Original Article

Risk of Mortality after Colonoscopy in Taiwan: A Nationwide Population-Based Nested Case-Control Study

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Purpose. Colonoscopic perforation is widely recognized as one of the most serious complications of lower gastrointestinal endoscopy procedures. Using the National Health Insurance Research Database, this study aimed to assess the incidence and risk factors associated with mortality after colonoscopic perforation in Taiwan.

Methods. Data was collected from the National Health Insurance Research Database over an 10-year period. Variables were analyzed with Pearson's chi-squared test and Fisher's exact test. Risk factors for mortality were examined using the adjusted hazard ratio. Kaplan-Meier analysis was performed to compare survival of patients after colonoscopic perforation.

Results. A total of 307 patients with colonoscopic perforation comprised the study cohort, and 103,505 patients without colonoscopic perforation comprised the control cohort. The rate of colonoscopic perforation within 30 days was 0.3% (307/103,812). The overall mortality rate within 30 days in patients with colonosopic perforation was 3.91% (12/307). Based on the multivariate analysis results, males, older patients, and patients with comorbidities (e.g., diabetes mellitus, end-stage renal disease, stroke, diverticulitis) and post-polypectomy showed an increased risk of mortality after colonoscopic perforation.

Conclusions. Based on a retrospective follow-up study in Taiwan, males, elderly patients, and patients with comorbidities and post-polypectomy had an increased risk of mortality after colonoscopic perforation. Further studies are needed to confirm the association and the underlying mechanisms.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2020;31:229-245*]

Key Words
Mortality;
Colonoscopic perforation;
National Health Insurance Research Database;
Retrospective cohort study

Received: May 11, 2020. Accepted: July 8, 2020.

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Colorectal cancer (CRC) is the most commonly diagnosed cancer and the third leading cause of cancer-related death in Taiwan. It can be prevented by regular screening. Colonoscopy is a screening tool used to detect and prevent CRC and other cancers of the colon. It plays an important role in the diagnosis and management of benign colorectal diseases and in the prevention of colon cancer.[1-3] Precancerous polyps of the colon can be removed via colonoscopy before they progress into cancer.

Colonoscopy is generally considered as a safe procedure; however, potential complications include intestinal perforation, bleeding, post-polypectomy electrocoagulation syndrome, adverse anesthetic reaction, and infection.[4-6] Although iatrogenic perforation is a rare complication, it is associated with high morbidity and mortality rates.[7-10] This unpleasant complication can necessitate surgery and lead to stoma formation, intra-abdominal sepsis, a prolonged hospital stay, and death. Total mortality following iatrogenic colonoscopic perforation (CP) ranges from 0% to approximately 0.65% in the United States.[11]

Iatrogentic perforation, which can result from colonoscopy, may be managed with conservative treatment or surgical intervention depending on the nature of the perforation. CP occurs due to one of three mechanisms: mechanical forces from the endoscope, barotrauma from air insufflation, or as a direct result of a therapeutic procedure (e.g., polypectomy). Knowing the risk factors, recognizing early signs of perforation, and providing early and optimal treatment may reduce the incidence of morbidity and mortality after CP.

In this study, we report a nationwide population-based nested case-control study to assess the risk factors of mortality after CP in Taiwan.

Materials and Methods

Data source

Data was obtained from Taiwan's National Health Insurance Research Database (NHIRD), a large database provided by single-payer, universal, compulsory healthcare system for the ~23.7 million residents in Taiwan. The NHIRD contains comprehensive information, such as demographic data, inpatient and ambulatory claims, prescription claims, surgeries, and other medical procedure claim records. Diseases in the database are defined according to the International Classification of Disease, 9th Revision (ICD-9) codes. The NHIRD has been previously used for epidemiologic research, and information on diagnoses, prescriptions, and hospitalizations is of a high quality.[12,13] This study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH IRB No. 2-105-05-082; Taipei, Taiwan).

Study design and setting

This study is a population-based nested case-control study. Patients were retrospectively enrolled if they were ≥ 18 years of age and underwent an inpatient or outpatient colonoscopy procedure at any facility within the NHIRD during the period from 2000 to 2010 in Taiwan. The NHIRD contains registration files and original claim data for reimbursement. Large computerized databases derived from this system by the National Health Insurance Administration [formerly the Bureau of National Health Insurance] and the Ministry of Health and Welfare [formerly the Department of Health] in Taiwan and maintained by the National Health Research Institutes in Taiwan were made accessible to scientists in Taiwan for research purposes.

The study included the diagnosis of CP and used the ICD-9 codes 569.83 and 998.2, which are defined as intestinal perforation and accidental puncture or laceration during a procedure, respectively, 30 days after colonoscopy. Both inpatient and outpatient procedures were included. Data obtained from the electronic health records included age at colonoscopy, gender, season, location (i.e., northern Taiwan, middle Taiwan, southern Taiwan, eastern Taiwan, or outlet islands), level of urbanization (1-4), level of care (i.e., hospital center, regional hospital, local hospital), operator specialty (i.e., surgeon or gastroenterologist), and indications for colonoscopy (identified by procedure codes in the colonoscopy report). Race was not assessed in this study.

The exclusion criteria were as follows: (1) a history of cancer in the colon or rectum; (2) a history of inflammatory bowel disease; (3) previous colon surgery; (4) perforation before colonoscopy; (5) age, < 18 years; and (6) unknown gender. Comorbidities were also assessed, such as a history of hypertension, hyperlipidemia, coronary artery disease, diabetes mellitus, end-stage renal disease, chronic obstructive pulmonary disease, stroke, diverticulitis, and cancer.

Statistical analysis

The distribution of sociodemographic data and comorbidities were compared between the CP cohort and the control cohort using the chi-squared test to examine categorical variables and the t-test to examine continuous variables. Kaplan-Meier analysis was performed to estimate mortality after CP in these two cohorts, and the log-rank test was used to examine the difference between the curves. The incidence density rate of CP (per 100,000 person-years) at follow-up for each cohort was calculated. Univariable and multivariable Cox proportional hazards regression were used to examine the effect of CP on the risk of mortality and shown as hazard ratios with 95% confidence intervals. All statistical analyses were performed using SPSS software (Version 22.0; SPSS Inc., Chicago, IL, USA). The comparisons used a significance level of 0.05 for two-sided testing.

