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Short title: Pouch failures

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ABSTRACT

BACKGROUND The ileal pouch-anal anastomosis is a procedure offered to patients with ulcerative colitis who opt for restoration of bowel continuity. The aim of this study was to determine the risk of pouch failure and ascertain risk factors associated with failure.

METHOD 1,991 patients with ulcerative colitis operated with ileal pouch-anal anastomosis in Denmark in the period 1980–2013 were included. Pouch failure was defined as excision of the pouch or presence of a stoma un-reversed within one year after its creation. We used Cox

proportional hazards regression to explore the association between pouch failure and age, gender, synchronous colectomy, primary fecal diversion, annual hospital volume (very low=1-5 cases/year, low=6-10/year, intermediate=11-20/year, high>20/year), calendar year, laparoscopy, and primary sclerosing cholangitis.

RESULTS Over a median 11.4 years, 295 failures occurred, corresponding to 5-, 10-, and 20-year cumulative risks of 9.1%, 12.1%, and 18.2%, respectively. The risk of failure was higher for females (adjusted hazard ratio [aHR] 1.39, 95% CI: 1.10-1.75). Primary non-diversion (aHR 1.63, 95% CI: 1.11-2.41) and a low hospital volume (aHR, very low-volume vs. high-volume 2.30, 95% CI: 1.26-4.20) were also associated with a higher risk of failure. The risk of failure was not associated with calendar year, primary sclerosing cholangitis, synchronous colectomy, or laparoscopy.

CONCLUSION In a cohort of patients with ulcerative colitis and ileal pouch-anal anastomosis from Denmark, where pouch surgery is centralized, females had a higher risk of pouch failure. Of modifiable factors, low hospital volume and non-diversion were associated with a higher risk of pouch failure.

WHAT DOES THIS PAPER ADD TO THE EXISTING LITERATURE?

Using validated pouch failure definitions in a national cohort of patients with UC and IPAA, we found that omission of diverting ileostomy at the index IPAA operation significantly increased the risk of pouch failure. Within an already established organization of centralized reconstructive IBD surgery, low hospital volume was also associated with an increased risk of failure. Furthermore, females had a higher risk of pouch failure.

INTRODUCTION

The gold standard of intestinal reconstructive surgery in *ulcerative colitis* (UC) is a restorative proctocolectomy with *ileal pouch-anal anastomosis* (IPAA), which is preferred by most patients to avoid the social stigmatization and morbidity associated with the presence of a stoma. Long-term pouch function is excellent for 90-95% of patients who retain their pouch(1-4) and remains relatively stable over time.(5,6) However, a poor functional result or pouch-related complications may force permanent fecal diversion with or without pouch

excision and therefore by definition failure of the pouch. This occurs in approximately 20% of cases depending on the length of follow-up.(7) The most important risk factors for pouch failure are pelvic sepsis,(8-11) *Crohn's disease* (CD), chronic antibiotic-resistant pouchitis, and "idiopathic" pouch dysfunction.(9,12,13) Currently, controversy exists as to the importance of timing of the restorative pouch procedure in relation to the colectomy(14) and the merits of temporary fecal diversion to reduce the risk of failure of the pouch are debated.(15-18)

While specialization of surgery has been found to improve perioperative outcomes for a wide variety of procedures, especially in the treatment of malignant conditions,(19,20) the benefits of specialization in primary pouch surgery are less documented, since most studies examining risk factors for pouch failure are single-center cohort studies.(7) Of the existing multicenter, national cohort studies on pouch failure, two are limited by short follow-up (median 4.8 and 5.4 years, respectively)(21,22) while a third used a non-validated administrative claims code of abdominoperineal excision to define pouch failure.(23) The aim of this study was to ascertain the long-term risk of pouch failure covering more than three decades in a national cohort of patients with UC using validated failure definitions. The impact of several variables on the risk of failure was also explored.

METHOD

We conducted this national cohort study covering the period 1980-2013 using a previously defined IPAA cohort, as described below. Individual level data were linked using the civil registration number, which is a unique 10-digit personal identifier assigned to all Danish citizens at birth or upon emigration by the Civil Registration System(24) (CRS). Vital status was also obtained through the CRS.

The study was approved by the Danish Data Protection Agency under file number 1-16-02-315-15 and followed the principles described in the STROBE guidelines.(25)

STUDY COHORT

Patients operated in the period 1980-2010

The different data sources used to construct the overall cohort are depicted in the flowchart (Figure 1). In the period 1980-2010, UC patients with IPAA were identified from a

previously established national cohort.(26) To determine the consecutive order of surgical stages with corresponding operation dates for each individual patient, data from the Danish *National Patient Registry* (NPR) were retrieved for this cohort. The NPR contains information on all in-hospital contacts in Denmark since 1977 and on out-patient contacts since 1995. (27) For each contact, diagnoses based on the *International Classification of Diseases* (ICD) 8th and 10th revisions are recorded with admission and discharge dates. Procedures were initially coded using consecutive editions of the Danish Classification of Surgical Procedures and Therapies until replaced by the *Nordic Medico-Statistical Committee Classification of Surgical Procedures* (NOMESCO) classification in 1996.

