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Epidemiology and age-related mortality in critically ill patients with intra-abdominal infection or sepsis: an international cohort study

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ABSTRACT

Objective: To describe epidemiology and age-related mortality in critically ill older adults with intra-abdominal infection.

Methods: A secondary analysis was undertaken of a prospective, multi-national, observational study (Abdominal Sepsis Study, ClinicalTrials.gov #NCT03270345) including patients with intra-abdominal infection from 309 intensive care units (ICUs) in 42 countries between January and December 2016. Mortality was considered as ICU mortality, with a minimum of 28 days of observation when patients were discharged earlier. Relationships with mortality were assessed by logistic regression analysis.

Results: The cohort included 2337 patients. Four age groups were defined: middle-aged patients [reference category; 40–59 years; *n*=659 (28.2%)], young-old patients [60–69 years; *n*=622 (26.6%)], middle-old patients [70–79 years; *n*=667 (28.5%)] and very old patients [≥80 years; *n*=389 (16.6%)]. Secondary peritonitis was the predominant infection (68.7%) and was equally prevalent across age groups. Mortality increased with age: 20.9% in middle-aged patients, 30.5% in young-old patients, 31.2% in middle-old patients, and 44.7% in very old patients ($P<0.001$). Compared with middle-aged patients, young-old age [odds ratio (OR) 1.62, 95% confidence interval (CI) 1.21–2.17], middle-old age (OR 1.80, 95% CI 1.35–2.41) and very old age (OR 3.69, 95% CI 2.66–5.12) were independently associated with mortality. Other independent risk factors for mortality included late-onset hospital-acquired intra-abdominal infection, diffuse peritonitis, sepsis/septic shock, source control failure, liver disease, congestive heart failure, diabetes and malnutrition.

Conclusions: For ICU patients with intra-abdominal infection, age >60 years was associated with mortality; patients aged ≥80 years had the worst prognosis. Comorbidities and overall disease severity further compromised survival. As all of these factors are non-modifiable, it remains unclear how to improve outcomes.

1. Introduction

Due to demographic changes, older adults constitute a growing proportion among critically ill patients. The clinical status of these patients is often burdened with multiple underlying comorbidities, making them particularly vulnerable to healthcare-associated complications, such as infection. Many critical care studies have focused on older adults. This increased interest is related to the growing proportion of older adults in the general patient population, contributing to a rise in hospital and intensive care unit (ICU) admissions, and to increased mortality among critically ill older adults [1–5]. Age-related features, such as physiological alterations in immunity, chronic underlying diseases, malnutrition, frailty and socio-economic status, further contribute to the increased risk of infection in older adults [6].

Intra-abdominal infections, particularly complicated intra-abdominal infections, are difficult to treat. They differ from other severe infections in terms of complexity of identification and diagnosis, diversity of aetiology, degree of severity, and need for source control [7–13]. Moreover, the increasing prevalence of multi-drug-resistant (MDR) pathogens challenges the appropriateness of empiric antibiotic therapy, thereby increasing the risk of adverse outcomes [14]. Also, critical illness and age contribute to increased morbidity and mortality for patients with intra-abdominal infection [7,8]. Age >75 years increases the risk of death in patients with intra-abdominal infection or peritonitis related to viscous perforation [15,16]. The impact of advanced age on outcome after intra-abdominal infection and sepsis has not been explored adequately for ICU patients specifically. Furthermore, it is unclear whether older adults are more prone to particular intra-abdominal infections, require more source control interventions, or have a higher risk for the involvement of MDR pathogens. All of these issues may change the clinical approach for the older ICU patient with intra-abdominal infection.

The purpose of this study was to assess the epidemiology and mortality of intra-abdominal infection in young-old, middle-old and very old ICU patients compared with middle-aged patients.

2. Methods

This study was reported according to the STROBE statement for observational studies [17]. Ethical approval for participating centres was obtained at hospital, regional or national level. The study has been registered at ClinicalTrials.gov (No. NCT03270345).

2.1. Study design

A secondary analysis of data from the Abdominal Sepsis Study (AbSeS), an observational, prospective, international cohort containing adult patients from 309 ICUs and 42 countries between January and December 2016, was conducted [8]. Protocols and procedures followed for inclusion/exclusion criteria, definitions, methods and collection of data for AbSeS are reported elsewhere [8]. The aims of the present study were to describe the epidemiological features of intra-abdominal infection, and identify factors related to ICU mortality in older ICU patients.

