Impact of age and comorbidities on colorectal endoscopic submucosal dissection outcomes: Large multicenter study in a Western cohort

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ABSTRACT

Background and study aims Endoscopic submucosal dissection (ESD) has emerged as the standard treatment for colorectal lesions. Considering aging of the global population, we aimed to assess effectiveness and safety of colorectal ESD in patients aged ≥ 80 years compared with those aged 65 to 79 years in a large Western cohort.

Patients and methods We retrospectively enrolled patients aged > 64 years undergoing colorectal ESD, classifying them into a very elderly group (VE-Group, aged > 80 years) and elderly group (E-Group, 65–79 years). Procedure outcomes and safety were compared between the VE-Group and E-Group and between patients with comorbidities and those who were healthy (1-CM-Group and H-Group).

Results A total of 980 patients were included (269; 27.5% in the VE-Group and 711; 72.5% in the E-Group). En-bloc, R0, and oncological curative resection rates did not differ, nor did intra-procedure or post-procedure adverse events (AEs). Delirium occurrence was registered in VE-group [6 (2.2%) in VE-Group vs 1 (0.1%) in E-Group; $P = 0.001$; OR = 16.2 (95% CI: 1.9–135.2)]. The 1-CM-Group had a higher rate of intra-procedure bleeding ($P = 0.001$), delayed perforation ($P = 0.03$), fever onset ($P < 0.001$), and systemic infections ($P = 0.02$) compared with the H-Group. Having one or more comorbidities was associated with increased overall AEs ($P < 0.001$; OR 2.3, 95% CI 1.5–3.6).

Conclusions Colorectal ESD is feasible in elderly patients. Physicians should consider delirium a possible AE in patients older than age 80 years. These findings, which bridge the gap between Asian and Western clinical data, underscore the importance of tailored pre-procedure and post-procedure assessments in a global clinical context.

Introduction

Endoscopic submucosal dissection (ESD) is an advanced technique performed for en-bloc resection of large non-pedunculated colorectal polyps (LNPCPs) [1]. According to the latest guidelines from the European Society of Gastrointestinal Endoscopy (ESGE), ESD is the standard of care for large rectal lesions and should be considered for large colonic lesions after careful endoscopic evaluation, ruling out invasive cancer [2, 3]. Incidence of this type of lesion is rising worldwide due to better diagnostic efficiency, advancements in endoscope resolution and surveillance programs, together with aging of the global population [4, 5]. Incidence of colorectal polyps, indeed, increases with age [4], with patients over 70 years having a 10% to 15% greater risk of developing polyps than those aged 50 to 55 years. According to the most recent World Health Organization (WHO) report on population aging [6], over 30% of the European population will be over 60 years old by 2050, leading to a higher prevalence of multimorbidity. Hence, it seems essential to recognize the specific challenges ESD poses for this population. Despite advances in strategy and devices, incidence of adverse events (AEs) related to ESD (intraprocedural and post-procedural) and anesthesia still reaches up to a 5% rate, even in expert centers [7]. Furthermore, it is unclear whether technical challenges associated with the procedure justify potential benefits of curative resection [8], especially for patients over 80. To date, there is a lack of data on the effectiveness and safety of ESD for older Western patients with LNPCPs. Kim et al. [9] have demonstrated that the procedure is feasible for Korean patients with a Charlson Comorbidity Index (CCI) ≥ 3. However, in that study, mean population age was 65.3 ± 11.2; thus excluding the very old patient group. Moreover, morbidity and mortality rates in Western populations differ according to presence of comorbidities compared with Eastern populations [10]. A retrospective study on diabetic populations from Eastern and Western regions demonstrated age-dependent variations in mortality, with higher rates observed in the Asian cohort before advanced age and lower rates thereafter [11].

Based on these assumptions, we aimed to evaluate feasibility and safety associated with ESD of LNPCPs in the elderly.

Patients and methods

Study design and data collection

We retrospectively analyzed a prospective consecutive database maintained by 10 Italian tertiary referral centers. All consecutive patients aged 65 years or older who had undergone ESD for LNPCPs between January 2019 and December 2023 were enrolled.

Demographic and clinical data were collected. Comorbidities were registered both through the CCI [12] and individually. The American Society of Anesthesiologists (ASA) physical status classification system was used to assess patient fitness before ESD [13]. Moreover, use of anticoagulants or antithrombotic medications was registered.