Codes for hospital and department are also recorded for each contact, which is ultimately linked to the individual person by the civil registration number.

The index IPAA operation was defined when a procedure code or a cluster of procedure codes which corresponded to IPAA surgery were registered (See suppl. Table I). If this procedure was preceded by a colectomy, the index procedure was defined as a completion proctectomy with IPAA. The occurrence of an ileostomy reversal following the index date was used to define the IPAA as being primarily diverted. In cases where no procedure codes for ileostomy reversal were registered following IPAA, manual chart reviews for each patient were performed in order to ascertain the true prevalence of primarily non-diverted procedures.

If procedure codes for the IPAA procedure were missing, hospital charts were scrutinized for the missing information.

Patients were excluded if no information on the date of the primary index procedure could be obtained in any way or if the IPAA operation was performed after a diagnosis of anal, rectal, or rectosigmoid cancer.

Patients operated in the period 2010-2013

Data on patients operated in the period 2010–2013 were collected from four national pouch centers' prospectively maintained surgical databases, where local access to the patients' hospital charts ensured correct classification of procedures and dates. Because pouch surgery has been centralized at these four departments in the period 2010–2013, nationwide capture of all patients operated in this period was guaranteed.

Outcome

Failure was defined as a procedure code in the NPR of pouch excision, a rectal resection/ excision following the index date or as the creation of a stoma that was not reversed within one year. Therefore, cases of primarily diverted pouches that were not reversed within one year were included (see Suppl. Table II). To assess the validity of the failure definition, we manually scrutinized hospital charts for 724 patients operated at Odense and Aarhus and compared the occurrence of failures with those obtained via the NPR for the equivalent observation periods. By this approach we found a sensitivity of 93.8% (95% CI: 87.7-97.5) and a specificity of 96.9% (95% CI: 95.2-98.1) for the failure definition.

Covariates

Laparoscopic IPAA procedures, including robot-assisted, were introduced in Denmark in 2009 and has only been performed at three centers (Odense, Hvidovre, Aarhus) (personal communication). Information on surgical approach was therefore derived directly from the pouch centers' surgical databases, while all IPAA procedures performed in 1980-2008 were *de facto* open procedures.

The study period was divided into three full decades (1980-1989, 1990-1999, 2000-2009). The fourth period covered the time from 2010–2013.

Based on the between-hospital differences in average annual pouch procedures performed per year, we categorized hospital volume in very low (1-5 cases/ year), low (6-10 cases/ year), intermediate (11-20 cases/ year), and high (>20 cases/ year). For this categorization, we divided the total number of procedures performed at a department with the total number of calendar years where pouch procedures were performed.

A diagnosis of *primary sclerosing cholangitis* (PSC) at any point during the full observation period was included as an explanatory variable (see Suppl. Table III).

We defined treatment with biological medicine within 12 weeks preceding the index date as the occurrence of at least one code for biological treatment in this period, regardless of the total number of treatments received (Suppl. Table I). Treatment with biological medicine has been registered in the NPR since 2001.

STATISTICAL ANALYSIS

Continuous variables are presented as mean (SD) or median (range), depending on distribution, while numbers (percent) describe categorical and binary variables. Patients were followed from the date of IPAA until the event of pouch failure, death, immigration, or May 10th 2016, whichever came first. The risk of pouch failure at 5, 10, and 20 years after the index date were calculated with 95% confidence interval, treating death as a competing risk. We also calculated crude incidence rates (IR) and incidence rate ratios (IRR) on univariate analysis, and adjusted hazard ratios (aHR) with 95% confidence intervals using Cox regression analyses. Age, gender, biological treatment within 12 weeks prior to pouch surgery, annual hospital volume, laparoscopic approach, synchronous colectomy, and fecal diversion at the index pouch operation were included as time-fixed explanatory variables, while a diagnosis of PSC was included as a time-dependent variable. The assumption of proportional hazards was assessed using Schoenfeld residuals, and it was not violated. Sensitivity analysis was performed using only pouch excisions to define pouch failure due to concerns that the formation of an ileostomy could be unrelated to pouch-specific problems. As a proxy for changes in the demographics of patients having IPAA performed over time, we evaluated differences in age distributions over the defined time periods.

Failure-free survival was illustrated as cumulative risks for the entire cohort, and also categorized by hospital volume, and diverting ileostomy.

All analyses were performed using Intercooled Stata 13 (College Station, TX: StataCorp LP).

RESULTS

In the period 1980–2013, 1,992 patients with UC had primary IPAA surgery performed (Figure 1). One patient was excluded due to an unidentifiable civil registration number, leaving 1,991 patients in the cohort. Of these, 1,512 (75.9%) IPAAs were performed on patients who had previously had a colectomy and 1,850 (92.9%) were primarily diverted. During a median follow-up of 11.4 years, 295 pouch failures occurred (171 pouch excisions and 124 ileostomies) reaching a 5-year risk of 9.1% (95% CI: 7.9-10.4), a 10-year risk of 12.1% (10.7-13.7), and a 20-year risk of 18.2% (16.1-20.4) (Figure 2). The crude IR of failure within the first two postoperative years was 29.8 (24.8-35.8)/ 1000 person years as opposed to 8.4 (7.2-9.7) per 1000 person years in the third and subsequent postoperative years.