2.2. Patient selection

Following the AbSeS protocol, patients with intra-abdominal infection, either as the primary ICU diagnosis or as a complication during ICU hospitalization, were included in the study. All patients aged ≥40 years were eligible for analysis in this study. Patients without outcome data were excluded from the analysis. Patients

were classified as middle-aged (40–59 years), young-old (60–69 years), middle-old (70–79 years) or very old (≥80 years).

2.3. Variables

For every included patient, the following data were retrieved from the AbSeS database: demographics (sex, age), type of ICU admission (medical, surgical or trauma), comorbidities, Simplified Acute Physiology (SAPS) II score at the time of ICU admission [18], Sequential Organ Failure Assessment (SOFA) score at the time of diagnosis [19], type of intra-abdominal infection, microbial aetiology and antimicrobial resistance profiles, intra-abdominal risk classification, and source control evaluation 7 days after diagnosis. In addition, information regarding ICU length of stay and mortality was retrieved.

2.4. Definitions

Intra-abdominal infection types were determined based on the International Sepsis Forum Consensus Conference Definitions [20]. Intra-abdominal infections were classified according to the AbSeS risk classification [8,21], which is based on: (i) severity of disease expression; (ii) presence or absence of anatomical disruption and consequent localized or diffuse peritonitis; and (iii) setting of infection acquisition. Severity of disease expression was defined as infection, sepsis or septic shock according to the Sepsis-3 criteria [22]. Intra-abdominal infections were classified as either without anatomical disruption, or with anatomical disruption resulting in either localized or diffuse peritonitis (i.e. contamination spread to entire abdominal cavity). Setting was classified as community-acquired, healthcare-associated and/or early-onset hospital-acquired (≤7 days of hospital admission), or late-onset hospital-acquired (>7 days of hospital admission). Healthcare-associated onset was defined by at least one of the following risk factors for MDR pathogens: nursing home resident, out-of-hospital parenteral nutrition or vascular access, chronic dialysis, recent hospital admission (<6 months), or recent antimicrobial exposure (<6 months). For the sake of convenience, 'healthcare-associated and/or early-onset hospital-acquired' cases were designated 'early-onset hospital-acquired'. All cultures of intra-operative or transabdominal fine needle aspiration samples, abdominal drains sampled <24 h post surgery and blood cultures related to intra-abdominal infection were evaluated by the physicians reporting to AbSeS. Empiric antimicrobial therapy targeting Gram-positive, Gram-negative or anaerobic bacteria and fungi were recorded. Antimicrobial resistance patterns were reported and evaluated according to the EUCAST breakpoints [23]. MDR pathogens were defined as extended-spectrum beta-lactamase-producing strains, carbapenem- or fluoroquinolone-resistant Gram-negative bacteria [24], methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci. Source control was evaluated at day 7. Failure of source control represented either the need for re-intervention following the initial approach (conservative management or source control intervention), or the presence of persistent inflammation reflecting clinical evidence of a remaining source of infection.

2.5. Outcomes

Mortality was the primary outcome. More precisely, the impact of age on mortality was assessed after adjustment for other potential risk factors for death. Mortality was defined as ICU mortality, with a minimum of 28 days of observation for patients with an earlier discharge. Sample size calculation was not performed due to the study design.