Results

According to the NHIRD, 103,812 patients received colonoscopy. The rate of CP within 30 days was 0.3% (307/103,812). The overall mortality rate within 30 days of the 307 patients diagnosed with CP was 3.91% (12/307).

A flowchart of sample selection from the NHIRD in Taiwan is shown in Fig. 1. Out of 1,000,000 people, 986,713 had medical records (outpatient department, emergency room, or admission). Out of 986,713 people, 105,264 had received colonoscopy and the colonoscopy rate was 10.67% (105,264/986,713). We excluded 1,452 people according to the exclusion criteria. A total of 103,812 people were included in the

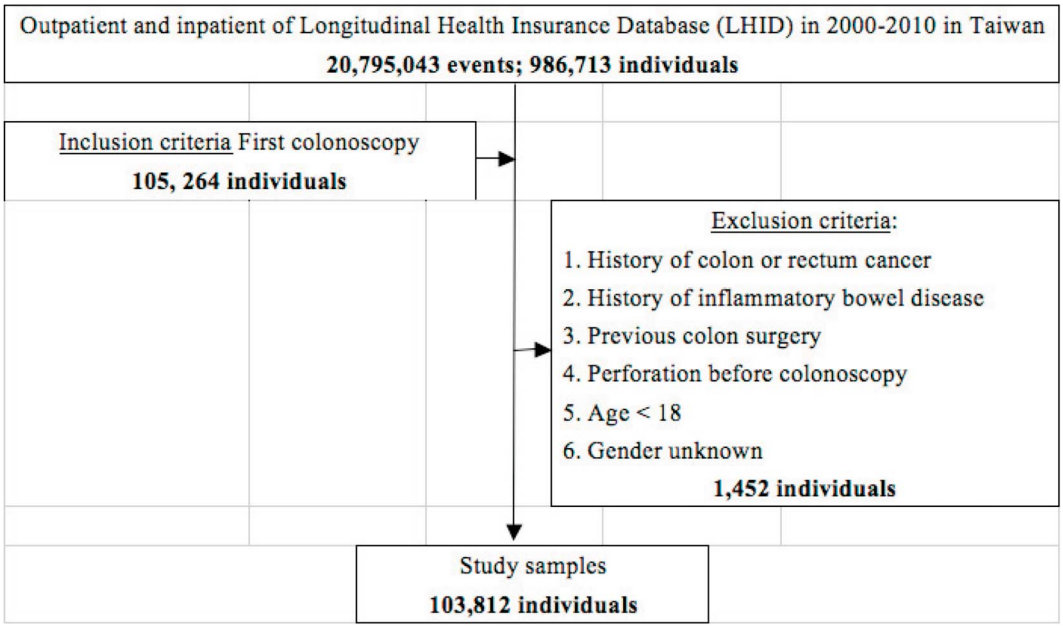


Fig. 1. The flowchart of study sample selection from National Health Insurance Research Database in Taiwan. Colonoscopy: ICD-9-CM OP45.22-OP45.23, OP45.25-OP45.27, OP45.42-OP45.43; claim codes 28017C. Colon or rectum cancer: ICD-9-CM 153-154. Inflammatory bowel disease: ICD-9-CM 555-556. Colon surgery ICD-9-CM OP45.4, OP45.7-OP45.9, OP46-48; claim codes 73001C-73050C, 74001C-74004C, 74201C-74223C. Perforation: ICD-9-CM 569.83, 998.2.

study. Fig. 2 shows the cumulative risk of perforation after colonoscopy within 30 days. Tables 4 and 5 show the time to perforation and mortality after colonoscopy within 30 days. The percentage of patients with CP was highest on the 1st day (76.5%), and mortality rate was higher on the 23rd day (5.31%) and the 26th day (5.69%).

Table 1 shows the demographic characteristics of the study population (103,812 patients), which was divided into patients with and without perforation (307/103,505 patients). The female sex was predominant in the group with perforation compared with the group without perforation (49.19% vs. 44.01%, respectively; $p = 0.039$). The proportion of patients with DM in the group with perforation was significantly lower compared with the group without perforation (11.73% vs. 16.63%, respectively; $p = 0.013$). The proportion of patients with stroke in the group with perforation was significantly lower compared with the group without perforation (7.49% vs. 11.40%, respectively; $p = 0.020$). The proportion of patients with diverticulitis in the group with perforation was significantly higher compared with the group without perforation (2.28% vs. 0.72%, respectively; $p = 0.008$). The proportion of patients with biopsy in the group with perforation was significantly higher compared with the group without perforation (40.07% vs. 31.83%, respectively; $p = 0.001$). The proportion of patients treated by a specialist in colon and rectal surgery in the group with perforation was significantly higher compared with the group without perforation (22.48% vs. 11.45%, respectively; $p = 0.001$), and the proportion of patients treated by a specialist in gastroenterology in the group with perforation was significantly lower compared with the group without perforation (23.45% vs. 42.39%, respectively; $p < 0.001$). The mortality rate in the group with perforation was significantly higher compared with the group without perforation (3.91% vs. 1.01%, respectively; $p < 0.001$).