Pouch failure IRs, IRRs, and adjusted HRs (aHR) are shown in Table 2. The risk of failure was greatest for females (aHR = 1.39 (95% CI: 1.10-1.75)). Compared to patients who were younger than 20 years at operation, the risk of failure was lower for patients 20-39 years old (aHR = 0.69 (0.51-0.95) and 40-59 years old (aHR = 0.80 (0.56-1.14). The risk was higher for patients older than 59 years compared to patients younger than 20 (aHR = 1.35 (0.57-3.21)). None of the four patients treated with biological treatment within 12 weeks before IPAA experienced failure, while patients who had their IPAA performed as a completion proctectomy had a statistically non-significantly lower risk of failure compared to patients who had a restorative proctocolectomy with IPAA (aHR = 0.86 (0.66-1.12)). The use of primary fecal diversion was associated with a lower risk of failure (aHR = 0.61 (0.41-0.90), corresponding to an aHR for primary non-diversion = 1.63 (1.11-2.41)) (Figure 3). A minimally invasive approach had no significant effect on the risk of failure (aHR = 1.25 (0.65-2.43)), and the risk did not change significantly over the consecutive historical periods (years 2010-2013 compared to 1980-1989, aHR = 1.09 (0.60-1.98)). Patients operated at a low or intermediate-volume center had a greater risk of failure compared to patients operated at a high-volume center (aHR = 1.59 (1.17-2.16) and aHR = 1.63 (1.19-2.25), respectively), while the risk was even greater for patients operated at a very low-volume center (aHR = 2.30 (1.26-4.20)) (Figure 4). Analyzing annual hospital volume as a continuous variable gave an aHR of 0.96 (0.94-0.98), corresponding to a decrease in the risk of failure of 4% (95% CI: 2%-6%) for every additional IPAA procedure performed per year. A diagnosis of PSC did not affect the risk of pouch failure (aHR = 0.65 (0.16-2.62)).

For the sensitivity analysis defining pouch failure as the occurrence of pouch excisions only, aHRs were virtually similar to those of the main analysis (data not shown). The proportion of patients who were older than 40 years at operation in the period 1980-1989 was 16%, increasing over time to 34% in the period 2010-2013 (Figure 4).

DISCUSSION

Since its introduction in the late 1970s,(28) the IPAA has gained widespread acceptance and popularity as the procedure of choice for restoration of bowel continuity in UC, offering an acceptable bowel function for most patients. The ultimate consequence of pouch dysfunction is the creation of a diverting ileostomy with or without excision of the pouch itself, and with this study we found that the risk of failure in Denmark over the past three decades at five and

ten years were 9.1% and 12.1%, respectively, comparable to results from high-volume specialist centers.(5,12)

We identified several covariates associated with pouch failure that could aid clinicians in the pre-procedural planning of IPAA surgery. The correlation between annual hospital volume and pouch failure has important implications, as it suggests that surgical expertise and accrued experience with perioperative care and management of complications benefits patients, even within an already established organization of centralized reconstructive IBD surgery.

Routine fecal diversion in primary pouch surgery is currently debated,(29,30) but we showed that primarily non-diverted pouches had a significantly higher risk of failing. Our data precluded any evaluation of the indications for loop ileostomy omission, but a direct causal link to a greater occurrence of postoperative complications cannot be dismissed. While the only randomized controlled trial of loop ileostomy omission in IPAA surgery with only 45 patients found no difference in the occurrence of complications,(17) a meta-analysis of high-quality observational studies found an increased risk of anastomotic leakage associated with ileostomy omission. This risk was however not mirrored in an increased risk of pouch failure, presumably because of a small sample size with just 11 failures in 347 cases combined.(31) The risk of pouch failure illustrated in figure 3 does nonetheless suggest that the greatest effect of temporary fecal diversion is during the first few postoperative years, possibly owing to differences in early surgical complications. In fact, the higher risk of pouch failure within the initial two postoperative years for the entire cohort indicates a substantial impact of early surgical complications on the risk of failure.

The low median age at operation and low proportion of patients treated with biological medicine prior to IPAA in addition to most of the procedures being performed as completion proctectomies consolidate the notion that patients in Denmark in general are selected and physiologically fit before being submitted to IPAA surgery. The major increase in the absolute number of procedures performed over the historical cohorts (Table 1) and the absence of lower hazard ratios of failure over time does however indicate that a greater proportion of patients who have had a colectomy have pouch surgery performed today. Growing experience with the procedure and positive publicity have possibly spurred an increasing request for restoration of bowel continuity in the IBD population and it is likely surgeons have a less selective approach to patients today compared to when the procedure was still considered experimental in the 1980s. This hypothesis is also supported by a two-

fold increase (from 16%–34%) in the proportion of patients who were older than 40 years at the operation in recent years compared to earlier (Figure 2) and this case-mix may to some degree have countered the positive effects of gained surgical expertise on failure risk over time.

