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ORIGINAL ARTICLE

Clinical-pathological features and treatment of acute appendicitis in the very elderly: an interim analysis of the FRAILESEL Italian multicentre prospective study

Pietro Fransvea[1] · Valeria Fico[1] · Valerio Cozza[1] · Gianluca Costa[2,4] · Luca Lepre[3] · Paolo Mercantini[4] · Antonio La Greca[1] · Gabriele Sganga[1] on behalf of the ERASO study group

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Abstract

Background Emergency abdominal surgery in the elderly represents a global issue. Diagnosis of AA in old patients is often more difficult. Appendectomy remains the gold standard of treatment and, even though it is performed almost exclusively with a minimally invasive technique, it can still represent a great risk for the elderly patient, especially above 80 years of age. A careful selection of elderly patients to be directed to surgery is, therefore, fundamental. The primary aim was to critically appraise and compare the clinical–pathological characteristics and the outcomes between oldest old (≥ 80 years) and elderly (65–79 years) patients with Acute Appendicitis (AA).

Methods The FRAILESEL is a large, nationwide, multicentre, prospective study investigating the perioperative outcomes of patients aged ≥ 65 years who underwent emergency abdominal surgery. Particular focus has been directed to the clinical and biochemical presentation as well as to the need for operative procedures, type of surgical approach, morbidity and mortality, and in-hospital length of stay. Two multivariate logistic regression analyses were performed to assess perioperative risk factors for morbidity and mortality.

Results 182 patients fulfilled the inclusion criteria. Mean age, ileocecal resection, OAD and ASA score ≥ 3 were related with both overall and major complication. The multivariate analysis showed that MPI and complicated appendicitis were independent factors associated with overall complications. OAD and ASA scores ≥ 3 were independent factors for both overall and major complications.

Conclusions Age ≥ 80 years is not an independent risk factor for morbidities. POCUS is safe and effective for the diagnosis; however, a CECT is often needed. Having the oldest old a smaller functional organ reserve, an earlier intervention should be considered especially because they often show a delay in presentation and frequently exhibit a complicated appendicitis.

Keywords Acute appendicitis · Elderly · Very elderly

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✉ Pietro Fransvea
pietro.fransvea@gmail.com

[1] Emergency Surgery and Trauma—Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Catholic University of Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy

[2] Surgery Center, Campus Bio-Medico University Hospital, University Campus Bio-Medico of Rome, Rome, Italy

[3] General Surgery Unit, Santo Spirito in Sassia Hospital, ASL Roma 1, Rome, Italy

[4] Surgical and Medical Department of Translational Medicine, Sant'Andrea Teaching Hospital, Sapienza University of Roma, Rome, Italy

Abbreviations

FRAILESEL	Frailty and Emergency Surgery in the Elderly
AA	Acute appendicitis
AIRS	Appendicitis Inflammatory Response
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
CRP	C-Reactive Protein
ASA	American Society of Anesthesiologists
MPI	Mannheim Peritonitis Index
CD	Clavien–Dindo
SIRS	Systemic Inflammatory Response Syndrome
q-Sofa	Quick- Sequential Organ Failure Assessment

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ICD-9™	International Classification of Diseases versions 9
LOS	Length of in-hospital Stay
CECT	Contrast Enhancement Computerized Tomography
POCUS	Point-of-Care-Ultrasound
IQR	Interquartile Range
OOG	Oldest Old Group
CEG	Control Elderly Group
OAD	Oral Anticoagulant Drugs
BMI	Body Mass Index
BT	Body Temperature
WBC	White Blood Cells Count

Introduction

As the world population is aging rapidly, emergency abdominal surgery for acute abdomen in the elderly represents a global issue, both in developed and developing countries [1–4]. More than 20% of the Italian population is over the age of 65 and, by the year 2050, this percentage is expected to grow to 34%. Over the last 20 years, country's life expectancy has increased from 78 to 80 years for men and from 84 to 85 years for women. It is estimated that 21% of the total population older than 60 years will require surgery, compared with only 12% of people in the 45–60 age group [5, 6]. Demographic changes in the population have also modified the profile of emergency abdominal surgery, where typical causes of acute abdomen in the elderly include acute cholecystitis, incarcerated hernia, bowel obstruction, acute diverticulitis and acute appendicitis (AA) [7, 8]. Although AA is the most common general surgical emergency procedure worldwide, its diagnosis remains challenging and when compared to the general population, the diagnosis of AA in the elderly is often more difficult [9–11]. Older patients generally present later in the course of the disease and may have nonspecific symptoms [12, 13]. To improve diagnosis of appendicitis, international guidelines recommend routine clinical risk scoring [14, 15]. Although the Appendicitis Inflammatory Response (AIRS) and Alvarado scores are recommended most frequently, no one of these score is widely used in clinical practice and none is specific for elderly patients [16–19]. In addition, their higher comorbidity rate and the less systemic reserve capacity may potentially lead to severe consequences in case of such an acute event. They often have other conditions such as diverticulitis or neoplasms that can mimic acute appendicitis [20]. Appendectomy remains the gold standard of treatment and, even though it is now performed almost exclusively with a minimally invasive technique, it can still represent a great risk for the elderly patient, especially above 80 years of age and in the event of multiple comorbidities [14, 21–23]. A careful selection of elderly patients to be directed to surgery versus those who can benefit only from antibiotic therapy is therefore fundamental, since if a negative appendectomy rate is acceptable in young people, especially in women, this cannot be reproduced in the elderly because they have not the same ability to tolerate the stress induced by the surgical procedure [1, 24]. In this study, we focus our attention on the subgroup over 80 years old compared to the subgroup of elderly patient between 65–79 years old. The primary aim was to analyze the differences between the two groups in the clinical–pathological data, management strategies, and in the short-term outcomes after emergency surgery for Acute Appendicitis.

