: end of data collection for the main study, interim analysis.
- 1 January 2018–30 June 2018: additional data collection on specific topics.
- 1 July 2018–30 September 2018: completion of missing data and end of additional data collection.
- 1 October 2018–31 December 2018: final analysis.

Statistical analysis

The report of this study will be prepared in accordance with guidelines set by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies [30]. Statistical analysis will be performed with SPSS software, version 21 (IBM Analytics Italy, Segrate, MI) for MacOSX and/or MedCalc version 14.10.2 (MedCalc Software, Ostend, Belgium) for Windows. Based on previous reports with a comparable case mix, the expected 30-day mortality rate of the population in this study was estimated to be 20%. First, data normality will be tested using the Shapiro–Wilk test or Kolmogorov–Smirnov test. Dichotomous data and counts will be presented in frequencies. Continuous data will be presented as mean values plus standard deviations, or as median values and interquartile ranges. The 95% confidence interval will always be reported where appropriate. Differences between means will be compared using the independent sample Student's *t* test, the pairwise comparison Student's *t* test, the Mann–Whitney *U* test, the Kruskal–Wallis test or other analysis of variance (ANOVA) tests. To compare differences in frequencies, Fisher's exact test or χ^2 test, with or without Yates correction will be performed. Receiver operating characteristic (ROC) curve analysis will be performed to estimate sensitivity and specificity of each score. Linear correlation will be assessed by Pearson's or Spearman's test,

if needed. Multivariate analyses will be performed using linear or logistic regression models that consider mortality and morbidity as dependent variables. A *P* value of < 0.05 will be considered statistically significant.

Dissemination policy

The results of the FRAILESEL study will be disseminated through national and international conference presentations and peer-reviewed journals. The results will also be available through the study record website at ClinicalTrials.gov. Furthermore, additional studies and publications could be performed that analyze specific aspects of the data that will be presented. We are committed to ensuring that appropriate recognition is given to everyone who works on the study.

Discussion

In the mid-to-late 1990s, Rockwood et al. reviewed the definition and concept of frailty and developed several systems to classify frailty [31, 32]. At the beginning of the 2000s, the concept of frailty was later extended by Fried et al., [28] who defined the so-called Frailty Phenotype using objective diagnostic criteria to separate the concept of fragility from those of disability and comorbidity. The criteria used to define frailty were unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. As a matter of fact, it is possible to identify different phenotypes: “frail” (three or more deficits), “pre-frail” (one or two deficits), or “robust” (none of the deficits present). These conditions are predictors of varying degrees of adverse health outcomes, as shown in the Cardiovascular Health Study (CHS) dataset, by Fried et al. [33].

Following the work of Rockwood and Fried, frailty has become the focus of considerable research interest, not only among geriatricians. Many surgeons and anesthesiologists have established a relationship between the presence of frailty and morbidity and mortality, as well as with ICU admissions and prolonged hospitalization [34–43].

For a variable to be considered as deficit it needs to be acquired, age-associated, and associated with an adverse outcome, it should also not saturate too early. This means that the proportion of people who have the deficit should not be close to 100% because the deficit would be uninformative at this point [44]. Many of these deficits have been incorporated into complex systems, such as the Canadian Study on Health and Aging Frailty Index, a tool that is not practical and rarely applicable in the emergency setting [45]. A large number of modified frailty indexes, including a number of clinical criteria, have then flourished in the literature [46–52].

When emergency surgery is deemed necessary, it is important to evaluate the patient's living conditions, autonomy, life-expectancy, and long-term prognosis. In elderly patients, even when there are no recognized relevant problems in the patient's medical history, frailty must be considered when planning surgery because this can be linked to one of three possible outcomes: death, dependency, and institutionalization. The use of a frailty index should be implemented into routine acute and emergency care procedures. In addition to the frailty index, a lot of scoring systems have been developed to estimate the risk of mortality in the elderly, especially in an emergency setting [53–56].

Conclusion

Presently in Italy, recommendations to guide evaluation and management of elderly patients requiring emergency surgery are lacking. In this article we present a protocol for a nationwide study designed to investigate the elderly population undergoing emergency surgery. To improve the level of care that should be reserved for these patients, we aim to create and validate a simplified frailty index suitable for emergency surgery. As a matter of fact, it could ameliorate outcomes and avoid futile treatments. These results may potentially influence the survival of many high-risk elderly surgical patients.

Appendix list List of ERASO Collaborative Study Group members on behalf of SICUT, ACOI, SICG, SICE, and the WSES Italian Chapter: Agresta F, Anania G, Ansaloni L, Antropoli M, Argenio G, Atzeni J, Avenia N, Azzinnaro A, Balani A, Baldazzi G, Balducci G, Barbera G, Bellanova G, Bergamini C, Bersigotti L, Bianchi PP, Bombardini C, Borzellino G, Bozzo S, Brachini G, Buccoliero F, Buonanno GM, Buonomato M, Campanile FC, Canini T, Cardella S, Carrara G, Cascini F, Cassini D, Castriconi M, Catalini G, Catena F, Ceccarelli G, Celi D, Ceresoli M, Chiarugi M, Cillara N, Cimino F, Cobuccio L, Coccolini F, Cocorullo G, Colangelo E, Costa G, Crafa F, Crucitti A, Dalla Caneva P, De Luca M, de Manzoni Garberini A, De Nisco C, De Sol A, Falcioni T, Falco N, Farina C, Filippone G, Finotti E, Fiume S, Fontana T, Francioni G, Fransvea P, Frezza B, Gemini S, Genna M, Giannessi S, Giofrè A, Giordano A, Gozzo D, Grimaldi S, Gulotta G, Iarussi T, Laterza E, Lepre L, Lorenzon L, Lotti R, Luridiana G, Marini P, Marzaioli R, Massa G, Mingoli A, Mulas S, Nagliati C, Nigri G, Niolu P, Noviello A, Occhionorelli S, Paderno N, Palini GM, Paradies D, Paroli M, Perrone F, Petruzzelli L, Pezzolla A, Piazza D, Piazza V, Piccoli M, Pisanu A, Podda M, Poillucci G, Porfidia R, Rossi G, Ruscelli P, Santella S, Sartelli M, Spagnoli A, Sulis R, Tarasconi A, Tranà C, Travaglino A, Valeri A, Vasquez G, Zago M, Zanoni E.

Compliance with ethical standards

Conflict of interest No competing interests were disclosed.

Research involving Human Participants and/or Animals The final FRAILESEL protocol was approved by the Ethics Committee of the "Sapienza" University of Rome, Italy on 12/12/2016 (allocated under approval number 4252_2016). Secondary approval has been obtained

from all Ethics Committees of the other participating centers. The DCC provided assistance to each participating center during their local IRB application.

Informed consent Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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