Females were found to have a 39% greater risk of failure over time in our study than men. The reasons for this significant difference were not explored, but previous studies have found that fistula formation more often affects women,(32) just like vaginal child births have a detrimental impact on pouch function(33) and subsequently failure risk. In Denmark, elective caesarian section is standard practice for female IPAA patients, and so, vaginal delivery is unlikely to explain the greater risk of pouch failure for females. A cross-sectional Danish study from 2012 evaluating pouch function in a cohort including most of the patients from the present study found that a greater proportion of women suffered from severe pouch dysfunction compared to men.(34) Our results indicate that the poorer function and greater occurrence of fistulas are reflected in a greater risk of pouch failures.

Methodological considerations

We did not have information concerning preoperative steroid use, body mass index, type of anastomosis (handsewn vs. stapled), pouch design (J, W, S, etc.) or rectal dissection method, all of which may have an impact on the risk of pouch failure.(8,35,36) Pelvic sepsis is considered the most important determinant of pouch failure, (10,11) but the use of procedure codes and diagnostic codes from health registries does not allow a sufficiently specific ascertainment of postoperative complications. Although we used valid data with documented high sensitivity and specificity for pouch failure, the validity of PSC diagnoses and treatment with biological medicine from registry data has not been evaluated.

In the present study, we regarded all patients as having a definitive preoperative diagnosis of UC, because CD is generally considered a contraindication to IPAA surgery. However, the use of administrative data does not give sufficient insight to the careful evaluation and selection of patients that typically have taken place before IPAA surgery. Consequently, some of the patients included in the present series will probably have a preoperative diagnosis of indeterminate colitis, but since this diagnosis was first added to the ICD-classification in 2009 and its validity is uncertain it was not included as a potential risk factor for pouch

failure. While the validity of IBD diagnoses in the NPR has proven excellent,(37) a protocolled assessment of all cases would be necessary to sufficiently classify patients as having 'indeterminate colitis' and determine the effect of this diagnosis on failure risk.

Information on the reasons for pouch failure were not available in this study. Of note, the reasons for failure may not have been pouch-related for all the 124 patients, whose failure was defined as a stoma left unreversed for at least one year and this could potentially bias a presumed causal effect between the explanatory variables and pouch failure towards null. Limiting our definition of pouch failure to only pouch excisions did however reveal similar associations, indicating that substantial bias was not introduced by including unreversed stomas to our pouch failure definition.

In conclusion, the risk of pouch failure was 9.1% at 5 years and 12.1% at 10 years in this national cohort, which is comparable to international high-volume specialist centers. Low annual hospital volume, primary non-diversion, and female gender were factors associated with a significantly increased risk of failure.

REFERENCES

(1) Michelassi F, Lee J, Rubin M, et al. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: a prospective observational study. Ann Surg 2003 Sep;238(3):433-41; discussion 442-5.

(2) Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg 1995 Aug;222(2):120-127.

(3) Berndtsson I, Lindholm E, Oresland T, et al. Long-term outcome after ileal pouch-anal anastomosis: function and health-related quality of life. Dis Colon Rectum 2007 Oct;50(10):1545-1552.

(4) Delaney CP, Fazio VW, Remzi FH, et al. Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis. Ann Surg 2003 Aug;238(2):221-228.

(5) Meagher AP, Farouk R, Dozois RR, et al. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998 Jun;85(6):800-803.

(6) Hahnloser D, Pemberton JH, Wolff BG, et al. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg 2007 Mar;94(3):333-340.

(7) Hueting WE, Buskens E, van der Tweel I, et al. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. Dig Surg 2005;22(1-2):69-79.

(8) MacRae HM, McLeod RS, Cohen Z, et al. Risk factors for pelvic pouch failure. Dis Colon Rectum 1997 Mar;40(3):257-262.

(9) Korsgen S, Keighley MR. Causes of failure and life expectancy of the ileoanal pouch. Int J Colorectal Dis 1997;12(1):4-8.

(10) Fazio VW, Tekkis PP, Remzi F, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. Ann Surg 2003 Oct;238(4):605-14; discussion 614-7.

(11) Prudhomme M, Dehni N, Dozois RR, et al. Causes and outcomes of pouch excision after restorative proctocolectomy. Br J Surg 2006 Jan;93(1):82-86.

(12) Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. Ann Surg 2003 Aug;238(2):229-234.

(13) Gemlo BT, Wong WD, Rothenberger DA, et al. Ileal pouch-anal anastomosis. Patterns of failure. Arch Surg 1992 Jul;127(7):784-6; discussion 787.

(14) Zittan E, Wong-Chong N, Ma GW, et al. Modified Two-stage Ileal Pouch-Anal Anastomosis Results in Lower Rate of Anastomotic Leak Compared with Traditional Two-stage Surgery for Ulcerative Colitis. J Crohns Colitis 2016 Jul;10(7):766-772.

(15) Sahami S, Buskens CJ, Fadok TY, et al. Defunctioning Ileostomy is not Associated with Reduced Leakage in Proctocolectomy and Ileal Pouch Anastomosis Surgeries for IBD. J Crohns Colitis 2016 Jul;10(7):779-785.

(16) Gorfine SR, Gelernt IM, Bauer JJ, et al. Restorative proctocolectomy without diverting ileostomy. Dis Colon Rectum 1995 Feb;38(2):188-194.