2.6. Statistical analysis

Descriptive statistics included percentages as *n* (%) for categorical variables, and median values with interquartile range (IQR) for continuous variables. Patients' baseline characteristics, implicated pathogens, antimicrobial resistance profiles and outcomes were compared between the four age groups. Chi-squared test and Fisher exact test were used, as appropriate, for the comparison of categorical variables, and analysis of variance (ANOVA) was used for comparison between quintiles. Logistic regression analysis with the logit link function was used to assess independent associations between single variables and mortality, and results were reported as odds ratios (OR) and 95% confidence intervals (CI). A stable model based on both clinical and methodological reasoning and statistical results was sought. All variables potentially related to the outcome sought were considered, and those that fulfilled feature selection were included. Feature selection and final fit was done through a stepwise forward and backward approach, depending on the Akaike Information Criterion (AIC) value (dropping and adding variables that lead to the smallest AIC). Irrespective of their relationship with mortality in univariate analysis, the following variables were considered in the logistic regression model: age group, sex, setting of infection acquisition, anatomical disruption, severity of disease expression, SAPS II score, comorbidities (i.e., chronic pulmonary disease, chronic renal failure, neurologic disease, liver disease, myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes, immunosuppression, malnutrition (body mass index <20 kg/m^2), obesity (body mass index >30 kg/m^2), source control achievement, empiric antimicrobial coverage, MDR pathogens and length of ICU stay. The decision was made not to include SOFA score in the model as it strongly overlapped with the severity of disease classification used to define the phenotype of intra-abdominal infections. For the logistic regression model, only cases with no missing values were considered. To rule out length time bias, a sensitivity analysis was planned using 28-day mortality instead of the main outcome used throughout the study (i.e. ICU mortality with a minimum of 28 days of observation).

Survival curves for middle-aged, young-old, middle-old and very old critically ill patients with intra-abdominal infection were prepared by the Kaplan–Meier method. Cox proportional-hazards regression was used to adjust survival distributions for setting of infection acquisition, anatomical barrier disruption, severity of disease expression, comorbidities and source control achievement. Patients were censored at 28 days. Adjusted relationships of older age categories with mortality were reported as hazard ratios (HR) and 95% CI relative to middle-aged patients (i.e. reference category). Statistical analyses were performed using R Version 3.2.2 (R Foundation for Statistical Computing) and SPSS Statistics Version 28 (IBM Corp., Armonk, NY, USA). All tests were two-tailed and $P<0.05$ was considered to indicate statistical significance.

3. Results

3.1. Characteristics of the patients

The present study included 2337 patients (Figure 1). Among these, 659 (28.2%) were middle-aged patients, 622 (26.6%) were young-old patients, 667 (28.5%) were middle-old patients and 389 (16.6%) were very old patients. Patient characteristics are presented in Table 1. Neurological disease, chronic renal failure, myocardial infarction, congestive heart failure and peripheral vascular disease were reported more frequently in very old patients compared with the other groups. Chronic pulmonary disease, diabetes mellitus, liver-related diseases, immunodeficiency, malignancy and obesity were more common in middle-aged patients. Very old patients presented more often with community-acquired and early-onset

Table 1
Characteristics of critically ill patients with intra-abdominal infection by age group.