Table 2 shows the characteristics of the study population (103,812 patients), which was divided into survivor and mortality groups (1054/102,758 patients). The proportion of patients with perforation in the survivor group was significantly lower compared with the mortality group (0.29% vs. 1.14%, respectively; $p < 0.001$). The female sex was predominant in the survivor group compared with the mortality group (44.09% vs. 38.24%, respectively; $p < 0.001$). The proportion of patients aged > 65 years in the survivor group was significantly higher compared with the mortality group

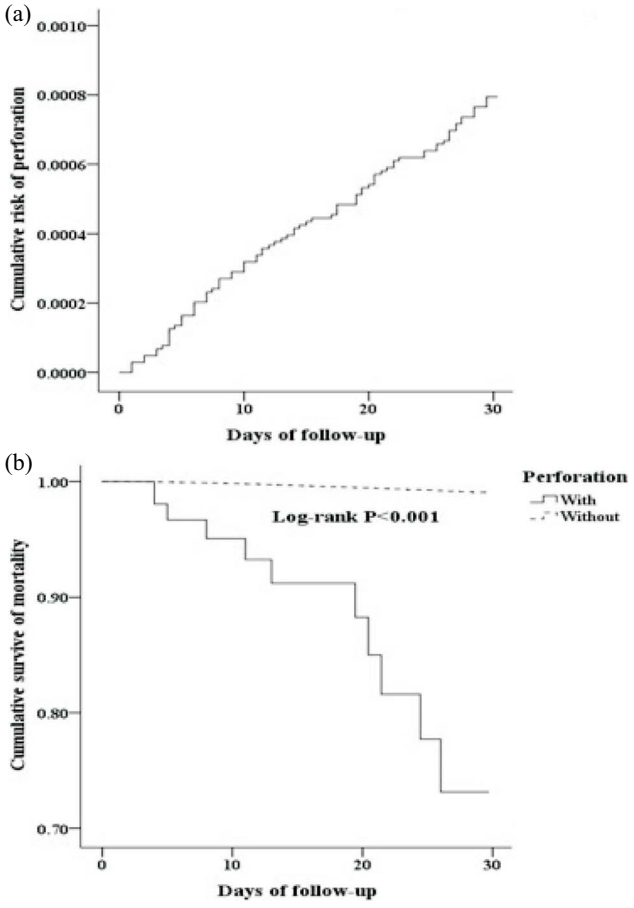


Fig. 2. (a) Kaplan-Meier for cumulative risk of perforation aged 18 and over in 30 days. (b) Kaplan-Meier for cumulative survive of mortality aged 18 and over in 30 days stratified by perforation with log-rank test.

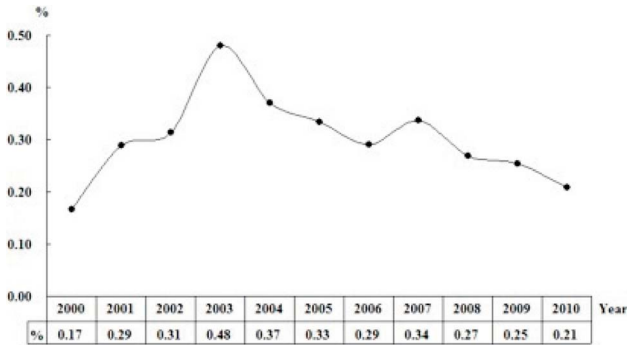


Fig. 3. Trend of perforation percentage after colonoscopy in 30 days.

Table 1. Characteristics of study samples with/without perforation

Perforation	Total		With		Without		*p*
Variables	n	%	n	%	n	%	
Total	103,812		307	0.30	103,505	99.70	
Gender							0.039
Male	58,104	55.97	156	50.81	57,948	55.99	
Female	45,708	44.03	151	49.19	45,557	44.01	
Age group (years)							0.071
18-50	25,392	24.46	57	18.57	25,335	24.48	
51-64	23,978	23.10	73	23.78	23,905	23.10	
65-80	40,164	38.69	125	40.72	40,039	38.68	
≥ 81	14,278	13.75	52	16.94	14,226	13.74	
Insured premium (NT$)							0.936
< 18,000	102,335	98.58	303	98.70	102,032	98.58	
18,000-34,999	1,203	1.16	3	0.98	1,200	1.16	
≥ 35,000	274	0.26	1	0.33	273	0.26	
HT							0.076
Without	77,297	74.46	240	78.18	77,057	74.45	
With	26,515	25.54	67	21.82	26,448	25.55	
Hyperlipidemia							0.456
Without	97,400	93.82	289	94.14	97,111	93.82	
With	6,412	6.18	18	5.86	6,394	6.18	
CAD							0.258
Without	88,412	85.17	266	86.64	88,146	85.16	
With	15,400	14.83	41	13.36	15,359	14.84	
DM							0.013
Without	86,565	83.39	271	88.27	86,294	83.37	
With	17,247	16.61	36	11.73	17,211	16.63	
ESRD							0.492
Without	99,848	96.18	296	96.42	99,552	96.18	
With	3,964	3.82	11	3.58	3,953	3.82	
COPD							0.426
Without	95,910	92.39	285	92.83	95,625	92.39	
With	7,902	7.61	22	7.17	7,880	7.61	
Stroke							0.020
Without	91,989	88.61	284	92.51	91,705	88.60	
With	11,823	11.39	23	7.49	11,800	11.40	
Diverticulitis							0.008
Without	103,056	99.27	300	97.72	102,756	99.28	
With	756	0.73	7	2.28	749	0.72	
Other cancers							0.327
Without	95,570	92.06	280	91.21	95,290	92.06	
With	8,242	7.94	27	8.79	8,215	7.94	
CCI_R							< 0.001
0	71,935	69.29	253	82.41	71,682	69.25	
1	25,158	24.23	45	14.66	25,113	24.26	
≥ 2	6,719	6.47	9	2.93	6,710	6.48	
Biopsy							0.001
Without	70,747	68.15	184	59.93	70,563	68.17	
With	33,065	31.85	123	40.07	32,942	31.83	