(17) Grobler SP, Hosie KB, Keighley MR. Randomized trial of loop ileostomy in restorative proctocolectomy. Br J Surg 1992 Sep;79(9):903-906.

(18) Galandiuk S, Wolff BG, Dozois RR, et al. Ileal pouch-anal anastomosis without ileostomy. Dis Colon Rectum 1991 Oct;34(10):870-873.

(19) Borowski DW, Kelly SB, Bradburn DM, et al. Impact of surgeon volume and specialization on short-term outcomes in colorectal cancer surgery. Br J Surg 2007 Jul;94(7):880-889.

(20) Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998 Nov 25;280(20):1747-1751.

(21) Nordenvall C, Olen O, Nilsson PJ, et al. The Fate of Reconstructive Surgery Following Colectomy for Inflammatory Bowel Disease in Sweden: A Population-based Cohort Study. J Crohns Colitis 2016 Mar 14.

(22) Burns EM, Bottle A, Aylin P, et al. Volume analysis of outcome following restorative proctocolectomy. Br J Surg 2011 Mar;98(3):408-417.

(23) Kennedy ED, Rothwell DM, Cohen Z, et al. Increased experience and surgical technique lead to improved outcome after ileal pouch-anal anastomosis: a population-based study. Dis Colon Rectum 2006 Jul;49(7):958-965.

(24) Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014 Aug;29(8):541-549.

(25) von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007 Oct 16;147(8):573-577.

(26) Brandsborg S, Tottrup A, Nicholls J, et al. Restorative proctocolectomy in patients with ulcerative colitis: a cross-sectional Danish population study on function and quality of life. Colorectal Dis 2013 Aug;15(8):e453-61.

(27) Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015 Nov 17;7:449-490.

(28) Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978 Jul 8;2(6130):85-88.

(29) Sugerman HJ, Sugerman EL, Meador JG, et al. Ileal pouch anal anastomosis without ileal diversion. Ann Surg 2000 Oct;232(4):530-541.

(30) Peirce C, Remzi FH. Operative Strategy, Risk Factors for Leak, and the Use of A Defunctioning Ileostomy with Ileal Pouch-Anal Anastomosis: Let's Not Divert from Diversion and the Traditional 3-Stage Approach for Inflammatory Bowel Disease. J Crohns Colitis 2016 Jul;10(7):755-757.

(31) Weston-Petrides GK, Lovegrove RE, Tilney HS, et al. Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. Arch Surg 2008 Apr;143(4):406-412.

(32) Kjaer MD, Kjeldsen J, Qvist N. Poor Outcomes of Complicated Pouch-Related Fistulas after Ileal Pouch-Anal Anastomosis Surgery. Scand J Surg 2015 Oct 27.

(33) Remzi FH, Gorgun E, Bast J, et al. Vaginal delivery after ileal pouch-anal anastomosis: a word of caution. Dis Colon Rectum 2005 Sep;48(9):1691-1699.

(34) Brandsborg S, Nicholls RJ, Mortensen LS, et al. Restorative proctocolectomy for ulcerative colitis: development and validation of a new scoring system for pouch dysfunction and quality of life. Colorectal Dis 2013 Dec;15(12):e719-25.

(35) Shen B, Fazio VW, Remzi FH, et al. Risk factors for diseases of ileal pouch-anal anastomosis after restorative proctocolectomy for ulcerative colitis. Clin Gastroenterol Hepatol 2006 Jan;4(1):81-9; quiz 2-3.

(36) Heuschen UA, Hinz U, Allemeyer EH, et al. Risk factors for ileoanal J pouch-related septic complications in ulcerative colitis and familial adenomatous polyposis. Ann Surg 2002 Feb;235(2):207-216.

(37) Fonager K, Sorensen HT, Rasmussen SN, et al. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. Scand J Gastroenterol 1996 Feb;31(2):154-159.

Baseline	Number (percent)
Number of patients	1,991
Age at operation, mean (SD)	33.3 (11.9)
Age groups:	
- < 20 years	266 (13.4)
- 20 – 39 years	1,164 (58.5)
- 40 – 59 years	526 (26.4)
- > 59 years	35 (1.8)
Male gender	1,037 (52)
Biological treatment within 12 weeks before IPAA	4 (0.2)
Primary sclerosing cholangitis	47 (2.4)
Annual hospital volume (number of patients):	
- ≤ 5 (2 hospitals)	47 (2.4)
- 6-10 (3 hospitals)	535 (26.8)
- 11-19 (2 hospitals)	766 (38.5)
- ≥ 20 (1 hospital)	643 (32.3)
Restorative proctectomy	1,511 (75.9)
Primary diverting ileostomy	1,849 (92.9)
Laparoscopic procedures	165 (8.3)
Operations performed by time period:	
- 1980-1989	204 (10.3)
- 1990-1999	613 (30.8)
- 2000-2010	811 (40.7)
- 2011-2013	363 (18.2)
Observation time, median (interquartile range)	11.4 (5.9-18.7)
Pouches excised	171 (8.6)
Permanent ileostomy (with pouch in situ)	124 (6.2)

Table 1. Characteristics of the cohort. SD; standard deviation, NPR; Danish National Patient Registry.