	Parameters	Middle-aged (40–59 years) (*n*=659)	Young-old (60–69 years) (*n*=622)	Middle-old (70–79 years) (*n*=667)	Very old (≥80 years) (*n*=389)	*P*-values
	Age (years)	52 (47–57)	65 (62–67)	74 (72–77)	84 (82–86)	<0.001
	Sex (male)	369 (56.0)	385 (62.2)	385 (57.9)	200 (51.4)	0.007
	ICU stay (days)	10 (4–20)	9 (4–18)	8 (4–16)	8 (4–17)	0.129
Underlying conditions						
	Chronic pulmonary disease	58 (8.8)	102 (16.4)	119 (17.8)	45 (11.6)	<0.001
	Malignancy	162 (24.6)	200 (32.2)	207 (31.0)	105 (27.0)	0.010
	Neurologic disease	19 (2.9)	47 (7.6)	50 (7.5)	56 (14.4)	<0.001
	Liver disease	42 (6.4)	46 (7.4)	19 (2.8)	6 (1.5)	<0.001
	Chronic renal failure	43 (6.5)	64 (10.3)	89 (13.3)	75 (19.3)	<0.001
	Myocardial infarction	21 (3.2)	42 (6.8)	73 (10.9)	47 (12.1)	<0.001
	Congestive heart failure	16 (2.4)	33 (5.3)	73 (10.9)	55 (14.1)	<0.001
	Peripheral vascular disease	20 (3.0)	49 (7.9)	60 (9.0)	39 (10.0)	<0.001
	Diabetes mellitus	90 (13.7)	132 (21.2)	172 (25.8)	78 (20.1)	<0.001
	Impaired immunity	88 (13.4)	71 (11.4)	55 (8.2)	16 (4.1)	<0.001
	Malnutrition	50 (7.6)	38 (6.1)	31 (4.6)	32 (8.2)	0.067
	Obesity	197 (29.9)	188 (30.2)	203 (30.4)	73 (18.8)	<0.001
Severity of acute illness						
	SAPS II score[a]	48 (38–59)	50 (40–62)	49 (38–60)	48 (37–60)	0.258
	SOFA score[b]	6 (3–9)	7 (3–10)	6 (3–10)	6 (3–9)	0.242
Intra-abdominal infection risk classification						
	Setting of infection acquisition					<0.001
	Community-acquired	201 (30.5)	160 (25.7)	215 (32.2)	143 (36.8)	
	Early-onset hospital-acquired	155 (23.5)	145 (23.3)	163 (24.4)	115 (29.6)	
	Late-onset hospital-acquired	303 (46.0)	317 (51.0)	289 (43.3)	131 (33.7)	
	Anatomical barrier disruption					0.942
	No disruption	163 (24.7)	148 (23.8)	152 (22.8)	86 (22.1)	
	Yes, with localized peritonitis	237 (36.0)	232 (37.3)	251 (37.6)	141 (36.2)	
	Yes, with diffuse peritonitis	259 (39.3)	242 (38.9)	264 (39.6)	162 (41.6)	
	Severity of disease expression					0.043
	Infection	36 (5.5)	48 (7.7)	33 (4.9)	21 (5.4)	
	Sepsis	422 (64.0)	363 (58.4)	382 (57.3)	237 (60.9)	
	Septic shock	201 (30.5)	211 (33.9)	252 (37.8)	131 (33.7)	
Source control intervention	588 (96.1)	554 (95.3)	604 (96.0)	352 (95.9)	0.920	
Time to source control intervention (h)[c]					0.783	
<2	230 (39.1)	240 (43.3)	263 (43.5)	148 (42.0)		
2–12	246 (41.8)	217 (39.2)	248 (41.1)	144 (40.9)		
12–24	52 (8.8)	46 (8.3)	42 (7.0)	34 (9.7)		
24–48	24 (4.1)	21 (3.8)	16 (2.6)	10 (2.8)		
>48	36 (6.1)	30 (5.4)	35 (5.8)	16 (4.5)		
Source control evaluation at day 7					0.218	
	Success	380 (57.7)	343 (55.1)	363 (54.4)	205 (52.7)	
	Persistent inflammation	173 (26.3)	191 (30.7)	198 (29.7)	132 (33.9)	
	Source control intervention within 7 days required	106 (16.1)	88 (14.1)	106 (15.9)	52 (13.4)	
Mortality at 28 days		113 (17.1)	163 (26.2)	175 (26.2)	157 (40.4)	<0.001
ICU mortality with minimum of 28 days of observation		138 (20.9)	190 (30.5)	214 (32.1)	174 (44.7)	<0.001

Middle-aged, 40–59 years; young-old, 60–69 years; middle-old, 70–79 years; very old, ≥80 years; ICU, intensive care unit; SAPS, Simplified Acute Physiology; SOFA, Sequential Organ Failure Assessment.
Values are presented as percentage or interquartile range.
[a] At the time of ICU admission.
[b] At the time of diagnosing intra-abdominal infection.
[c] Calculated from time of diagnosis or suspicion of intra-abdominal infection.

hospital-acquired infection compared with other age groups. Conversely, late-onset hospital-acquired infection was more common in young-old patients compared with other age groups. No differences were observed between the age groups in terms of SAPS II and SOFA scores, empiric antimicrobial therapy, anatomical barrier disruption, source control achievement and length of ICU stay.

Tables S1 (see online supplementary material) shows the distribution of distinct types of intra-abdominal infection between the age groups. Secondary peritonitis was the predominant infection, with no difference in prevalence between the age groups. The prevalence of biliary tract infection increased with increasing age, whereas intra-abdominal abscesses and pancreatic infections became less prevalent as age increased. No differences in empiric antimicrobial coverage were observed between the age groups (Table 2).

3.2. Microbiological findings

Cultures were sampled from 1776 patients (76%), with similar sampling rates in all study groups (*P*=0.789). No differences in culture results (Table S2, see online supplementary material) or antimicrobial resistance patterns (Table 3) were observed between the four age groups. However, when all three older age groups were pooled, *Enterococcus faecium* was isolated more frequently from older patients compared with middle-aged patients (11.9% vs 8.1%; *P*=0.019).