Table 1. Continued

Perforation	Total		With		Without		*p*
Variables	n	%	n	%	n	%	
Polypectomy							0.457
Without	88,880	85.62	264	85.99	88,616	85.62	
With	14,932	14.38	43	14.01	14,889	14.38	
Stricture dilations							0.071
Without	103,787	99.98	306	99.67	103,481	99.98	
With	25	0.02	1	0.33	24	0.02	
Season							0.118
Spring (March-May)	26,443	25.47	76	24.76	26,367	25.47	
Summer (June-August)	26,833	25.85	64	20.85	26,769	25.86	
Autumn (September-November)	26,423	25.45	82	26.71	26,341	25.45	
Winter (December-Feburary)	24,113	23.23	85	27.69	24,028	23.21	
Location							0.728
Northern Taiwan	40,626	39.13	122	39.74	40,504	39.13	
Middle Taiwan	28,527	27.48	84	27.36	28,443	27.48	
Southern Taiwan	26,832	25.85	73	23.78	26,759	25.85	
Eastern Taiwan	7,676	7.39	27	8.79	7,649	7.39	
Outlets islands	151	0.15	1	0.33	150	0.14	
Urbanization level							0.852
1 (The highest)	32,743	31.54	92	29.97	32,651	31.55	
2	49,556	47.74	148	48.21	49,408	47.73	
3	6,146	5.92	17	5.54	6,129	5.92	
4 (The lowest)	15,367	14.80	50	16.29	15,317	14.80	
Level of care							0.426
Hospital center	33,364	32.14	109	35.50	33,255	32.13	
Regional hospital	54,082	52.10	154	50.16	53,928	52.10	
Local hospital	16,366	15.77	44	14.33	16,322	15.77	
Department							< 0.001
Division of colon & rectal surgery	11,923	11.49	69	22.48	11,854	11.45	
Gastric & intestine medicine	43,951	42.34	72	23.45	43,879	42.39	
Others	47,938	46.18	166	54.07	47,772	46.15	
Prognosis							< 0.001
Survive	102,758	98.98	295	96.09	102,463	98.99	
Mortality	1,054	1.02	12	3.91	1,042	1.01	

Note. CCI_R, Charlson comorbidity index removed sleep apnea; HTN, medication use of tetracycline, minocycline and doxycycline; HTN, hypertension; Spring, March-May, Summer, June-August; Autumn, September-November; Winter, December-Feburary.
p-value (category variable: Chi-square/Fisher exact test; continue variable: t-test).

(70.98% vs. 52.25%, respectively; $p < 0.001$). The proportion of patients with hypertension in the survivor group was significantly lower compared with the mortality group (25.46% vs. 33.87%, respectively; $p < 0.001$). The proportion of patients with coronary artery disease in the survivor group was significantly lower compared with the mortality group (14.78% vs. 20.59%, respectively; $p < 0.001$). The proportion of patients with DM in the survivor group was significantly lower compared with the mortality group (16.56% vs. 22.11%, respectively; $p < 0.001$). The proportion of patients with end-stage renal disease in the survivor group was significantly lower compared with the mortality group (3.78% vs. 7.78%, respectively; $p < 0.001$). The proportion of patients with chronic obstructive pulmonary disease in the survivor group was significantly lower compared with the mortality group (7.56% vs. 12.71%, respectively; $p < 0.001$). The proportion of patients with stroke in the survivor group was significantly lower compared with the mortality group

Table 2. Characteristics of prognosis of colonoscopic perforation

Prognosis	Total		Survive		Mortality		*p*
Variables	n	%	n	%	n	%	
Total	103,812		102,758	98.98	1,054	1.02	
Perforation							< 0.001
Without	103,505	99.70	102,463	99.71	1,042	98.86	
With	307	0.30	295	0.29	12	1.14	
Gender							< 0.001
Male	58,104	55.97	57,453	55.91	651	61.76	
Female	45,708	44.03	45,305	44.09	403	38.24	
Age group (years)							< 0.001
18-50	25,392	24.46	123	11.78	25,269	24.59	
51-64	23,978	23.10	180	17.24	23,798	23.16	
65-80	40,164	38.69	459	43.97	39,705	38.64	
≥ 81	14,268	13.75	282	27.01	13,986	13.61	
Insured premium (NT$)							0.115
< 18,000	102,335	98.58	101,289	98.57	1,046	99.24	
18,000-34,999	1,203	1.16	1,195	1.16	8	0.76	
≥ 35,000	274	0.26	274	0.27	0	0.00	
HT							< 0.001
Without	77,297	74.46	76,600	74.54	697	66.13	
With	26,515	25.54	26,158	25.46	357	33.87	
Hyperlipidemia							0.244
Without	97,400	93.82	96,417	93.83	983	93.26	
With	6,412	6.18	6,341	6.17	71	6.74	
CAD							< 0.001
Without	88,412	85.17	87,575	85.22	837	79.41	
With	15,400	14.83	15,183	14.78	217	20.59	
DM							< 0.001
Without	86,565	83.39	85,744	83.44	821	77.89	
With	17,247	16.61	17,014	16.56	233	22.11	
ESRD							< 0.001
Without	99,848	96.18	98,876	96.22	972	92.22	
With	3,964	3.82	3,882	3.78	82	7.78	
COPD							< 0.001
Without	95,910	92.39	94,990	92.44	920	87.29	
With	7,902	7.61	7,768	7.56	134	12.71	
Stroke							< 0.001
Without	91,989	88.61	91,123	88.68	866	82.16	
With	11,823	11.39	11,635	11.32	188	17.84	
Diverticulitis							0.353
Without	103,056	99.27	102,008	99.27	1,048	99.43	
With	756	0.73	750	0.73	6	0.57	
Other cancers							< 0.001
Without	95,570	92.06	94,727	92.18	843	79.98	
With	8,242	7.94	8,031	7.82	211	20.02	
CCI_R							< 0.001
0	72,598	69.93	71,941	70.01	657	62.33	
1	24,658	23.75	24,364	23.71	294	27.89	
≥ 2	6,556	6.32	6,453	6.28	103	9.77	