Materials and methods

Study settings and protocol

This report originates from the FRAILESEL (Frailty and Emergency Surgery in the Elderly) study (ClinicalTrials.gov identifier: NCT02825082). The FRAILESEL is a large, nationwide, multicentre prospective study that investigated the perioperative outcomes of patients aged ≥ 65 years who underwent emergency abdominal surgery over a period of consecutive 18 months (January 2017 and June 2018) and the protocol has been already extensively described [8, 23, 24]. Briefly, data regarding elderly patients discharged from the participating centres were prospectively collected. Centres were included on a volunteer basis, and neither investigators nor participating hospitals were paid for their collaboration. Clinical decisions, including operative technique, were based on the criteria of individual centres and attending surgeons. The investigators were informed about the objectives of the study and asked for complete details about the surgical management of acute abdomen in the elderly following standard methods and collection protocols.

The final FRAILESEL Study protocol was approved by the Ethics Committee of Sapienza University and of all the centres and by the boards of the involved societies. The work has been reported in line with the Strengthening the reporting of cohort studies in surgery (STROCSS) criteria [25].

Exclusion criteria and collected data confirmation

Exclusion criteria were the following: patients younger than 65 years old at the day of surgery; diagnostic laparoscopy/laparotomy with no further surgical procedures performed with the exception of intestinal ischemia; lack of informed consent for the study participation; endoscopic procedures and emergency reoperations after elective surgery; patients already hospitalized and scheduled for the same procedure; patients participating in another trial. Submissions

made by unconfirmed participants, duplicate submissions, record with more than 5% of missing data, and data submitted by residents from dual or more residency programs were excluded. Although demographic information was collected on the patients, all data were anonymized before analysis even for centre identification. The FRAILESEL study encompassed the final enrolment of 2635 patients but 2563 with confirmed data. For the purposes of the present study, two other centres were recruited which enrolled only patients with AA.

Patient characteristics, preoperative variables and objectives of this study

The FRAILESEL study investigates over 130 variables, exploring five domains such as patient demographic and clinical data, preoperative risk factors and operative variables, frailty condition, and postoperative outcomes and follow-up. Data collected included patient demographic characteristics (age, gender, weight, height), medical and surgical history (comorbidities), common preoperative biochemical blood examination at the admission to the Emergency Department (ED) (including White Blood Cell Count [WBC $\times 10^3$/ml], C-reactive protein [CRP as mg/dl], and arterial blood gas analysis), pathological features, and operative details. The onset of symptoms was categorized with 12-h steps. Preoperative risk was assessed with anesthesiologist-assigned American Society of Anesthesiologists (ASA) class. Comorbidity was recorded if the condition was being medically treated at the time of admission, or if previous treatment for the condition was described in the admission report and it was categorized according to the age-adjusted Charlson Comorbidity Index (Age-CACI) [26]). Frailty profile as operative risk has been investigated also by the following indexes: 5-modified Frailty Index (5-mFI) [27], Emergency Surgery Frailty Index (EmSFI) [28], and Urgent Surgery Elderly Mortality (USEM) risk score [29]. The Mannheim Peritonitis Index (MPI) was calculated [30]. Systemic inflammatory response syndrome (SIRS) and quick-Sofa (q-Sofa) were also evaluated. Postoperative complications have been reported and categorized according to the Clavien–Dindo (C-D) classification system by the study leader in each of the participating centres [31]. Morbidity and mortality have been considered as the conventional 30-day outcome. With regard to the aims of the present paper, patients were selected from the dataset using the International Classification of Diseases versions 9 (ICD-9™) (codes 540.xx to 543.xx). After the final revision, appendicitis due to neoplastic lesion and incidental appendectomy were excluded. Primary aim was to critically appraise and compare the clinical-pathological characteristics and the outcomes between oldest old (≥ 80 years) and elderly (65–79 years) patients with a diagnosis of AA. Particular focus has been directed to the clinical and biochemical presentation as well as to the need for operative procedures, type of surgical approach, morbidity and mortality rate, and length of in-hospital stay (LOS). An open conversion was defined as when a procedure was attempted via the minimally invasive approach but required an open incision to be completed. The decision for preoperative work-up was made by the attending surgeon and/or the attending emergency physician. Computerized tomography scan was performed with intravenous contrast material (CECT). Results of CECT scans and point-of-care-ultrasound (POCUS) were interpreted by a staff radiologist. CECT and POCUS were considered positive in accordance with current literature guidelines while complicated appendicitis was defined according to AAST Emergency General Surgery Scoring System [32–34]. Secondary aim was to determine the frequencies of elderly with acute appendicitis and the elderly to oldest old patient ratio. For this purpose, we randomly selected 19 centres and asked the principal investigator in each centre to select the total number of patients with acute appendicitis submitted to surgery in the study period. Eleven centres were able to provide the requested data.