In all patients, ESD was performed for treatment of large (> 20 mm) rectal sessile polyp or lateral spreading tumors (LSTs), colonic nongranular type or with one or more nodular components (LST-mixed type), recurrent adenomas, and difficult-to resect by endoscopic mucosal resection colorectal superficial lesions or polyps, according to the ESGE guidelines [2]. ESD was also performed in selected cases of suspected deep submucosal invasion (JNET 3) after careful imaging staging and when major surgery was contraindicated due to comorbidities or patients explicitly refused it.

Endoscopic procedure

All ESDs were performed by experienced endoscopists with more than 250 cases under general anesthesia or deep sedation. Procedures were conducted with CO_2 insufflation, using different techniques described across the literature (i. e. conventional ESD, traction-assisted ESD, tunnel ESD, underwater ESD, pocket creation method ESD) [1] based on operator preference. Hybrid ESD (h-ESD) was performed for < 30-mm lesions or as a rescue treatment for difficult-to-resect lesions. Devices used included Dual-knife J (Olympus, Tokyo, Japan), Flush knife (Fujifilm, Tokyo, Japan), Hybrid knife T-type (ERBE, Tübingen, Germany) or ClearCut knife J (Finemedix, Daegu, South Korea). Depending on the type of cutting device used, a submucosal injection with a hypertonic solution and indigo carmine (and epinephrine diluted 1:100000 based on operator preference) was performed to lift the lesion. A high-frequency electrosurgical unit (VIO300 D, VIO 3; ERBE, Tübingen, Germany) was used for mucosal incision, submucosal dissection, and coagulation. If necessary, a monopolar coagulation forceps (Coagrasper, Olympus, Tokyo, Japan) was employed during the procedure. Defect closure was performed based on operator evaluation.

Outcomes and measurements

The primary endpoint was assessment of procedure outcomes (en-bloc, R0 and oncological curative resections) and AEs among very elderly (VE-Group) vs. elderly group (E-Group) and comorbid (CM-group) vs. healthy groups (H-group).

The secondary endpoint was assessment of safety and independent predictors of overall AEs.

The VE-Group was defined as individuals aged 80 years or older, whereas the E-Group as individuals aged between 65 and 79 years. The CM-Group included patients with at least one significant comorbidity, whereas the H-Group included patients without comorbidity. Significant comorbidities included all those that have been demonstrated to reduce short-term general population survival, according to literature data [14, 15, 16].

En-bloc was defined as complete resection in one piece of the lesion according to macroscopic view; R0 was defined as absence of residual lesion to the lateral (LM) and vertical (VM) margins on the pathological report. Oncological curative resection was defined as presence of R0 resection without lymphovascular invasion (LVI) and high-grade tumor budding (HGTB).

Following the ESGE guidelines [2], adenocarcinoma was graded as pT1a if limited to the lamina propria, pT1b if superficial submucosal invasion was present (sm1, < 1000 µm submucosal invasion), and deeply invasive if ≥ 1000 µm (sm2) of submucosal invasion was present.

Lesion morphology was described according to the Paris classification [17], whereas endoscopic superficial pattern was evaluated according to the Japanese NBI Expert Team classification (JNET) [18].

All procedure-related AEs were registered as intraprocedural or post-procedural [19]. Bleeding was defined as a 2-point drop in hemoglobin levels or clinically evident bleeding with need for endoscopic intervention/blood transfusion. Post-procedure perforation was recorded when radiological signs were present, whereas it was classified as intraprocedural when evident during the intervention. After the procedure, laboratory values such as C-reactive protein (CRP) and procalcitonin (PCT) were collected. All patients were followed up for 30 days after the procedure to monitor for potential occurrence of additional events or mortality, such as episodes of fever, sepsis, or other cardiovascular, pulmonary or neurological issues, diagnosed according to updated diagnostic criteria [20, 21]. All AEs reported were named as overall AEs.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), and categoric variables were summarized as frequency and percentage. As appropriate, variables were compared using the *t*-test or Mann-Whitney, Chi square test, and Fisher's exact test. $P < 0.05$ was considered to indicate statistical significance.

A multivariate logistic regression analysis was performed using the Wald test to identify independent risk factors for different outcomes. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess strength of the association.

All statistical analyses were performed using IBM SPSS Statistics for Windows v. 26.0 (Armonk, New York, United States).

Ethics

The study received Ethics Committee approval and was conducted following the principles of the Declaration of Helsinki and good clinical practice. Patients provided written informed consent.