Variable	Incidence rates (IR) for failure, pr. 1000 person years	Incidence rate ratios (IRR) for failure	Cox proportional hazards regression (HR)
Gender:			
- Male	9.7 (8.2-11.6)	Reference	Reference
- Female	13.8 (11.8-16.0)	1.41 (1.12-1.79)	1.39 (1.10-1.75)
Age group:			
- < 20 years	15.6 (11.9-20.5)	Reference	Reference
- 20 – 39 years	10.2 (8.8-11.9)	0.65 (0.48-0.91)	0.69 (0.51-0.95)
- 40 – 59 years	12.7 (10.1-16.0)	0.81 (0.56-1.18)	0.80 (0.56-1.14)
- > 60 years	21.9 (9.8-48.8)	1.40 (0.49-3.26)	1.35 (0.57-3.21)
Biological treatment within 12 weeks before operation:			
No	11.7 (10.4-13.1)	Reference	Reference
Yes	NA	NA	NA
Primary sclerosing cholangitis:			
No	11.7 (10.5-13.2)	Reference	Reference
Yes	5.9 (1.5-23.5)	0.50 (0.06-1.83)	0.65 (0.16-2.62)
Restorative procedure:			
Restorative proctocolectomy with IPAA	12.4 (10.0-15.2)	Reference	Reference
Restorative proctectomy with IPAA	11.4 (9.9-13.0)	0.92 (0.71-1.19)	0.86 (0.66-1.12)
Primary diverting ileostomy:			
No	21.5 (15.0-30.7)	Reference	Reference
Yes	11.1 (9.8-12.5)	0.52 (0.35-0.78)	0.61 (0.41-0.90)
Laparoscopy:			
No	11.4 (10.1-12.8)	Reference	Reference
Yes	22.1 (13.1-37.4)	1.94 (1.05-3.32)	1.25 (0.65-2.43)
Time period:			
- 1980-1989	9.0 (6.8-12.1)	Reference	Reference
- 1990-1999	10.4 (8.6-12.5)	1.15 (0.81-1.66)	1.18 (0.81-1.74)
- 2000-2009	13.5 (11.2-16.3)	1.49 (1.04-2.16)	1.20 (0.79-1.82)
- 2010-2013	19.5 (13.6-27.9)	2.16 (1.31-3.50)	1.09 (0.60-1.98)
Annual hospital volume:			
≥20	8.0 (6.3-10.1)	Reference	Reference
11-19	14.9 (12.4-17.8)	1.87 (1.37-2.55)	1.59 (1.17-2.16)
6-10	12.0 (9.8-14.7)	1.50 (1.09-2.09)	1.63 (1.19-2.25)
≤ 5	14.0 (8.5-23.3)	1.76 (0.93-3.11)	2.30 (1.26-4.20)

Table 2. Risk of pouch failure. NA; not applicable (no events in exposed group), NPR; Danish National Patient Registry.

Figure 1. Flowchart of UC patients operated with IPAA in Denmark 1980-2013. *Cancer diagnoses refers to rectal, rectosigmoid, and anal cancer diagnosed before the operation.
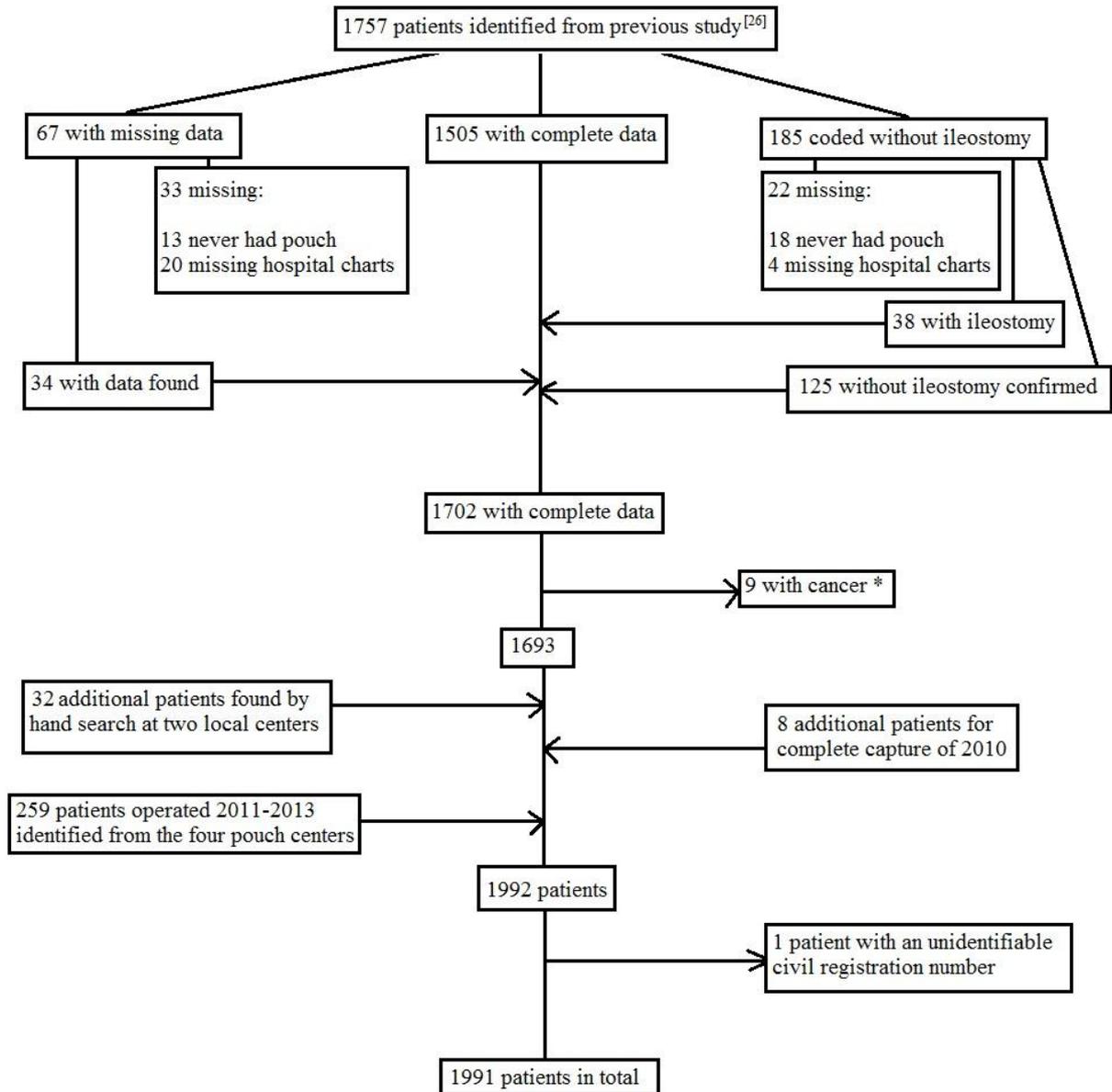
Figure 2. Cumulative risk of pouch failure for the entire cohort. Grey lines indicate upper and lower 95% confidence limits.