Table 2
Empiric antimicrobial coverage for intra-abdominal infection by age group.

Empiric antimicrobial coverage[a]		Middle-aged (40–59 years) (*n*=659)	Young-old (60–69 years) (*n*=622)	Middle-old (70–79 years) (*n*=667)	Very old (≥80 years) (*n*=389)	*P*-values
	Basic schedule covering aerobic Gram-positive, Gram-negative and anaerobic bacteria	584 (95.0)	541 (94.1)	589 (94.8)	325 (92.1)	0.252
	Pseudomonas coverage	508 (82.7)	476 (82.8)	489 (80.7)	282 (80.6)	0.664
	Enterococcal coverage (targeting *Enterococcus faecalis*)	462 (75.2)	426 (74.1)	450 (72.5)	253 (71.7)	0.571
	VRE coverage	32 (5.2)	29 (5.0)	47 (7.6)	20 (5.7)	0.218
	MRSA coverage	158 (25.7)	139 (24.2)	173 (27.9)	101 (28.6)	0.363
	Candida coverage	105 (17.1)	100 (17.4)	121 (19.5)	56 (15.9)	0.497

VRE, vancomycin-resistant enterococci; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] Data on empiric antimicrobial therapy was available in 2164 patients, i.e. 92.6% of the study cohort.

Table 3
Antimicrobial resistance profiles in critically ill older patients with intra-abdominal infection by age group.

		Middle-aged (40–59 years) (*n*=508)	Young-old (60–69 years) (*n*=472)	Middle-old (70–79 years) (*n*=507)	Very old (≥80 years) (*n*=289)
Resistance in Gram-negative bacteria					
	ESBL	81 (15.9)	78 (16.5)	72 (14.2)	55 (19.0)
	Carbapenem-resistance	39 (7.7)	35 (7.4)	37 (7.3)	15 (5.2)
	Fluoroquinolone resistance	93 (18.3)	83 (17.4)	80 (15.8)	47 (16.3)
	Difficult-to-treat resistance[a]	28 (5.5)	21 (4.4)	16 (3.2)	11 (3.8)
Resistance in Gram-positive bacteria					
	MRSA	4 (0.8)	4 (0.8)	10 (2.0)	2 (0.7)
	VRE	8 (1.6)	16 (3.2)	16 (3.2)	7 (2.4)
Total antimicrobial resistance[b]	96 (18.9)	103 (21.8)	108 (21.3)	64 (22.1)	

ESBL, extended-spectrum beta-lactamase-producing Gram-negative bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
[a] Resistant to all beta-lactam antibiotics, carbapenems and fluoroquinolones.
[b] Patients with either ESBL-producing Gram-negative bacteria, carbapenem-resistant Gram-negative bacteria, MRSA or VRE.

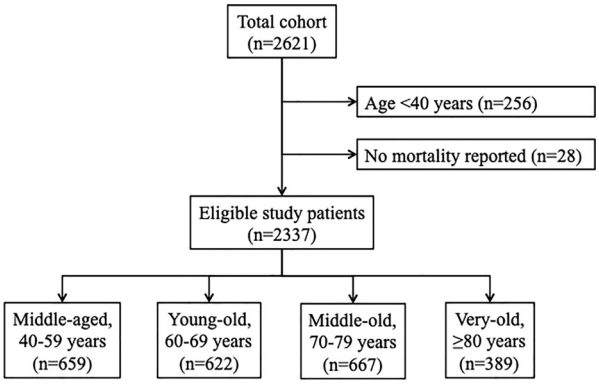

Fig. 1. Patient selection flowchart.