Results

Demographic data, lesion characteristics and procedures

A total of 980 patients presenting with the same number of lesions that had undergone ESD were enrolled, with 269 (27.5%) included in the VE-Group and 711 (72.5%) in the E-Group. ▶ **Table 1** summarizes baseline demographic data for the two cohorts. The VE-Group had a significantly higher CCI than the E-Group (5 vs 3; $P < 0.001$), with higher rates of cardiovascular diseases and higher prevalence of at least one comorbidity (59.1% vs 15.4%; $P < 0.001$). Patients with multiple comorbidities were 69 (25.7%) in the VE-Group, whereas 83 (11.7%) in the E-Group ($P < 0.001$). The VE-Group showed higher ASA 2 or 3 rates ($P < 0.001$) and significantly higher rates of antithrombotic medications assumption. No difference in terms of lesion location was reported, except for a higher prevalence of rectal lesions in VE-Group (168; 62.5% vs 383; 59.3%) ($P = 0.02$) (▶ **Table 2**). Regarding lesion morphology and superficial pattern, no specific morphology was prevalent in each group; the JNET 2a pattern was more prevalent in the E-Group ($P < 0.001$), whereas the JNET 2b and 3 were more prevalent in the VE-Group ($P = 0.02$ and $P = 0.001$, respectively). Despite lesions being larger in median size in the VE-Group, no procedure time difference was registered ($P = 0.66$). The rate of hospitalization was higher in the VE-Group (202; 75.1% vs 541; 63.4) ($P < 0.001$], without differences in terms of days of hospital stay ($P = 0.27$).

▶ **Table 1** Baseline demographic characteristics of the two cohorts.

	Total population (n = 980)	Very Elderly group (n = 269)	Elderly group (n = 711)	*P* value
Female sex, n (%)	431 (44.0)	120 (44.6)	311 (43.7)	0.81
Age (years), median (IQR)	74 (69–80)	83 (81–85)	72 (68–75)	**< 0.001**
CCI, median (IQR)	4 (3–5)	5 (4–6)	3 (3–4)	**< 0.001**
At least one comorbidity, n (%)	436 (42.7)	159 (59.1)	277 (38.9)	**< 0.001**
Type of comorbidity, n (%)				
▪ Prev MI	79 (10.1)	37 (13.8)	42 (5.9)	**< 0.001**
▪ CHD	88 (9.0)	48 (17.8)	40 (5.6)	**< 0.001**
▪ PVD	76 (7.8)	35 (13.0)	41 (5.8)	**< 0.001**
▪ Prev CVA/TIA	27 (2.8)	15 (5.6)	12 (1.7)	**0.002**
▪ Dementia	18 (1.8)	6 (2.2)	12 (1.7)	0.57
▪ COPD	38 (3.9)	15 (5.6)	23 (3.2)	0.09
▪ Liver disease	8 (0.8)	–	8 (1.1)	0.08
▪ DM	101 (10.3)	39 (14.5)	62 (8.7)	**0.008**
▪ CKD	111 (11.3)	33 (12.3)	78 (11.0)	0.57
▪ Solid tumor	59 (6.0)	14 (5.2)	45 (6.3)	0.51
▪ Leukemia	4 (0.4)	2 (0.7)	2 (0.3)	0.31
▪ Lymphoma	4 (0.4)	1 (0.4)	3 (0.4)	0.91
Multiple comorbidities, n (%)	152 (15.5)	69 (25.7)	83 (11.7)	**< 0.001**
ASA physical status, n (%)				
▪ 1	209 (21.3)	16 (5.9)	193 (27.1)	**< 0.001**
▪ 2	540 (55.1)	133 (49.4)	407 (57.2)	**0.03**
▪ 3	221 (22.6)	114 (42.4)	107 (15.0)	**< 0.001**
▪ 4	10 (1.0)	6 (2.2)	4 (0.7)	**0.02**
Antithrombotic medications, n (%)				
▪ None	601 (61.3)	103 (38.3)	498 (70.0)	**< 0.001**
▪ Aspirin	238 (24.3)	94 (34.9)	144 (20.3)	**< 0.001**
▪ P2Y12 inhibitors	24 (2.5)	11 (4.1)	13 (1.8)	**0.04**
▪ Warfarin	24 (2.5)	13 (4.8)	11 (1.5)	**0.003**
▪ DOAC	93 (9.5)	45 (16.7)	43 (6.0)	**< 0.001**
▪ DAPT	5 (0.5)	3 (1.1)	2 (0.3)	0.26

ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; CHD, chronic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; DOAC, direct anticoagulant; IQR, interquartile range; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischemic attack.

▶ **Table 2** Lesion characteristics and procedure in the two cohorts.