Table 2. Continued

Prognosis	Total		Survive		Mortality		*p*
Variables	n	%	n	%	n	%	
Biopsy							< 0.001
Without	70,747	68.15	70,104	68.22	643	61.01	
With	33,065	31.85	32,654	31.78	411	38.99	
Polypectomy							< 0.001
Without	88,880	85.62	87,931	85.57	949	90.04	
With	14,932	14.38	14,827	14.43	105	9.96	
Stricture dilations							0.775
Without	103,787	99.98	102,733	99.98	1,054	100.00	
With	25	0.02	25	0.02	0	0.00	
Season							0.145
Spring	26,443	25.47	26,160	25.46	283	26.85	
Summer	26,833	25.85	26,538	25.83	295	27.99	
Autumn	26,423	25.45	26,174	25.47	249	23.62	
Winter	24,113	23.23	23,886	23.24	227	21.54	
Location							0.511
Northern Taiwan	40,626	39.13	40,208	39.13	418	39.66	
Middle Taiwan	28,527	27.48	28,218	27.46	309	29.32	
Southern Taiwan	26,832	25.85	26,578	25.86	254	24.10	
Eastern Taiwan	7,676	7.39	7,604	7.40	72	6.83	
Outlets islands	151	0.15	150	0.15	1	0.09	
Urbanization level							0.005
1 (The highest)	32,743	31.54	32,456	31.58	287	27.23	
2	49,556	47.74	49,027	47.71	529	50.19	
3	6,146	5.92	6,066	5.90	80	7.59	
4 (The lowest)	15,367	14.80	15,209	14.80	158	14.99	
Level of care							0.602
Hospital center	33,366	32.14	33,018	32.13	348	33.02	
Regional hospital	54,082	52.10	53,549	52.11	533	50.57	
Local hospital	16,366	15.76	16,193	15.76	173	16.41	
Department							< 0.001
Division of colon & rectal surgery	11,923	11.49	11,882	11.56	41	3.89	
Gastric & intestine medicine	43,951	42.34	43,469	42.30	482	45.73	
Others	47,938	46.18	47,407	46.13	531	50.38	

Note. CCI_R, Charlson comorbidity index removed sleep apnea; HTN, medication use of tetracycline, minocycline and doxycycline; HTN, hypertension; Spring, March-May; Summer, June-August; Autumn, September-November; Winter, December-Feburary.
p-value (category variable: Chi-square/Fisher exact test; continue variable: t-test).

(11.32% vs. 17.84%, respectively; $p < 0.001$). The proportion of patients with other cancers in the survivor group was significantly lower compared with the mortality group (7.82% vs. 20.02%, respectively; $p < 0.001$). The proportion of patients with biopsy in the survivor group was significantly lower compared with the mortality group (31.78% vs. 38.99%, respectively; $p < 0.001$). The proportion of patients with polypectomy in the survivor group was significantly higher compared with the mortality group (14.43% vs. 9.96%, respectively; $p < 0.001$). The proportion of patients with an urbanization level of 1 in the survivor group was significantly higher compared with the mortality group (31.58% vs. 27.23%, respectively; $p = 0.005$). The proportion of patients treated by a specialist in colon and rectal surgery in the survivor group was significantly higher compared with the mortality group (11.56% vs. 3.89%, respectively; $p < 0.001$).

Table 3 shows the results of univariate and multivariate analyses of the influencing factors of CP after

Table 3. Factors of perforation after colonoscopy in 30 days by using Cox regression

Variables	Crude HR	95% CI	95% CI	*p*	Adjusted HR	95% CI	95% CI	*p*
Gender								
Male	0.813	0.650	1.107	0.069	0.879	0.711	1.078	0.238
Female	Reference				Reference			
Age group (yrs)								
18-50	Reference				Reference			
51-64	1.357	0.960	1.919	0.084	1.375	0.983	1.922	0.063
65-80	1.388	1.015	1.898	0.040	1.402	1.025	1.918	0.034
≥ 81	1.626	1.117	2.368	0.011	1.891	1.313	2.724	0.001
Insured premium (NT$)								
< 18,000	Reference				Reference			
18,000-34,999	0.842	0.270	2.625	0.767	0.787	0.253	2.454	0.680
≥ 35,000	1.232	0.173	8.772	0.835	1.195	0.167	8.547	0.859
HT								
Without	Reference				Reference			
With	0.814	0.621	1.067	0.137	0.907	0.669	1.229	0.528
Hyperlipidemia								
Without	Reference				Reference			
With	0.946	0.589	1.523	0.820	1.124	0.694	1.822	0.635
CAD								
Without	Reference				Reference			
With	0.885	0.637	1.230	0.468	0.982	0.698	1.383	0.919
DM								
Without	Reference				Reference			
With	0.667	0.471	0.944	0.022	0.733	0.519	1.034	0.077
ESRD								
Without	Reference				Reference			
With	0.937	0.513	1.711	0.833	1.259	0.747	2.121	0.388
COPD								
Without	Reference				Reference			
With	0.938	0.608	1.447	0.771	1.056	0.699	1.594	0.797
Stroke								
Without	Reference				Reference			
With	0.630	0.412	0.964	0.033	0.768	0.515	1.144	0.195
Diverticulitis								
Without	Reference				Reference			
With	3.184	1.505	6.737	0.002	2.794	1.318	5.295	0.007
Other cancers								
Without	Reference				Reference			
With	1.120	0.754	1.882	0.575	1.144	0.791	1.655	0.474
CCI_R								
0	Reference				Reference			
1	0.416	0.295	0.586	< 0.001	0.525	0.370	0.747	< 0.001
≥ 2	0.338	0.167	0.683	0.003	0.475	0.233	0.966	0.040
Biopsy								
Without	Reference				Reference			
With	1.431	1.139	1.798	0.002	1.417	1.136	1.769	0.002
Polypectomy								
Without	Reference				Reference			
With	0.969	0.702	1.338	0.849	1.015	0.737	1.397	0.927