Statistical analysis

Statistical analysis and ROC curve was carried out and generated using the Jamovi Software (Version 1.2.22) integrated with the plug-in module for the R Statistical software. (The Jamovi project (2019) retrieved from https://www.jamovi.org and R Core Team (2018). *R: A Language and environment for statistical computing* retrieved from https://cran.r-project.org/). Dichotomous data and counts were presented in frequencies, whereas continuous data were presented as mean values ± standard deviations and/or median with 25–75 Interquartile Range (IQR) and minimum–maximum range. Differences between means were compared using the independent sample Student's *t* test or the Mann–Whitney *U* test when indicated. Fisher's exact test or χ^2 test, with or without Yates correction, were implemented to compare differences in frequencies. Receiver operating characteristic (ROC) curve analysis was performed to test the specificity and sensitivity of the Age-CACI and the frailty assessment tools in predicting short-term adverse post-operative outcomes. The c-statistic evaluates model discrimination and represents the area under the ROC curve (AUC). A value of 0.5 indicates that the model is equivalent to chance; a value of 1.0 indicates perfect discrimination. Two further logistic regression analyses were performed to assess perioperative risk factors for morbidity and mortality in the entire population. Continuous variables were analysed either as mean or if necessary in a dichotomous manner using the corresponding conventional literature cut-off. All variables with p value < 0.20 at univariate analysis were entered into

a multivariate model. A p value < 0.05 was considered statistically significant. G-Power for MacOSX version 3.1 was used to carry out a post hoc analysis for the $\chi 2$ test and t test to evaluate the power estimation aimed at assessing the adequacy of groups and subgroups sample sizes.

Results

During the study period, 182 patients underwent emergency surgery procedure for acute appendicitis, fulfilled the inclusion criteria for this study. Table 1 reports patients' characteristics in detail. The overall mean age was 74.5 ± 7.3 years and there was a male predominance (141 male patients, 77.5%). Of these, 41 (22.5%) were aged ≥ 80 years and constituted the oldest old Group (OOG); the remaining 141 (77.9%) patients had an age between 65 and 79 years and represented the Control Elderly Group (CEG). Table 1 shows also the comparison between the OOG and the CEG group. In the OOG, 75.6% were male, and we observed the same male/female ratio in CEG with 78.0% of male. The survey revealed that the overall mean rate of elderly patients with acute appendicitis was 10.7% (range 4.6–14.2%), while the mean rate of oldest old patients was 23.8% (range 19.4–26.3%). The OOG showed a higher rate of patients with the onset of symptoms between 24 and 36 h prior to admission. The difference was not statistically significant, but it was clinically relevant ($p = 0.371$ [effect size w 0.3291; power 0.9493]). Regarding pre-operative biochemical values, the OOG show higher creatinine levels (1.5 ± 1.2 vs 1.0 ± 0.5 mg/dl, $p < 0.05$) and higher lactate level (2.0 ± 3.9 vs 0.6 ± 0.8 mmol/L; $p < 0.05$) compared to the CEG. However, no differences were evidenced between the two groups in terms of SIRS (7 patients, 17.1% vs 34 patients, 24.1% in the OOG compared to CEG, respectively; $p = 0.46$). The mean q-SOFA was 0.29 ± 0.51 vs 0.10 ± 0.33, in the OOG compared to CEG, respectively; $p = 0.006$) while no difference was found when q-SOFA classes were analysed. According to the Mannheim Peritonitis Index, there was no statistically significant difference between the two groups (10.8 ± 5.9 vs 10.4 ± 4.8,

Table 1 Patients clinical features and laboratories values at admin to the Emergency Departmente (ED)