	Very Elderly group (n = 269)	Elderly group (n = 711)	*P* value
Location, n (%)			
▪ Rectum	168 (62.5)	383 (59.3)	**0.02**
▪ Sigmoid colon	33 (12.3)	117 (16.5)	0.12
▪ Descending colon	5 (1.9)	18 (2.5)	0.53
▪ Transverse colon	22 (8.2)	42 (5.9)	0.20
▪ Ascending colon	32 (11.9)	63 (8.9)	0.15
▪ Caecum	9 (3.3)	34 (4.8)	0.32
Morphology (Paris class), n (%)			
▪ 0-Is	42 (15.6)	110 (15.5)	0.95
▪ GH-LST	37 (13.8%)	99 (13.9%)	0.94
▪ GMT-LST	134 (49.8)	321 (45.1)	0.19
▪ NG-LST	56 (20.8%)	181 (25.5%)	0.13
JNET classificiation, n (%)			
▪ 1	1 (0.4)	4 (0.6)	0.7
▪ 2a	92 (34.2)	335 (47.1)	**< 0.001**
▪ 2b	156 (58.0)	352 (49.5)	**0.02**
▪ 3	20 (7.4)	20 (2.8)	**0.001**
Long axis (mm), median (IQR)	40 (30–55)	35 (25–50)	**< 0.001**
Short axis (mm), median (IQR)	30 (20–40)	30 (20–40)	**0.007**
General anesthesia, n (%)	50 (18.6)	163 (22.9)	0.17
ESD technique, n (%)			
▪ C-ESD	104 (38.7)	314 (44.2)	0.13
▪ PCM-ESD	38 (14.1)	75 (10.5)	0.12
▪ TA-ESD	16 (5.9)	58 (8.2)	0.24
▪ T-ESD	78 (29.9)	161 (22.6)	**0.04**
▪ H-ESD	33 (12.3)	103 (14.5)	0.37
Procedure time (minutes), median (IQR)	90 (57–120)	90 (60–125)	0.66
Hospitalization, n (%)	202 (75.1)	451 (63.4)	**0.001**
Length of hospital stay (days), median (IQR)	3 (2–4)	2 (2–4)	0.27

C, conventional; ESD, endoscopic submucosal dissection; GH-LST, granular homogeneous lateral spreading tumor; GMT-LST, granular mixed type lateral spreading tumor; H, hybrid; IQR, interquartile ranges; JNET, Japan NBI Expert team; NG-LST, non-granular lateral spreading tumour; PCM, pocket creation method; T, tunnelling; TA, traction assisted.

Procedure outcomes and adverse events: Very elderly vs. elderly group

▶ **Table 3** compares treatment outcomes in the two cohorts.

En bloc (92.9% vs 94.7%, $P = 0.3$), R0 (87.4% vs 91.6%, $P = 0.05$), and oncological curative resection rates (84% vs 86.1%, $P = 0.4$) did not differ between the VE-Group and E-Group, respectively). Consistently, histopathological characteristics did not differ, except for LVI, which was more prevalent in the VE-Group (14; 5.2% vs 14; 2.0%) ($P = 0.007$]. No statistically significant differences were registered regarding intraprocedural AEs.

Delirium occurrence was higher in the VE-Group than in the E-Group (6; 2.2% vs 1; 0.14%) ($P = 0.001$, OR 16.2, 95% CI 1.9–135.2). All delirium cases occurred in an inpatient setting. Multivariate analysis confirmed that the sole independent risk factor for delirium occurrence was age ≥ 80 years (OR 18.1, 95% CI 2.0–164.0, $P = 0.01$). Other variables, including high anesthe-

▶ **Table 3** Comparison of treatment outcomes between the two cohorts.