Table 3. Continued

Variables	Crude HR	95% CI	95% CI	*p*	Adjusted HR	95% CI	95% CI	*p*
Stricture dilations								
Without	Reference				Reference			
With	13.696	1.923	97.536	0.009	9.951	1.390	71.248	0.022
Season								
Spring	Reference				Reference			
Summer	0.830	0.595	1.157	0.271	0.830	0.608	1.133	0.242
Autumn	1.080	0.790	1.475	0.630	1.070	0.798	1.434	0.652
Winter	1.227	0.900	1.671	0.196	1.241	0.929	1.658	0.144
Location					Had collinearity with urbanization level			
Northern Taiwan	Reference				Had collinearity with urbanization level			
Middle Taiwan	0.981	0.743	1.295	0.890	Had collinearity with urbanization level			
Southern Taiwan	0.906	0.678	1.211	0.504	Had collinearity with urbanization level			
Eastern Taiwan	1.171	0.772	1.777	0.457	Had collinearity with urbanization level			
Outlets islands	2.207	0.308	15.795	0.430	Had collinearity with urbanization level			
Urbanization level								
1 (The highest)	0.863	0.612	1.218	0.403	0.758	0.527	1.092	0.137
2	0.918	0.666	1.265	0.600	0.885	0.641	1.222	0.468
3	0.850	0.491	1.474	0.564	0.924	0.553	1.545	0.763
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	1.215	0.856	1.724	0.276	1.367	0.932	2.005	0.109
Regional hospital	1.059	0.757	1.480	0.738	1.283	0.916	1.797	0.147
Local hospital	Reference				Reference			
Department								
Division of colon & rectal surgery	1.671	1.262	2.213	< 0.001	1.509	1.145	1.989	0.003
Gastric & intestine medicine	0.473	0.359	0.624	< 0.001	0.469	0.358	0.615	< 0.001
Others	Reference				Reference			

HR, hazard ratio; CI, confidence interval; Adjusted HR, adjusted variables listed in the table; Spring, March-May; Summer, June-August; Autumn, September-November; Winter, December-Feburary.

colonoscopy within 30 days. Based on the multivariate analysis results and by controlling gender, insured premium, comorbidities, season, urbanization level, and level of care, the incidence of CP in patients aged 65-80 years and > 81 years was higher compared with the 18-50-year age group (1.434 times, $p = 0.030$; 1.748 times, $p = 0.005$). The incidence of CP in patients with diverticulitis was 3.357 times that of CP in patients without diverticulitis ($p = 0.002$). The incidence of CP in patients who underwent biopsy was 1.399 times that of patients who did not undergo biopsy ($p = 0.005$). The incidence of CP in patients who underwent stricture dilation was 12.944 times that of patients who did not undergo stricture dilation ($p = 0.011$). The incidence of CP, which was performed by a specialist in colon and rectal surgery, was 1.549 times that of CPs caused by other departments ($p = 0.002$), while the incidence of CP was 0.462 times when colonoscopy was performed by a specialist in gastroenterology ($p < 0.001$).

Table 4 shows the results of univariate and multivariate analyses of the influencing factors of mortality after colonoscopy within 30 days. Based on the multivariate analysis results and by controlling gender, insured premium, comorbidities, season, and level of care, the incidence of mortality in the group with perforation was 4.420 times higher than the group without perforation ($p < 0.001$). The incidence of mortality in males was 1.304 times higher compared with that in females ($p < 0.001$). The incidence of mortality in the groups aged 51-64 years, 65-80 years, and > 81 years was higher compared with the 18-50-year age group (1.473 times, $p = 0.001$; 2.137 times, $p < 0.001$; 3.695 times, $p < 0.001$). The incidence of mortality in

Table 4. Factors of prognosis after colonoscopy in 30 days by using Cox regression

Variables	Crude HR	95% CI	95% CI	*p*	Adjusted HR	95% CI	95% CI	*p*
Perforation								
Without	Reference				Reference			
With	3.946	2.233	6.970	< 0.001	4.194	3.203	5.492	< 0.001
Gender								
Male	1.272	1.123	1.440	< 0.001	1.280	1.197	1.369	< 0.001
Female	Reference				Reference			
Age group (yrs)								
18-50	Reference				Reference			
51-64	1.553	1.234	1.953	< 0.001	1.496	1.312	1.704	< 0.001
65-80	2.367	1.840	2.888	< 0.001	2.237	1.991	2.515	< 0.001
≥ 81	4.258	3.449	5.257	< 0.001	4.072	3.598	4.608	< 0.001
Insured premium (NT$)								
< 18,000	Reference				Reference			
18,000-34,999	0.649	0.324	1.302	0.224	0.686	0.466	1.009	0.055
≥ 35,000	0.000	-	-	0.867	0.000	-	-	0.710
HT								
Without	Reference				Reference			
With	1.497	1.318	1.701	< 0.001	1.014	0.935	1.100	0.743
Hyperlipidemia								
Without	Reference				Reference			
With	1.098	0.863	1.397	0.446	0.802	0.699	1.192	0.120
CAD								
Without	Reference				Reference			
With	1.493	1.286	1.734	< 0.001	1.052	0.965	1.147	0.251
DM								
Without	Reference				Reference			
With	1.427	1.234	1.651	< 0.001	1.284	1.184	1.392	< 0.001
ESRD								
Without	Reference				Reference			
With	2.138	1.707	2.679	< 0.001	1.595	1.420	1.791	< 0.001
COPD								
Without	Reference				Reference			
With	1.774	1.480	2.127	< 0.001	1.163	1.054	1.284	0.003
Stroke								
Without	Reference				Reference			
With	1.694	1.447	1.983	< 0.001	1.202	1.098	1.317	< 0.001
Diverticulitis								
Without	Reference				Reference			
With	0.780	0.350	1.740	0.544	1.002	0.707	1.421	0.989
Other cancers								
Without	Reference				Reference			
With	2.924	2.514	3.400	< 0.001	2.284	2.108	2.476	< 0.001
CCI_R								
0	Reference				Reference			
1	1.320	1.150	1.514	< 0.001	1.254	1.089	1.445	0.002
≥ 2	1.742	1.415	2.144	< 0.001	1.706	1.379	2.112	< 0.001
Biopsy								
Without	Reference				Reference			
With	1.370	1.210	1.550	< 0.001	1.325	1.239	1.416	< 0.001