	Total	%	Oldest old > 80 Group	%	Control Elderly < 80 Group	%	*P* value
Number of Patients	182		41		141		
Age Mean (SD)	74.5 ± 7.3		85.5 ± 4.3		71.3 ± 4.0		**< 0.001**
Age Median (IQR)	74 (65–95)		84 (80–95)		71 (65–79)		**< 0.001**
Sex							
Female	41	22.5	10	24.4	31	22.0	0.91
Male	141	77.5	31	75.6	110	78.0	
BMI	26.13 ± 4.7		24.9 ± 4.2		26.5 ± 4.8		0.98
WBC ($\times 10^{3}$/ml)	13.2 ± 4.4		11.3 ± 3.2		13.7 ± 4.6		0.35
PCR (mg/l)	7.4 ± 8.2		8.6 ± 8.6		7.0 ± 8.0		0.50
Creatinine (mg/dl)	1.15 ± 0.8		1.5 ± 1.2				**< 0.05**
Lactate	0.9 ± 1.7	31.3	2.0 ± 3.9		0.6 ± 0.8		**< 0.05**
SIRS							
Yes	41	22.5	7	17.1	34	24.1	0.46
No	141	77.5	34	82.9	107	75.9	
Mannheim Peritonitis Index	10.5 ± 5.0		10.8 ± 5.9		10.4 ± 4.8		0.082
Comorbidity							
Yes	153	84.1	35	85.4	118	83.7	0.98
No	29	15.9	6	14.6	23	16.3	
ASA							
1	11	6.0	1	2.4	10	7.1	0.35
2	65	35.7	13	31.7	52	36.9	
3	99	54.4	24	58.5	75	53.2	
4	6	3.3	3	7.3	3	2.1	
5	1	0.5	0	0.0	1	0.7	

Bold values are statistically significant

in the OOG compared to CEG, respectively; $p = 0.893$). The overall mean American Society of Anaesthesiology (ASA) score was ASA 3 (99 patients, 54.4%) followed by ASA 2 (66 patients, 35.7%). The same distribution of patients according to the ASA score was observed in the two groups, with no statistically significant differences ($p = 0.35$). According to 5-mFI the overall severe frailty rate was 36.8%. Severe frailty was higher in the OOG being present in 48.8% and in 33.3% in the CEG. Although the difference was not statistically significant, it was clinically relevant ($p = 0.071$ [effect size w 0.3090; power 0.9169]). The results regarding the frailty tools evaluated are shown in Table 2. Under the clinical point of view, a POCUS was performed in 106 patients (58.2%) and a CECT of the abdomen was performed in 149 patients (81.9%). Regarding the difference between the two groups, CT scan was performed in 92% of patients in the OOG and in 78.7% in the CEG ($p < 0.05$). POCUS was positive in 66.0% of the cases with no difference between the two groups while CT scan was positive in 85.9% again with no difference between OOG and CEG. Table 3 summarized some pre-operative data and outcomes. All but seven patients underwent surgical procedure (175 patients, 96.7%) with just one negative exploration (0.5%). Of these seven patients, 6 (3.3%) underwent a pure non-operative management with only antibiotic therapy and one (0.5%) underwent percutaneous drainage associated with antibiotic therapy. However, even if it is not possible to make any statistical comparison, we want to underline how six out of the seven conservative treatments belonged to the OOG. Appendectomy was performed in 129 (91.5%) of the CEG patients while it was performed in 75.6% of the OOG. The difference was statistically significant ($p < 0.05$). More specifically, a laparoscopic approach was most commonly adopted in the CEG group (100 patients—70.9%) as compared to the OOG (13 patients—31.7%) ($p < 0.001$). Furthermore, there was a clinical but no statistically significant difference regarding the conversion rate between the two groups (four patients, 30.8% vs 16 patients, 15.8. % in the OOG compared to CEG, respectively, $p = 0.189$; OR 2.33, 95% CI 0.64–8.51; effect size w 0.4028; power 0.9950]). Complicated appendicitis was found in the

Table 2 Frailty index tools analysis

	Total	%	Oldest old > 80 Group	%	Control Elderly < 80 Group	%	*P* value
Frailty							0.18
5-mFI 0/0.2 (not or moderate frailty)	115	63.2	21	51.2	94	66.7	
5-mFI ≥ 0.4 (severe frailty)	67	36.8	20	48.8	47	33.3	
USEM	1.0 ± 1.27		1.97 ± 2.0		0.72 ± 0.8		**< 0.001**
EmSFI	182		41		141		
EmSFI 1–3	130	71.4	17	41.5	113	80.1	**< 0.001**
EmSFI 4–7	50	27.5	23	56.1	27	19.1	
EmSFI 8–14	2	1.1	1	2.4	1	0.7	
Q-Sofa Score	0.148 ± 0.4		0.123 ± 0.5		0.106 ± 0.3		**0.006**
CLASS 0	157	86.3	30	73.2	127	90.1	**0.021**
CLASS 1	23	12.6	10	24.4	13	9.2	
CLASS 2	2	1.1	1	2.4	1	0.7	
Age-adjusted Charlson Comorbidities Index (age-CACI)							
CACI 2	35	19.2	0	0	35	24.8	**< 0.001**
CACI 3	50	27.5	0	0	50	35.5	
CACI 4	36	19.8	16	39.0	20	14.2	
CACI 5	31	17	9	22.0	22	15.6	
CACI 6	13	7.1	5	12.2	5	3.5	
CACI 7	10	5.5	5	12.2	5	3.5	
CACI 8	5	2.7	4	9.8	1	0.7	
CACI 9	2	1.1	2	4.9	0	0.0	
Age CACI cut-off 6							**< 0.001**
CACI < 6	152	83.5	25	61.0	127	90.1	
CACI > 6	30	16.5	16	39.0	14	9.9	