	Very Elderly group (n = 269)	**Elderly group (n = 711)**	***P* value**	**OR (95% CI)**
En bloc resection, n (%)	250 (92.9)	673 (94.7)	0.30	
R0 resection, n (%)	235 (87.4)	651 (91.6)	0.05	
Complete defect closure, n (%)	80 (29.7)	238 (33.5)	0.26	
Oncological curative resection, n (%)	226 (84.0)	612 (86.1)	0.41	
Histology, n (%)				
▪ LGD	61 (22.7)	166 (23.3)	0.82	
▪ HGD	147 (54.6)	392 (55.1)	0.89	
▪ pT1a adenocarcinoma	27 (10.0)	69 (0.7)	0.88	
▪ pT1b adenocarcinoma	34 (12.6)	84 (11.8)	0.72	
≥ 1000 μ submucosal invasion	31 (11.5)	65 (9.1)	0.27	
Lymphovascular invasion	14 (5.2)	14 (2.0)	0.007	**2.9 (1.3–6-6)**
High-grade tumor budding	21 (7.8)	34 (4.8)	0.07	
Surgery for histopathology	19 (7.1)	71 (10.0)	0.09	
	CM-group (n = 436)	**H-group (n = 544)**	***P* value**	**OR (95% CI)**
En bloc resection, n (%)	402 (92.2)	521 (95.8)	0.02	**1.4 (1.1–1.7)**
R0 resection, n (%)	383 (87.8)	503 (92.5)	0.02	**1.3 (1.1–1.6)**
Complete defect closure, n (%)	139 (31.9)	179 (32.5)	0.73	
Oncological curative resection, n (%)	365 (83.7)	473 (86.9)	0.2	
Histology, n (%)				
▪ LGD	101 (23.2)	126 (23.2)	0.9	
▪ HGD	232 (53.2)	307 (56.4)	0.3	
▪ pT1a adenocarcinoma	44 (10.1)	52 (9.6)	0.78	
▪ pT1b adenocarcinoma	59 (13.5)	59 (10.8)	0.2	
≥ 1000 μ submucosal invasion	51 (11.7)	45 (8.3)	0.2	
Lymphovascular Invasion	19 (4.4)	9 (1.6)	0.03	**2.5 (1.1–6.0)**
High-grade tumor budding	33 (7.6)	22 (4.0)	0.04	**1.9 (1.1–3.6)**
Surgery for histopathology	41 (9.4)	49 (9.0)	0.8	

HGD, high-grade dysplasia; LGD, low-grade dysplasia; OR, odds ratio.

siologic risk (*P* = 0.60), presence of comorbidities (*P* = 0.38), and general anesthesia (*P* = 0.12), were not significantly associated with delirium occurrence (Supplementary Table 1).

Regarding clinical course, no difference in events of sepsis, fever, heart failure, acute kidney injury, laboratory marker increases, or rehospitalization within 30 days were reported (▶ **Table 4**). One death, which occurred in the E-Group, was registered at the end of follow-up after acute leukemia occurrence.

Procedure outcomes and adverse events: Comorbid vs. healthy group

Overall, 436 (44.5%) belonged to the CM-group and 544 (55.5%) to the H-group, with a difference of 2 points in terms of median CCI (*P* < 0.001). A slight difference in terms of en bloc (402; 92.2% vs 521; 95.8%) (*P* = 0.02, OR 1.4, 95% CI 1.1–1.7) and R0 resection rates (383; 87.8% vs 503; 92.5%)(*P* = 0.02, OR 1.3, 95% CI 1.1–1.6) was found, with a lower proportion in the CM-groups. Conversely, oncological curative resection rates did not differ (▶ **Table 3**).

▶ **Table 4** Comparison of clinical course and AEs between Very Elderly vs Elderly groups and between CM-Group and H-Group.

	Very Elderly Group (n = 269)	**Elderly Group (n = 711)**	***P* value**	**OR (95% CI)**
Sepsis, n (%)	2 (0.7)	5 (0.7)	0.95	
Average time to sepsis (hours), median (IQR)	36 (24–36)	48 (30–48)	0.80	
Fever, n (%)	16 (5.9)	38 (5.3)	0.71	
Average time to fever (hours), median (IQR)	12 (3–24)	12 (2.5–24)	0.88	
CRP increase, n (%)	16 (5.9)	50 (7.0)	0.55	
Average time to CRP increase (hours), median (IQR)	(24 (8–24)	24 (12–24)	0.29	
PCT increase, n (%)	1 (0.4)	9 (1.3)	0.21	
Average time to PCT increase (hours), median (IQR)	24 (8–24)	24 (24–48)	0.6	
HF, n (%)	0	2 (0.3)	0.38	
AKI, n (%)	1 (0.4)	3 (0.4)	0.91	
Intraprocedural AEs, n (%)				
▪ Perforation	10 (3.7)	46 (6.5)	0.10	
▪ Bleeding	16 (5.9)	32 (4.5)	0.35	
▪ Cardiovascular	2 (0.7)	1 (0.1)	0.13	
▪ Pulmonary	2 (0.7)	1 (0.1)	0.13	
▪ Pain	19 (7.1)	43 (6.0)	0.56	
▪ Drug-related	0	1 (0.1)	0.54	
Postprocedural AEs, n (%)				
▪ Perforation	1 (0.4)	6 (0.8)	0.43	
▪ Bleeding	6 (2.2)	36 (5.1)	0.05	
Other events, n (%)				
▪ Cardiovascular	0	2 (0.3)	0.38	
▪ Pulmonary	0	2 (0.3)	0.38	
▪ Delirium	6 (2.2)	1 (0.14)	**0.001**	16.2 (1.9–135.2)
▪ Systemic infections	3 (1.1)	12 (1.7)	0.51	
Rehospitalization within 30 days, n (%)	4 (1.5)	12 (1.7)	0.82	
	CM-Group (n = 436)	**H-Group (n = 544)**	***P* value**	**OR (95% CI)**
CCI, median (IQR)	5 (4–6)	3 (2–4)	***P* < 0.001**	
Sepsis, n (%)	5 (1.1)	2 (0.4)	0.15	
Average time to sepsis (hours), median (IQR)	36 (24–48)	48 (48)	0.53	
Fever, n (%)	40 (9.2)	14 (2.6)	**< 0.001**	**3.8 (2.1–7.1)**
Average time to fever (hours), median (IQR)	12 (2–24)	10 (3.5–30)	0.69	
CRP increase, n (%)	40 (9.2)	26 (4.8)	**0.006**	**2.0 (1.2–3.4)**
Average time to CRP increase (hours), median (IQR)	24 (10.5)	(24)	0.08	
PCT increase, n (%)	8 (1.8)	2 (0.4)	0.02	5.1 (1.1–24.0)
Average time to PCT increase (hours), median (IQR)	36 (24–48)	72 (24–72)	0.53	
HF, n (%)	1 (0.2)	1 (0.2)	0.88	
AKI, n (%)	4 (0.9)	0	0.25	