3.3. Mortality

Unadjusted mortality rates were higher in very old patients (44.7%) compared with middle-old patients (32.1%), young-old patients (30.5%) and middle-aged patients (20.9%) ($P<0.001$). Similar results were observed when adjusted stepwise logistic regression was used (Table 4). Compared with middle-aged patients (reference group), mortality was significantly higher among young-old patients, middle-old patients and very old patients. Additional factors related to mortality were late-onset hospital-acquired intra-abdominal infection, diffuse peritonitis, sepsis or septic shock, failure of source control, liver disease, congestive heart failure, diabetes and malnutrition. Executing the logistic regression by using 28-day mortality did not alter the results (Table S3, see online supplementary material). Figure 2 shows the survival curves for the distinct age groups as adjusted for independent risk factors for mortality. Compared with middle-aged patients, cumulative survival was significantly lower in all three older age categories. However, cumulative survival curves for young-old and middle-old patients were very similar. Due to the overall high mortality in patients aged ≥80 years (45%), the authors tried to define specific phenotypes with a particularly poor prognosis within this age group. This was done according to the AbSeS risk classification (Table 5). Among octogenarians, mortality most often exceeds 50% in patients presenting with sepsis or septic shock, and either localized or diffuse peritonitis.

4. Discussion

This secondary analysis of the AbSeS cohort presented comorbidities, severity of acute disease and infection characteristics of critically ill older patients with intra-abdominal infection. Mortality was considerably higher among patients aged ≥60 years compared with middle-aged patients (40–59 years). Patients aged ≥80 years had significantly higher mortality compared with younger patients. In very old patients (≥80 years), mortality was exceptionally high (up to 70%) among those presenting with either sepsis or septic shock, and either localized or diffuse peritonitis. None of the identified risk factors for death are modifiable, and therefore this study cannot provide action targets to potentially improve survival. At the same time, the data presented illustrate the importance of timely organized patient- and family-centred care conferences, as suggested by the Surviving Sepsis Campaign guidelines [25–27]. These meetings should promote awareness about sepsis, and discuss realistic goals of care.

Similar to the present results, a large observational cohort of severely septic ICU and non-ICU patients in the USA reported higher mortality among patients aged >85 years compared with their general study population (38.4% vs. 28.6%, respectively) [28].

Table 4
Independent relationships with mortality in critically ill patients with intra-abdominal infection.

	Variables	OR (95% CI)
Age		
	Middle-aged (40–59 years)	Reference
	Young-old (60–69 years)	1.62 (1.21–2.17)
	Middle-old (70–79 years)	1.80 (1.35–2.42)
	Very old (≥80 years)	3.69 (2.67–5.12)
Setting of infection acquisition		
	Community-acquired infection	Reference
	Early-onset hospital-acquired infection (≤7 days)	1.10 (0.82–1.47)
	Late-onset hospital-acquired infection (>7 days)	1.65 (1.28–2.12)
Anatomical disruption		
	No anatomical barrier disruption	Reference
	Anatomical disruption with localized peritonitis	1.23 (0.93–1.64)
	Anatomical disruption with diffuse peritonitis	1.77 (1.35–2.32)
Severity of disease expression		
	Infection	Reference
	Sepsis	2.17 (1.28–3.87)
	Septic shock	4.03 (2.36–7.24)
Underlying conditions		
	Liver disease	2.07 (1.31–3.26)
	Congestive heart failure	2.01 (1.38–2.94)
	Diabetes mellitus	1.44 (1.12–1.86)
	Malnutrition	2.09 (1.40–3.11)
Empiric antimicrobial therapy with coverage of MRSA	0.74 (0.58–0.94)	
Source control achievement at day 7		
	Success	Reference
	Failure, persistent signs of inflammation	5.20 (4.14–6.54)
	Failure, additional intervention required following initial approach	2.02 (1.49–2.71)

OR, odds ratio; CI, confidence interval; MRSA: methicillin-resistant *Staphylococcus aureus*.
Only cases without missing values were considered for the logistic regression model; 181 cases were excluded from the analysis. As such, the reported model is based on 2156 patients (overall, no variable in the database had >5% missing values).