Bold values are statistically significant

Table 3 Perioperative variable and outcomes

	Total	%	Oldest old > 80 Group	%	Control Elderly < 80 Group	%	*P* value
Onset of Symptoms	182		41		142		
< 12 (h)	15	8.2	3	7.3	12	8.5	
12–24 (h)	115	63.2	22	53.7	93	66.0	
24–36 (h)	40	22.0	13	31.7	27	19.1	
> 36 (h)	12	6.6	3	7.3	9	6.4	
							0.37
Preoperative abdominal US	106	58.2	19	46.3	87	61.7	0.08
Positive	70/106	66	10/19	52.6	60/87	69.0	0.17
Preoperative abdominal CT	149	81.9	38	92.7	111	78.7	**< 0.05**
Positive	128/149	85.9	35/38	92.1	93/111	83.8	0.28
Complicated appendicitis	62	34.6	17	41.5	45	31.9	0.25
Time to surgery	15.2 ± 1.6		12.9 ± 2.1		15.9 ± 1.9		0.44
Appendectomy	160	87.9	31	75.6	129	91.5	**< 0.05**
Ileo-cecal resection	14	7.7	4	9.8	10	7.1	0.39
Negative exploration	1	0.5	–	–	1	0.7	na
Non-Operative Management	6	3.3	5	12.2	1	0.7	na
Percutaneous Drainage	1	0.5	1	2.4	–	–	na
Surgical approach							
Open	69	37.9	28	68.3	41	29.1	**< .001**
Laparoscopic	113	62.1	13	29.2	100	70.9	
Conversion rate	20	17.5	4	30.8	16	16.0	0.19
Lenght of stay (LOS)	7.23 ± 6.03		8.2 ± 6.2		6.9 ± 5.9		0.08
Operative time	83.4 ± 32.0		89.4 ± 35.4		81.7 ± 30.8		0.20
Morbidity	64	35.2	10	24.4	54	38.3	0.10
Infective complications	32	17.6	6	14.6	26	18.4	0.74
Clavien–Dindo 2–4	39	21.4	6	14.6	33	23.4	0.28
Mortality	2	1.1	1	2.4	1	0.7	0.40

Bold values are statistically significant

34.6% of patients with a slightly higher rate in the OOG (45 patients, 31.9% vs 17 patients, 41.5% in the CEG compared to OOG, respectively). The difference is not statistically significant ($p = 0.256$; OR 1.51, 95% CI 0.74–3.09) but with regard to this topic the study should be considered underpowered (effect size w 0.2059; power 0.5470). The mean operative time was 89.4 ± 35.5 min. in the OOG and 81.7 ± 30.8 min. in the ECG. The difference was not statistically significant ($p = 0.204$). There was no difference in terms of morbidity, Surgical Site Infections (SSI), intra-abdominal abscess and mortality, with an overall morbidity and mortality rate of 64 patients, 35.2% and two patients, 1.1% respectively. Contrary to what we would expect, the mean age of patients experienced complications was significantly lower both when overall morbidity (73.0 ± 7.0 vs 75.4 ± 7.3 yrs; $p < 0.017$) and when C–D II–IV (71.8 ± 6.4 vs 75.3 ± 7.4 yrs; $p < 0.006$) were considered. With regard to C-D II-IV complications, the analysis of the ROC curves indicated that the four analysed scores showed poor discrimination ability even below the chance (Fig. 1). The USEM score showed the best performance, with an AUC of 0.600 (95% CI 0.502–0.698), compared to 0.455 (95% CI 0.357–0.553) for the EmSFI, to 0.413 (95% CI 0.334–0.491) for the 5-mFI, and to 0.412 (95% CI 0.304–0.519) for the age-CACI. Moreover, the scores showed results even worst when overall morbidity has been considered. The univariate and multivariate analysis for overall and major complications are showed in Table 4. At multivariate analysis, factors statistically related to overall complications were complicated appendicitis ($p = 0.022$) and oral anticoagulant drugs ($p = 0.018$). When C–D II–IV have been considered, ileo-cecal resection ($p = 0.003$) and oral anticoagulant drugs ($p = 0.005$) were the only factors statistically relevant while the time from onset of symptoms to ED arrival was almost significant ($p = 0.086$).