▶ Table 4 (Continuation)				
Intraprocedural AEs, n (%)				
▪ Perforation	27 (6.2)	29 (5.3)	0.58	
▪ Bleeding	33 (7.6)	15 (2.8)	**0.001**	**2.8 (1.5–5.4)**
▪ Cardiovascular	2 (0.5)	1 (0.2)	0.43	
▪ Pulmonary	3 (0.7)	0	0.05	
▪ Pain	26 (6.0)	36 (6.6)	0.68	
▪ Drug-related	1 (0.2)	0	0.26	
Postprocedural AEs, n (%)				
▪ Perforation	6 (1.4)	1 (0.2)	**0.03**	**7.6 (0.9–63.1)**
▪ Bleeding	22 (5.0)	20 (3.7)	0.29	
Other events, n (%)				
Cardiovascular	1 (0.2)	1 (0.2)	0.88	
Pulmonary	2 (0.5)	0	0.11	
Delirium	5 (1.1)	2 (0.4)	0.15	
Systemic infections	11 (2.5)	4 (0.7)	**0.02**	**3.5 (1.1–11.1)**
Rehospitalization within 30 days, n (%)	10 (2.3)	6 (1.1)	0.14	

AE, adverse event; AKI, acute kidney injury; CCI, Charlson comorbidity index; CM-Group, patients with comorbidities; CRP, C-reactive protein; H-Group, patients without comorbidities; HF, heart failure; IQR, interquartile ranges; OR, odds ratio; PCT, procalcitonin.