Figure 3. Cumulative risk of failure, primary diverted pouches (grey) versus non-diverted (dashed black).
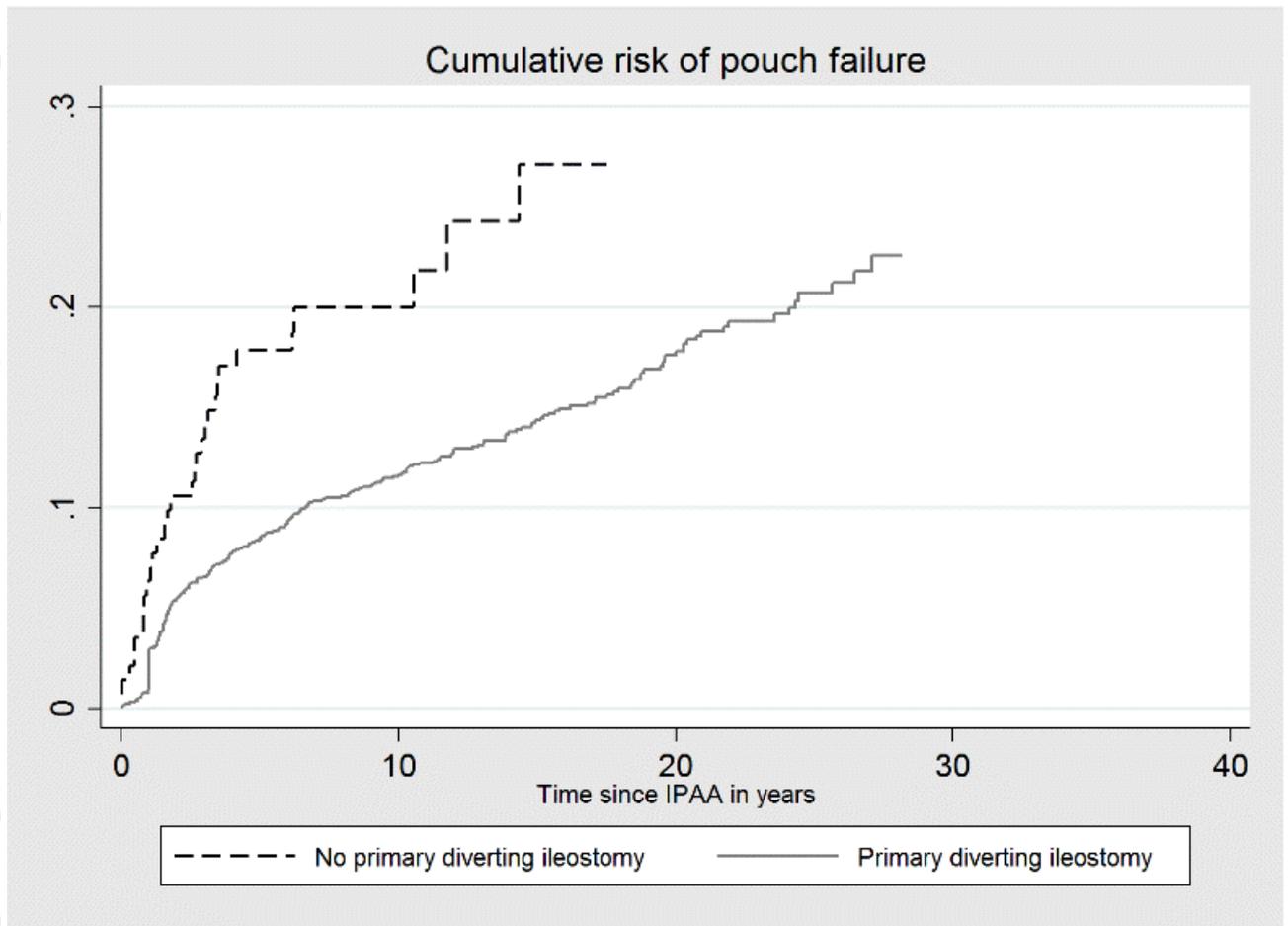