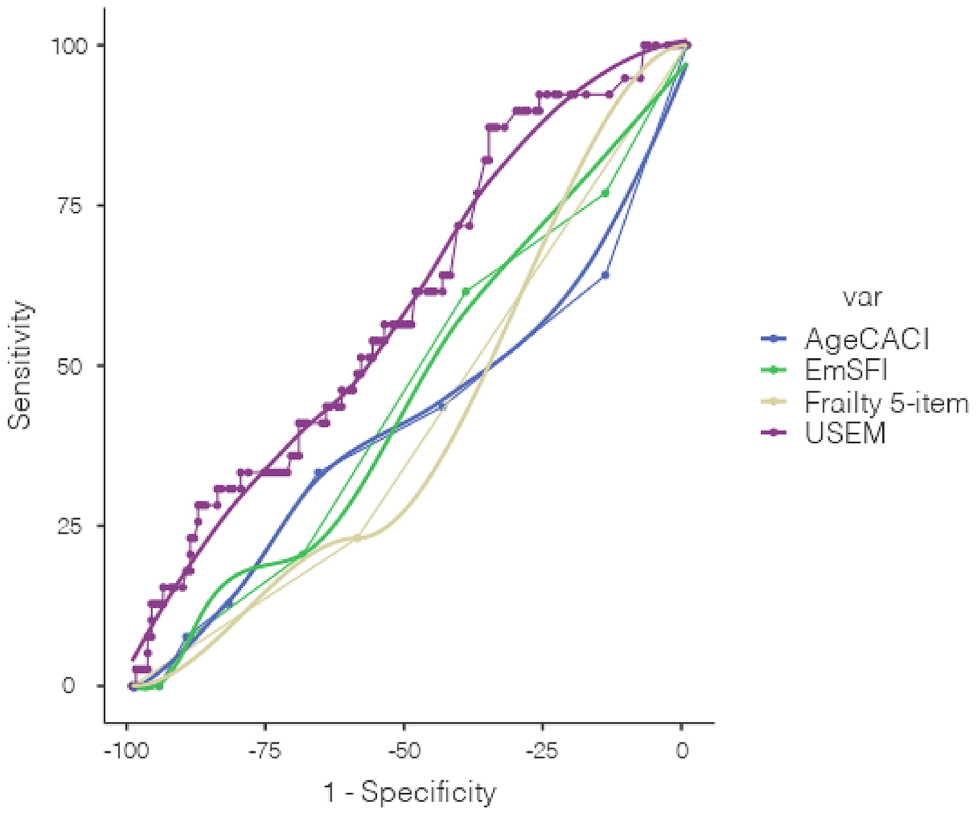

Fig. 1 ROC Curve: Combined frailty tools for Clavien–Dindo II–IV

Table 4 Univariate and multivariate analysis for Overall complications and Major complications (Clavien–Dindo II–IV)

	Overall Complications (C-D I–IV)				Major complications (C-D II–IV)			
	OR (95% CI) univariate	*P*	OR (95% CI) multivariate	*p*	OR (95% CI) univariate	*p*	OR (95% CI) multivariate	*p*
Time from onset to ED					1.420 (0.870–2.314)	0.160	1.629 (0.932–2.846)	0.086
MPI	**1.075 (1.010–1.145)**	**0.050**						
Ileo-cecal resection	**3.698 (1.183–11.560)**	**0.037**			**8.280 (2.590–3.360)**	**< 0.001**	**6.809 (1.933–23.978)**	**0.003**
Complicated appendicitis	**2.047 (1.087–3.856)**	**0.025**	**2.127 (1.115–4.060)**	**0.022**	1.629 (0.790–3.856)	0.184		
Oral anticoagulants	**2.317 (1.169–4.593)**	**0.015**	**2.309 (1.152–4.629)**	**0.018**	**3.038 (1.431–6.958)**	**0.003**	**3.285 (1.432–7.532)**	**0.005**
Kidney disease	2.667 (0.882–8.060)	0.133			2.190 (0.689–8.060)	0.184		
COPD	1.684 (0.878–3.230)	0.115						
ASA ≥ 3	**1.730 (0.916–3.265)**	**0.015**			**4.263 (1.766–10.288)**	**0.001**		
Age < 80	2.090 (1.138–3.867)	0.101						
Diabetes (Y/N)					**2.083 (1.002–4.333)**	**0.042**		
USEM score	1.249 (0.973–1.602)	0.080						

Bold values are statistically significant

Discussion

Life expectancy is increasing and consequently there is an increasing elderly population with multiple concomitant and more severe co-morbidities. (4, 6) With this increase of the lifespan, a growing incidence of acute appendicitis has been registered in the elderly (≥ 65 years old) population and also in the oldest old (> 80 years old) [9, 35]. Despite this, although acute appendicitis is the most frequent cause of emergency surgery worldwide, only 5% of elderly patients undergoing emergency procedure is

affected by AA [23, 24, 28]. In the present series, among the total number of patients with AA submitted to surgery in the study period in the participating centres, the elderly accounted for approximately 10% of the population and in this subgroup about a quarter was represented by patients > 80 years old.

Emergency surgery in the elderly is challenging in terms of decision-making, managing co-morbidity and post-operative rehabilitation with high morbidity and mortality rate [2, 3, 7]. On the light of this, it is pivotal to define the possible clinical-pathological features and treatment even for AA in a well-known frailer portion of the population.

New pathophysiology acknowledgement and improved surgical and anesthesiological skills allowed the surgeon to achieve better results in treating these high-risk patients [3]. However, diagnosis and treatment of acute appendicitis in elderly patients still remain a challenge [12–15].

We particularly focused on the age-related clinical differences and investigated the role of age as independent risk factor for the main clinical course and outcomes.