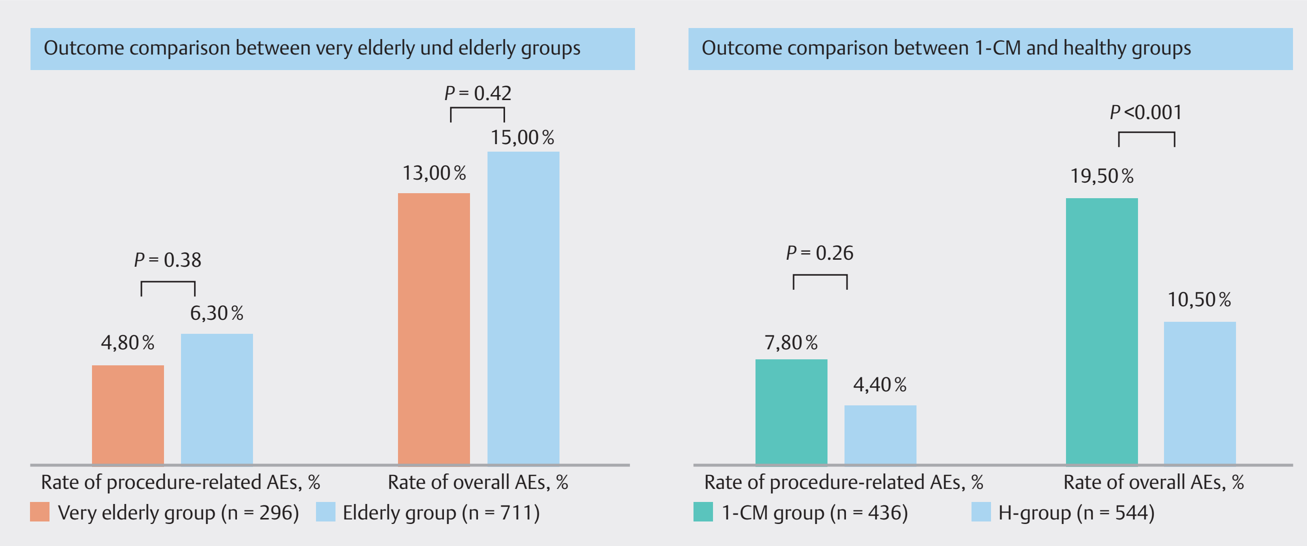
The CM-group showed a higher rate of intraprocedural bleeding [33 (7.6%) vs 15 (2.8%); *P* = 0.001, OR = 2.8 (95% CI: 1.5–5.4)], postprocedural perforation [6 (1.4%) vs 1 (0.2%); *P* = 0.03, OR = 7.6 (95% CI: 0.9–63.1)] compared with H-group. The CM-group had a higher rate of systemic infections [11 (2.5%) vs 4 (0.7%); *P* = 0.02, OR = 3.5 (95% CI: 1.1–11.1)], fever occurrence [40 (9.2%) vs 14 (2.6%); *P* < 0.001, OR = 3.8 (95% CI: 2.1–7.1)], CRP [40 (9.2%) vs 26 (4.8%); *P* = 0.006, OR = 2.0 (95% CI: 1.2–3.4)] and PCT increase [8 (1.8%) vs 2 (0.4%); *P* = 0.02, OR = 5.1 (95% CI: 1.1–24.0)]. The latter results are reported in Table 4. In multivariate analysis, presence of at least one comorbidity was confirmed to be the sole risk factor for intraprocedural bleeding with an OR of 4.2 (95% C: 1.3–14.4; *P* = 0.02), whereas no additional factors were found among those considered potential confounders (such as presence of LVI (*P* = 0.66), HGTB (*P* = 0.11), or antithrombotic medication use (*P* = 0.85) (Supplementary Table 2). Regarding delayed perforation, again, at least one comorbidity was confirmed to be not influenced by confounding factors (OR 11.2, 95% CI 1.3–97.3, *P* = 0.02) such as antithrombotic medications (*P* = 0.25) (Supplementary Table 3).

Evaluation of safety

No difference was reported between VE- and E-groups when procedure-related AEs and overall AEs were assessed. Conversely, the CM-group had a higher rate of overall AEs (60; 13.8% vs 36; 6.6%) (*P* < 0.001, OR 2.3, 95% CI 1.5–3.6). All reported associations are depicted in ▶ **Fig. 1a** and ▶ **Fig. 1b** and summarized in Supplementary Table 4. On linear regression, higher CCI values were not correlated with occurrence of overall AEs (*P* = 0.09). When only the H-group was considered, thus evaluating only the healthy population, patients aged more than 80 years did not show an higher rate of overall AEs compared with those aged 65 to 79 years (*P* = 0.40).

When we performed subgroup analysis, diabetes mellitus and leukemia were associated with occurrence of procedure-related AEs, showing an OR of 2.7 (95% CI 1.4–5.3; *P* = 0.006) and 16.4 (95% CI 2.3–118.8; *P* = 0.02), respectively.

Regarding occurrence of overall AEs, chronic heart disease, a previous cerebrovascular accident, and diabetes showed an OR of 1.8 (95% CI 1.1–3.2; *P* = 0.03), 2.6 (95% CI 1.1–6.0; *P* = 0.04) and 1.8 (95% CI 1.1–2.9; *P* = 0.04).



▶ **Fig. 1** **a** Comparison of procedure-related AEs and overall AE occurrence in very elderly group vs. elderly group. **b** Comparison of procedure-related AEs and overall AE occurrence in 1-Comorbidity group vs. Healthy group.

Discussion

Advanced endoscopic resection techniques such as ESD, have become an integral part of treatment for LNPCPs and are the gold standard in specific settings. With the increase in age of the population, the complexity of those procedures rises due to risks and consequences of possible complications and aesthetic-related AEs [22]. It is, indeed, well known from the literature that elderly patients carry a higher risk of mortality in emergency settings, especially those older than age 80 years [23]. However, many older adults remain in good health despite their age and tend to have a longer-than-average life expectancy [24]. Single-center retrospective data have demonstrated that esophageal and gastric ESD can be a feasible and safe option in patients older than age 80 years [25, 26, 27]. Conversely, most established literature on this topic is based on single-center studies and Asian cohorts [28], with the only one experience on comorbidities being the one of Kim et al. [9], which focused on a Korean population without specifically addressing advanced age. In a setting like third space endoscopy, which has been approaching mini-invasive general surgery in the last few years [29, 30] in terms of possible procedure-related complications and AEs, we conducted this retrospective cohort study on the Western population.