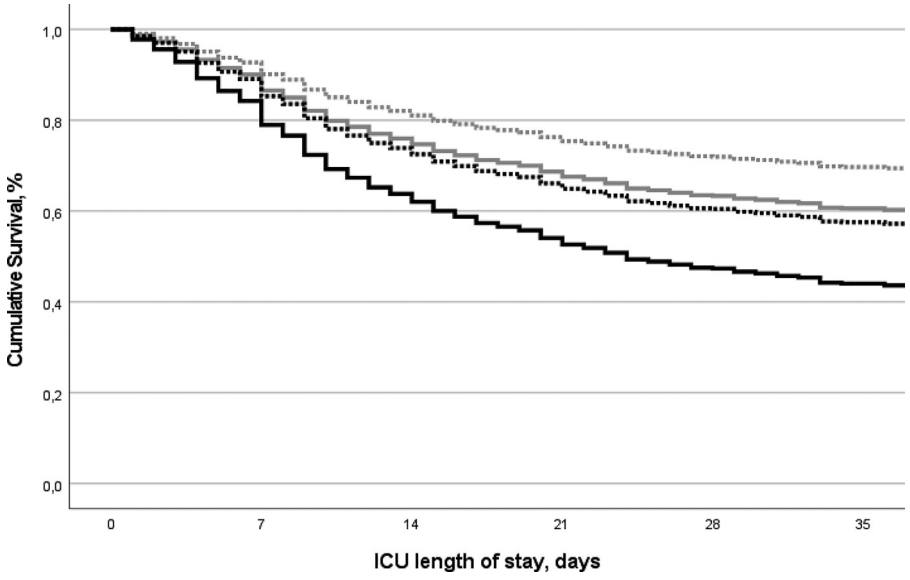

Fig. 2. Survival curves for middle-aged, young-old, middle-old and very old critically ill patients with intra-abdominal infection. Grey dashed line represents middle-aged patients; grey solid line represents young-old patients; black dashed line represents middle-old patients; black solid line represents very old patients. Survival curves were generated by Cox regression and have been adjusted for the intra-abdominal risk classification (i.e. setting of infection acquisition, anatomical barrier disruption, severity of disease expression), comorbidities (i.e. liver disease, congestive heart failure, diabetes and malnutrition) and source control achievement. Hazard ratios (HR) and 95% confidence intervals (CI) relative to middle-aged patients (i.e. reference category) are reported for older age categories: HR 1.39, 95% CI 1.11–1.73 for young-old patients (P=0.004); HR 1.53, 95% CI 1.23–1.90 for middle-old patients (P<0.001); and HR 2.27, 95% CI 1.80–2.86 for very old patients (P<0.001).

Dimopoulos et al. observed that age >85 years among ICU patients with infection was an independent risk factor for mortality [6]. Likewise, Bagshaw et al. concluded that age ≥80 years, regardless of ICU admission diagnosis, was associated with higher ICU and hospital mortality compared with younger patients [2]. Previous studies suggested that advanced age is a contributing factor for death in patients with secondary peritonitis, as well as in critically ill patients with community-onset intra-abdominal infection [7,16]. Recently, Martin-Loeches et al. reported that age >80 years constitutes an independent risk factor for mortality in a large cohort of septic critically ill patients, of whom 35.6% had peritonitis as the primary site of infection [29].

In contrast to the present results, Farmer et al. examined the correlation between age and outcome in patients with complicated intra-abdominal infection, and found that advanced age (>65 years) as an individual risk factor was not associated with in-

Table 5
Mortality among very old (≥80 years) intensive care unit patients with intra-abdominal infection according to the Abdominal Sepsis Study risk classification.

		Setting of infection acquisition								
		Community-acquired			Early-onset hospital-acquired			Late-onset hospital-acquired		
Severity of disease	Septic shock	5/14 35.7%	8/12 66.7%	14/20 70.0%	2/9 22.2%	2/11 18.2%	9/17 52.9%	0/8 0%	9/13 69.2%	15/27 55.6%
	Sepsis	5/19 26.3%	12/36 33.3%	21/35 60.0%	7/14 50.0%	10/32 31.3%	13/26 50.0%	3/17 17.6%	14/29 48.3%	19/29 65.5%
	Infection	0/2 0%	0/1 0%	2/4 50.0%	0/1 0%	0/2 0%	1/3 33.3%	1/2 50.0%	2/5 40.0%	0/1 0%
		No	Yes, with localized peritonitis	Yes, with diffuse peritonitis	No	Yes, with localized peritonitis	Yes, with diffuse peritonitis	No	Yes, with localized peritonitis	Yes, with diffuse peritonitis
		Anatomical disruption			Anatomical disruption			Anatomical disruption		

creased risk of mortality [30]. While neither the present study nor the study by Farmer et al. were powered for this outcome, the present study included almost five times more patients. Also, the threshold of 65 years may have led to a loss of age-related resolution. Furthermore, older patients in the study by Farmer et al. had a higher rate of colon or rectum infections, which was not observed in the present study (Table S1, upper vs. lower gastrointestinal tract perforation in secondary peritonitis).