Cumulative risk of pouch failure

Figure 4. Cumulative risk of failure according to average annual hospital volume, ≤5/ year (dashed black), 6-10/ year (solid black), 11-19/ year (solid grey), ≥20/ year (dashed grey).

Cumulative risk of pouch failure

Time since IPAA in years

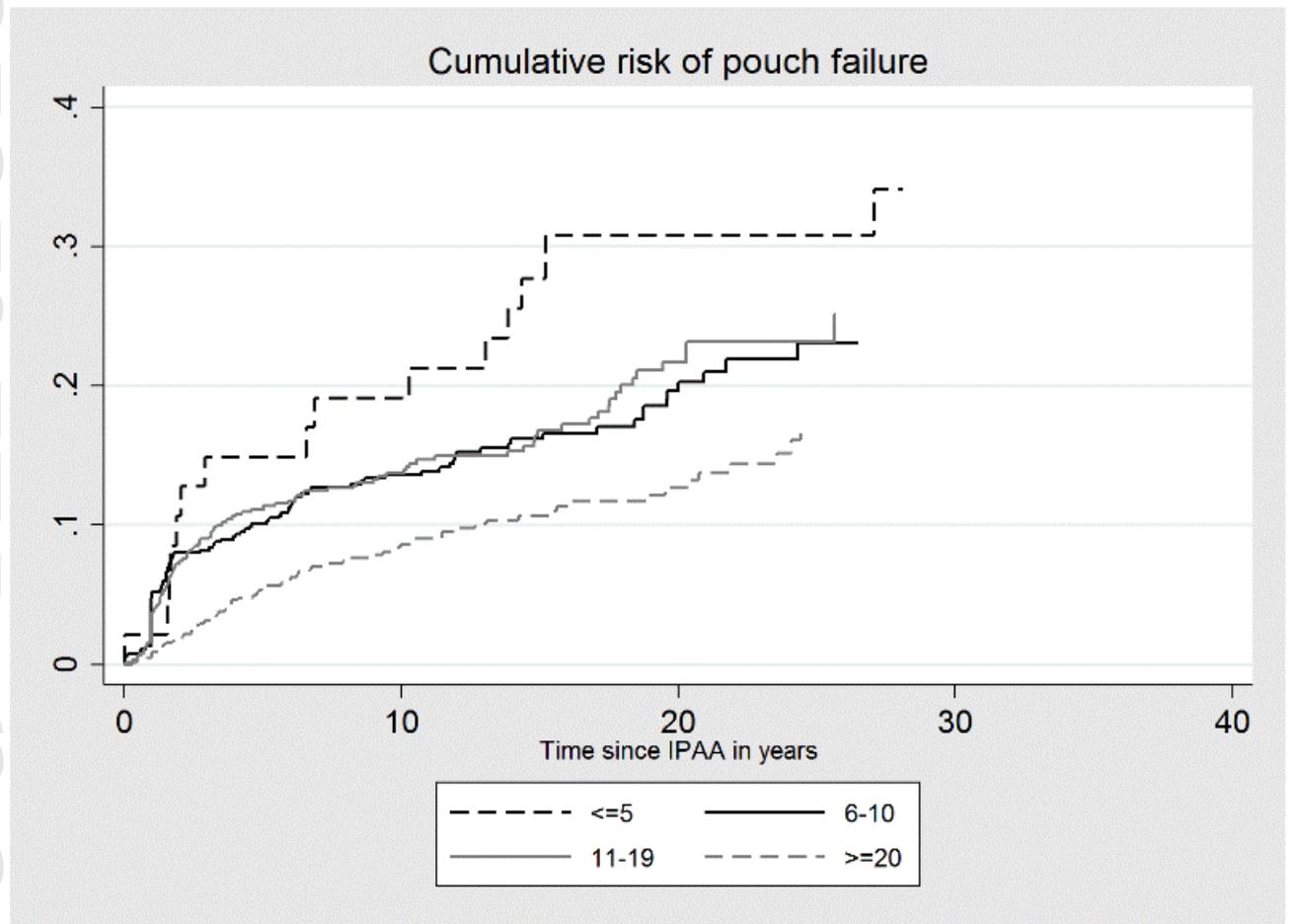|			
- - - -	<=5	———	6-10
———	11-19	- - - -	>=20

Figure 5. Changes in age distribution at the IPAA operation over time.