Globally, our 94.2% and 90.4% en-bloc and R0 rates have enabled us to achieve technical success outcomes comparable to those reported in Asian populations, effectively bridging a gap previously identified in the literature [7].

Our findings show that ESD for LNPCPs in a population aged 80 years and older can be feasible and safely performed. En-bloc and oncological curative resection rates were similar between the VE and E-groups, whereas the R0 rate was lower in the VE-Group, even if not significantly.

Interestingly, no differences in terms of procedure-related AEs or overall AEs were registered, except for delirium occurrence: Patients older than age 80 years were 16 times more likely to develop it than those aged 65 to 79 years. When considering procedure safety and overall events evaluation, no difference emerged between those two groups.

When the cohort was divided according to presence of at least one significant comorbidity (CM-group vs H-group), procedure outcomes reached different results: En-bloc and R0 resection rates were significantly different. Interestingly, more intraprocedural and post-procedural complications occurred. Comorbidities were independently associated with a higher risk of intraprocedural bleeding, perforations, and post-procedure systemic infection development (with subsequent elevation of laboratory markers) compared with the H-group. Consequently, when we considered overall AEs, comorbid patients demonstrated a double-fold higher risk of developing them than healthy individuals (Fig. 1b).

Based on the latter results, we can assume that presence of at least one significant comorbidity in patients undergoing colorectal ESD represents a risk factor for overall AEs. Evaluation of CCI, which considers age, did not correlate with this outcome ($P = 0.09$). Consequently, presence of at least one comorbidity and not age can predict an adverse clinical outcome for ESD. When we further evaluated differences between patients aged over 80 and 65 to 79 years among just the healthy population, no differences were noted regarding occurrence of overall events.

A possible explanation for this finding could be the higher relative contribution of specific comorbidities, such as diabetes or cardiovascular diseases, directly impairing tissue healing, predisposing patients to hemodynamic instability, bleeding, or infections [31]. Those factors, rather than age, contribute to patient frailty, which dramatically impacts surgical procedures [32].

Our findings underscore the importance of considering patient-specific factors in procedure management and evaluation, as has also emerged from mini-invasive general surgery studies [33, 34]. Presence of comorbidities likely complicates procedure course, necessitating implementation of comprehensive risk assessment tools and individualized treatment plans to mitigate these risks, such as considering closer monitoring and hospitalization. In our cohort, the VE-Group underwent the procedure mostly in an inpatient setting; however, hospitalization seemed more common in comorbid patients.

Our study is the first large multicenter experience on colorectal ESD procedures performed in a real-life elderly Western population, which has different characteristics from those of Asians, especially regarding baseline clinical features [35, 36] and stratifying for comorbidities. Moreover, the stratified analysis based on age and comorbidities clearly explains these factors impacting postoperative procedure in a real-world population, which is rarely reproducible in randomized controlled trials.

Although our study provides valuable insights into the feasibility and safety of ESD for LNPCPs in older patients, it is not without its limitations. Study limitations include the retrospective design, which could lead to underreport ing ofAEs. However, 75.1% of very elderly patients were hospitalized, and their data were extracted from a prospective database record, which minimizes the possibility of underreporting, at least in this specific population. Another limitation is the lack of long-term follow-up data, which did not allow us to calculate long-term recurrence and mortality rates.

Potential implications of this study in clinical practice are represented by the higher incidence of specific events in comorbid patients, suggesting that preoperative assessment should include detailed evaluations and comprehensive comorbidity assessments. Implementing multidisciplinary prehabilitation programs may improve patient outcomes by optimizing physical readiness before the procedure [37], especially for patients with comorbidities that require complex ESD treatments. Hence, correct procedure planning could allow for optimal resource allocation for patients at risk of a poor clinical course. Regarding elderly populations, which showed an independent higher risk of post-procedur delirium, the research could focus on performing ESD through effective modifications in sedation protocols, which have been proven effective in reducing its occurrence in other fields of surgery [38, 39].

Conclusions

Colorectal ESD can be considered a feasible and safe procedure in elderly patients. Physicians should consider delirium as a possible event in patients older than age 80 years. Presence of comorbidities should drive execution of a comprehensive pre-procedure assessment and post-procedure care to optimize outcomes and minimize complications.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Data availability statement

Data are shareable upon reasonable request by the corresponding author.

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