For sources of infection other than the abdomen, such as nosocomial bloodstream infection and ventilator-associated pneumonia (VAP), hospital mortality rates were amplified in older ICU patients, particularly in very old patients [31,32]. On the contrary, mortality did not differ between older (>75 years) and younger ICU patients with invasive aspergillosis (73.6% vs. 72.0%, respectively) [33]. The lack of a difference in mortality can be explained by the very high baseline mortality in this particular cohort. Furthermore, in a cohort study of non-critically ill older adults, nosocomial bloodstream infection was not recognized as an independent risk factor for death (HR 1.3, 95% CI 0.6–2.6) [34]. One explanation could be that the impact of severe infectious complications on mortality might be attenuated in the extremes of disease severity. The proportion of infections with *Escherichia coli* and enterococci was very high. The prevalence of infections caused by these pathogens has risen in the past decade, leading to concerns related to potential evolution of resistance [35,36]. With the exception of *E. faecium*, no substantial differences in microbial aetiologies were observed between the age groups. In a cohort of older (≥75 years) ICU patients, Dupont et al. reported that enterococcal involvement in intra-abdominal infections was associated with higher morbidity and mortality, but the present study could not confirm this association [37]. In the present analysis, MDR pathogens were not more common among the older adults, and were not associated with increased mortality. These findings contrast with the data by Blot et al. in a multi-centre European prospective cohort of VAP episodes where the risk of death was significantly higher in old (65–74 years) and very old (≥75 years) patients and in patients with high-risk pathogens (i.e. MRSA, *Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*) [32]. As reported earlier [8], one possible explanation is the equivocal sense of cultures sampled from peritonitis. Further investigation is needed to isolate the effect of MDR pathogens on the risk of mortality in older ICU patients with intra-abdominal infection from modifiers and covariates.

In addition to older age, several other factors were found to be associated with increased mortality. These included phenotypic characteristics of intra-abdominal infection, such as the setting of infection acquisition, anatomical disruption with diffuse peritonitis, and severity of disease expression. Furthermore, comorbidities and failure of source control were associated with increased risk of death. In a previous study on older ICU patients with intra-abdominal candidiasis, inadequate source control at day 2 was shown to have a negative effect on survival [38]. In the present study, the rate of source control intervention was high across all age groups (>95%). It could be presumed that this high rate of source control interventions can – at least in part – be explained by the fact that this study cohort consisted exclusively of ICU patients. ICU admission implies a certain preselection of patients with an anticipated chance of survival, encouraging immediate source control intervention if indicated. The present study has several strengths, namely the inclusion of a large number of older adult ICU patients, the prospective and multi-national design, the inclusion of both community- and hospital-acquired infections, and the investigation of a considerable number of predictors of mortality.

This study also had several limitations. Variables potentially influencing the outcome could have been missed as data collection was not targeted specifically for this outcome (i.e. medications, treatment delays, specific frailty score). Also 'do not resuscitate' (DNR) data were not available. However, as DNR practices are neither valid universally, nor supported universally by national laws in the participating countries, inclusion of these in the data collection would have resulted in inherent bias. Age classifications were chosen arbitrarily as no strict age definition for critically ill infected patients exists in the literature [6,32,33,38]. As age >80 years is often considered as a substantial risk factor for mortality, this threshold was adopted to define very old age [29,39,40]. Furthermore,

source control evaluation was left to the discretion of local investigators in charge, and was not evaluated by an independent panel. Finally, the authors were only able to report ICU mortality or 28-day mortality. It is not unthinkable that with a larger window of observation, mortality figures between the age groups would either diverge further or converge.

5. Conclusions

This international cohort study demonstrated an important relationship between older age and mortality in critically ill older adults with intra-abdominal infection or sepsis. Age >60 years, particularly age >80 years, was associated with increased risk of death. Comorbidities, anatomical disruption with diffuse peritonitis, sepsis or septic shock, and failure of source control were additional risk factors significantly related to mortality. As these risk factors for death are non-modifiable, the search for therapeutic targets that may improve outcomes continues. In the mean time, these data clearly stress the importance of care conferences to inform and discuss realistic goals of care with the family.

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Supplementary materials

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