We have herein reported, to the best of our knowledge, the largest series of comparison of clinical features and outcomes between patients aged 80 years and older and elderly patients with an age comprised between 65 and 79 years presenting with AA, since no series with similar design were found in the current literature. Several studies evidenced significant differences in terms of AA clinical course between patients older and younger than 65 years with an increased morbidity and length of stay in the elderly [12–15]. Interestingly enough, in our study population, age ≥ 80 years was not an independent risk factor for both major and overall morbidities as well as for frailty which surprisingly is not statistically associated with postoperative complications. Focusing on the clinical presentation of AA, we found no difference in terms of pre-operative variables such us sex, BMI, BT, MPI and presence of comorbidities between the two groups. Regarding laboratories value, only few studies have investigated the predictive role of preoperative laboratory parameters [37, 38]. According to the literature, the age of the patient is one of the most important factor affecting the degree of elevation in inflammatory markers. Although there are many studies that have evaluated the benefits of using WBC, consensus has not yet been reached [38, 39]. Moreover, elderly patients have generally less remarkable inflammatory factors, due to decreased immune system response ability [40, 41]. At this regard, our study shows no difference in terms of WBC, CRP, and SIRS between the two groups but a significant higher mean of q-SOFA along with a significant higher level of lactate and creatinine in the OOG. A possible explanation could be linked to the delay in presentation and higher rate of complicated AA in these patients in whom the reduced physiological functions might lead to a not sufficient organ reserve to promptly cope with an inflammatory insult. Several studies have shown a higher rate of complicated AA in the elderly group [24, 42, 43]. This finding may be explained by the fact that elderly patients with perforated appendix would show poor exacerbation of pain as well as more generalized lower abdominal tenderness and guarding leading to a delay in presentation to the hospital. (39,40) This is in line with other studies who report a reduction of pain in oldest old patients, probably linked to a greater capacity to endure or to report it [44–46]. However, complicated appendicitis itself is an independent risk factor for morbidity independently to age.

According to the recent literature, the role of diagnostic imaging, such as POCUS and CECT is another major controversy [14, 46–48]. In our series, more than half of the patients underwent preoperative POCUS with no difference in terms of positive findings between the elderly and the oldest old group. However, an abdomen CECT scan was done in the 81.0% of the patients, reaching a rate of 92.7% in the oldest-old group. This finding is consistent with the number of ileocolic resection performed, since in the presence of a not clear diagnosis of appendicitis only at CECT (e.i. ileocecal abscess or pseudo inflammatory tumour) a resection was carried out. The recently published Cochrane systematic review on CECT scan for diagnosis of AA in adults identified 64 studies including 71 separate study populations with a total of 10,280 participants (4583 with and 5697 without AA). Summary sensitivity of CECT scan was 0.95, and summary specificity was 0.94. At the median prevalence of AA (0.43), the probability of having AA following a positive CECT result was 0.92, and the probability of having AA following a negative CECT result was 0.04 [48]. According to the last World Society of Emergency Surgery guidelines (WSES), we agree that POCUS could be the most appropriate first-line diagnostic tool, however as the elderly have often not typical laboratories values and symptoms unlikely to be acute appendicitis, cross-sectional imaging such us CECT scan is recommended before surgery [14].

Delay in presentation was found by many authors to be the reason behind the higher rate of perforation seen in the elderly population while in a meta-analysis of van Dijk a delaying appendectomy for up to 24 h after admission does not appear to be a risk factor for complicated appendicitis, SSI or other morbidities [36, 49–51].

Our research showed a slight lower time to surgery in the OOG. This can be interposed in light of the fact that when facing with oldest old, having them a smaller functional reserve, a more timely intervention is needed, and it also run with the greater rate of major resection carried out in this group. However, time to surgery was not a risk factor for overall and major complications. Regarding treatment strategies, even if over the last few years, several reports have been published describing non-operative-management (NOM) of AA, in our series all but seven patients underwent

surgical procedure [52–55]. However six out of seven of NOM patients were > 80 years old. Such findings, reflects the tendency of avoiding surgical procedures in patients generally defined as not fit for surgery. In our series, the almost lack of patients undergoing percutaneous drainage is probably due to the FRAILESL protocol which did not provide for the enrolment of patients participating in other trials. Since percutaneous drainage is rarely carried out anyway, it is probable that some patients have been already recruited for other researches. Moreover, it is of note the paper of Sartelli et *al*. which in a study over 4282 patients reported that only 0.2% underwent percutaneous drainage [56].

Appendectomy was the overall most common surgical procedure. The rate of major surgery such as ileocecal resection was slightly higher but statistically similar in both groups and it was an independent risk factor for major postoperative complication at both univariate and multivariate analysis.

Concerning the surgical approach, several systematic reviews of randomized control trials comparing laparoscopic appendectomy (LA) versus open appendectomy (OA), conclude that LA leads to less postoperative pain, lower overall hospital stays, and significantly decreases postoperative complications, in particular SSI [14, 57]. From our experience, the laparoscopic approach was statistically more frequent in the CEG. We explored the reasons for this discrepancy but we were not able to find a reasonable explanation except for the presence of higher rate of associated medical diseases in the OOG deemed contraindications to laparoscopy or for a surgeon's choice because a need for ileocolic resection and/or for a notable higher conversion rate in very elderly which could lead to a possible prolonged operative time. Moreover, it is important to underline that in our analysis the conversion to open surgery was not a risk factor for post-operative morbidity.