Table 4. Continued

Variables	Crude HR	95% CI	95% CI	*p*	Adjusted HR	95% CI	95% CI	*p*
Polypectomy								
Without	Reference				Reference			
With	0.657	0.537	0.854	< 0.001	548.000	0.483	0.822	< 0.001
Stricture dilations								
Without	Reference				Reference			
With	0.000	-	-	0.735	0.000	-	-	0.817
Season								
Spring	Reference				Reference			
Summer	1.027	0.873	1.209	0.746	0.999	0.914	1.091	0.977
Autumn	0.880	0.742	1.044	0.142	0.913	0.834	1.001	0.051
Winter	0.879	0.738	1.047	0.148	973.000	0.888	1.066	0.552
Location					Had collinearity with urbanization level			
Northern Taiwan	Reference				Had collinearity with urbanization level			
Middle Taiwan	1.053	0.909	1.220	0.490	Had collinearity with urbanization level			
Southern Taiwan	0.920	0.787	1.075	0.293	Had collinearity with urbanization level			
Eastern Taiwan	0.911	0.710	1.170	0.467	Had collinearity with urbanization level			
Outlets islands	0.643	0.090	4.574	0.659	Had collinearity with urbanization level			
Urbanization level								
1 (The highest)	0.851	0.701	1.034	0.104	1.074	0.955	1.208	0.233
2	1.038	0.869	1.240	0.693	1.094	0.982	1.219	0.102
3	1.269	0.969	1.659	0.083	1.283	1.094	1.505	0.002
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	0.985	0.821	1.182	0.872	1.917	0.976	2.159	0.496
Regional hospital	0.931	0.785	1.106	0.417	1.440	0.892	1.605	0.456
Local hospital	Reference				Reference			
Department								
Division of colon & rectal surgery	0.309	0.225	0.425	< 0.001	0.284	0.240	0.335	< 0.001
Gastric & intestine medicine	0.991	0.876	1.121	0.883	0.890	0.445	1.285	0.205
Others	Reference				Reference			

HR, hazard ratio; CI, confidence interval; Adjusted HR, adjusted variables listed in the table; Spring, March-May; Summer, June-August; Autumn, September-November; Winter, December-Feburary.

patients with end-stage renal disease was 1.610 times that of patients without end-stage renal disease ($p < 0.001$). The incidence of mortality in patients with stroke was 1.225 times that of patients without stroke ($p = 0.025$). The incidence of mortality in patients with other cancers was 2.543 times that of patients without other cancers ($p < 0.001$). The incidence of mortality in patients who underwent biopsy was 1.250 times that of patients who did not undergo biopsy ($p = 0.001$). The incidence of mortality in patients who underwent polypectomy was 0.711 times that of patients who did not undergo polypectomy ($p = 0.011$). The incidence of mortality in patients who lived in a level 3 urbanization area was 1.355 times that of patients who lived in a level 4 urbanization area ($p = 0.027$). The incidence of mortality in patients who underwent colonoscopy performed by a specialist in colon and rectal surgery was 0.371 times the incidence of mortality after colonoscopies carried out by other departments ($p < 0.001$).

Table 5 shows the number of CPs per day (%) within 30 days. Among them, the proportion of CPs on the first day was highest (76.5%). Table 6 shows the number of hospitalized deaths per day (%) within 30 days. The proportion of hospitalized deaths was higher on the 23rd day (5.31%) and the 26th day (5.69%).

Discussion

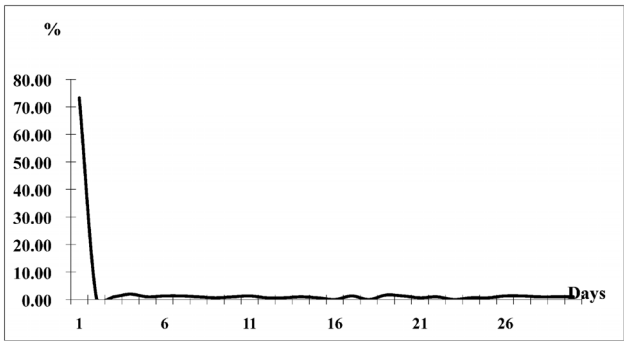
CP is one of the most serious complications of colonoscopy and is associated with a high morbidity and mortality rate. The incidence of CP is approxi-

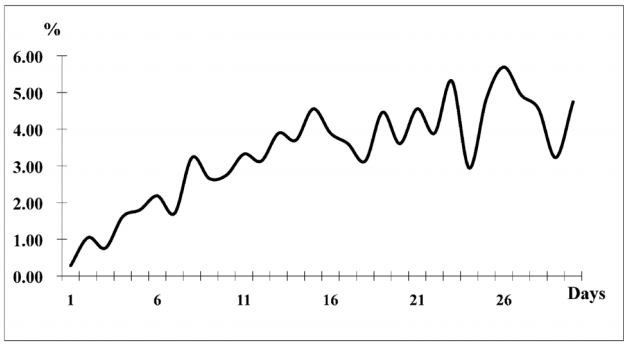
Tab1e 5. Time to perforation after colonoscopy in 30 days

Days	N	%
1	225	73.29
2	2	0.65
3	3	0.98
4	6	1.95
5	3	0.98
6	4	1.30
7	4	1.30
8	3	0.98
9	2	0.65
10	3	0.98
11	4	1.30
12	2	0.65
13	2	0.65
14	3	0.98
15	2	0.65
16	0	0.00
17	4	1.30
18	0	0.00
19	5	1.63
20	4	1.30
21	2	0.65
22	3	0.98
23	0	0.00
24	2	0.65
25	2	0.65
26	4	1.30
27	4	1.30
28	3	0.98
29	3	0.98
30	3	0.98
Total	307	100