Focusing on complications, another important finding of our study is that there was an inverse relationship between increasing age and AA related major complications, highlighted how the oldest old patients have probably achieved a more stable physiologic status compared to elderly with equal comorbidity rate. However, some specific comorbidities such us, diabetes, use of OAD, and kidney dysfunction are risk factors for major comorbidity regardless patient age. Although it does not strictly correlate with chronological age, frailty is a major concern in geriatric patients and it is well known that it is a risk factor for prolonged length of stay, morbidity and mortality [58]. Many tools have been developed to assess operative risk and frailty in elderly population within different medical and surgical specialties all arising from the two most known approach: the "Fried" phenotype and the "Rockwood-Mitnitski" deficit accumulation method [59–62]. Recently the Comprehensive Geriatric Assessment has emerged as the possible reference standard for identifying and managing frailty [63]. Most of these models are still cumbersome and include a lot of variables in their scoring algorithms proving to be difficult to use at the bedside, time-consuming and face restrictions when incorporated into surgical evaluation and management especially in emergency or trauma setting. This issue has been recently well addressed by Barbagallo which advocated the need to use simple tools for the evaluation of frailty and vulnerability in the surgical risk assessment [64].

Similarly to other authors, we recently developed a fast and time-sparing scoring system also retracing some of the Fried's criteria. Hence, mobility alterations and functional impairments were identified using clinical examination along with anamnestic data and/or information supplied by caregivers, avoiding measurements that require certain time to be performed. The developed tool has been called EmSFI which is the acronym of Emergency Surgery Frailty Index. Despite the probably confounding label, our EmSFI is not actually a mere measure of frailty, but it is rather an elderly risk score based on possible frail profile and global deficit accumulation. In the present paper we have compared our EmSFI with three other different risk score potentially exploring the presence and the role of frailty: the age-CACI, the modified 5-item Frailty Index, and the Urgent Surgery Elderly Mortality score. We have found a frailty patient rate slightly higher than it otherwise reported in literature, but consistently to what is described regarding emergency surgery. About this, it is important to consider that the mean age of the entire population was close to 75 years old. It has been shown by previous papers that frailty is predictor of morbidity and mortality but since our series was burdened by a low mortality rate, it was not advisable to test the scores in predicting the risk of death [65–69]. With regard to morbidity, risk scoring systems and frailty tools should be considered with caution because we confirm their limited predictive value in emergency setting [28, 70–72].

Limitations

As it clearly descends from above, some limitations should be outlined. First, although to the best of our knowledge this research represents the largest case series specifically focused on AA in the over 80-year population, the epidemiological data are limited by the number of responder centres. Moreover, the sample size could consider the study underpowered in some topics. In addition, the prospective data collection and "a priori" definition of criteria to identify postoperative complications might mitigate these limitations. Moreover, a wide multicentre study allows more variables and reproducible results than a single centre, while the large series of patients allowed us to exclude confounders by multiple logistic analyses.

Second, the observational multicentre cohort design without a control population to compare the results is another important limitation. For this reason, it was not possible for example to draw any conclusion about the role of POCUS and CECT in the preoperative work up of oldest old patients with suspected appendicitis.

Third, as last but not least, the lack of morbidity predictive value of the analysed frailty score which highlights the need to develop risk score models that should take into account not only patient's intrinsic factors but also extrinsic determinants such as the onset of symptoms, time to surgery, operative time, and disease's severity.

Conclusions

Our study suggests that age ≥ 80 years is not an independent risk factor for morbidities. Moreover, no difference in terms of pre-operative variables such as sex, BMI, BT, MPI and presence of comorbidities in the OOG were found. POCUS is safe and effective for the diagnosis of appendicitis in the elderly; however, our results could suggest that might be advisable to perform CECT considering the need for ileocolic resections often needed to exclude other age-related diseases such as tumours or less frequently the right-sided diverticulitis. Having the oldest old a smaller functional organ reserve, an earlier intervention should be considered especially because they often show a delay in presentation and frequently exhibit a complicated appendicitis.

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Author contributions PF: Study conception and design, literature search, acquisition, interpretation and analysis of data, drafting and critically revising the article for important intellectual content and final approval of the version to be published. VF: literature search, acquisition, interpretation and analysis of data VC: literature search, acquisition, interpretation and analysis of data GC: acquisition, interpretation and analysis of data, drafting and critically revising the article for important intellectual content and final approval of the version to be published LP: acquisition, interpretation and analysis of data PM: acquisition, interpretation and analysis of data ALG: drafting and critically revising the article for important intellectual content and final approval of the version to be published GS: drafting and critically revising the article for important intellectual content and final approval of the version to be published.

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Declarations

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