Tab1e 6. Time to mortality after colonoscopy in 30 days

Days	N	%
1	3	0.28
2	11	1.04
3	8	0.76
4	17	1.61
5	19	1.80
6	23	2.18
7	18	1.71
8	34	3.23
9	28	2.66
10	29	2.75
11	35	3.32
12	33	3.13
13	41	3.89
14	39	3.70
15	48	4.55
16	41	3.89
17	38	3.61
18	33	3.13
19	47	4.46
20	38	3.61
21	48	4.55
22	41	3.89
23	56	5.31
24	31	2.94
25	51	4.84
26	60	5.69
27	52	4.93
28	48	4.55
29	34	3.23
30	50	4.74
Total	1,054	100





mately 0.016% in the context of all diagnostic colonoscopy procedures.[14] The most common site of CP is the rectosigmoid (RS) colon.[7,15-17] The RS colon is susceptible to injury because there is a sharp angulation at the RS junction and the sigmoid colon is extremely mobile.

Therapeutic colonoscopies have a significantly higher rate of CP compared with diagnostic colonoscopies,[18,19] due to the need for endoscopic intervention. Several investigators have reported that some endoscopic interventions are associated with an increased CP rate, including polypectomy (especially

for polyps of > 20 mm)[20,21] and biopsy, which is compatible with our study results.

Stricture dilations should be defined as one of the therapeutic colonoscopies, but we could not tell statistically significance on CP comparing with those underwent polypectomy and biopsy according to Table 1 of our study. The reason could be there are few patients underwent stricture dilation in our study (25/103,812) and only one patient suffered from colonoscopic perforation (1/25), the sample size is too small to achieve statistically significance.

Elderly patients have a higher rate of CP compared with younger patients. As our results show, the incidence of mortality in patients aged > 50 years was higher compared with patients aged < 50 years. One possible explanation for this increase in CP in older patients is the fact that aged individuals experience a decline in the mechanical strength of the colon wall, which is recognized in colonic diverticular diseases. Thus, elderly patients often present with abnormal colorectal findings, which may require endoscopic intervention. Older patients also have a higher rate as they more commonly present with comorbidities compared with younger patients. In addition to these comorbidities, old age could be one possible reason for the higher mortality rate observed in older patients compared with younger patients. Based on our study results, patients with end-stage renal disease, stroke, and cancer have a higher mortality rate after CP.

How to reduce mortality after CP should be addressed. It is important to be aware of risk factors that increase the likelihood of CP, which include the female sex, older age, therapeutic colonoscopy procedures (e.g., polypectomy and biopsy), and the presence of diverticulitis and comorbidities.[22,23] With these risk factors, mortality from CP significantly increases. Thus, we should be aware of the depth of anesthesia and sedation, especially with propofol, which should be kept as light as possible, so that patients experiencing pain or discomfort can be identified and corrective measures taken.

According to Table 1 of our study, procedure performed by specialists of division of colon & rectal surgery is at higher risk of perforation compared with those by endoscopists, including division of gastric & intestine medicine and others. The ratio of CP by CRS specialists is 0.58% (69/11,923) which is higher than 0.16% (72/43,951) by GI specialists and 0.38% (166/43,938) by others specialists. Most patients with wide-base or malignant polyp will be refer to CRS division because CRS specialists have the abilities to perform either conservative treatment or surgical management if CP occurs. And this is the possible reason why CP by CRS specialist is higher than others.

If CP occurs, the choice between conservative and surgical management depends on the specific clinical situation. Conservative treatment is reserved for patients with CP who are in a good general condition and who do not show signs of peritonitis. This approach involves intravenous fluids, absolute bowel rest, and intravenous administration of broad-spectrum antibiotics. The overall success rate of conservative treatment for CP varies from 33% to 73%.[24,25] Management of CP remains a controversial issue as it can be effectively managed by both surgical and nonsurgical strategies. Although most patients with CP promptly require open surgery, there is an increasing use of nonsurgical and laparoscopic approaches in selected patients.[26-28]

With recent advances in endoscopic technologies and the increasing experience of surgeons with endoscopic interventions, endoscopic closure of CPs is now possible. In general, the perforation size that is suitable for endoscopic closure is < 10 mm.[29,30] After endoscopic repair, patients should be given intravenous broad-spectrum antibiotics and a clear liquid diet until bowel movement returns and any evidence of peritonitis disappears. Intensive monitoring and serial abdominal examinations are also essential. The success rate of endoclipping of CP is between 69% and 93%.[30]

Surgical management, as well as conservative treatment and endoclipping, is recommended in patients with diffuse peritonitis, clinical deterioration with nonsurgical treatment, or concomitant colonic pathologies that require surgery, such as CRC. Feasible choices of surgery have been described to manage CP depending on the patient's condition, the size of the perforation, the underlying pathology of the large intestine, the quality of bowel preparation, the time between injury and diagnosis, and the surgeon's pre-

ference, including simple closure of the perforation and bowel resection with or without ostomy.

This retrospective follow-up study in Taiwan showed that the male sex, age, presence of comorbidities, and post-polypectomy procedures are associated with an increased risk of mortality after CP. Endoclipping or surgical management may be more suitable for these patients than conservative treatment. We should take a positive attitude to treat this rare but deadly condition to lower the mortality rate.

Limitations

This study has several limitations. First, mortality following CP was based on diagnostic codes recorded by physicians in the NHI claim database; therefore, some registration bias may have been involved in the calculation of CP risk. Second, this is a retrospective cohort study and the data lack specific information about the prognosis of patients with CP who received aggressive surgical intervention versus those who did not. Third, no post-discharge follow-up data were included in the data set. Finally, although the NHIRD has been validated and vastly used across different specialties, errors related to variables in coding may occur.

Conclusions

To the best of our knowledge, this is the first study to indicate an increased risk of mortality after CP in Taiwan. As per our review of relevant literature, this is the first study to analyze data from a nationwide population-based database. Although CP is a rare complication following colonoscopy, it is associated with a high morbidity and mortality rate. Special precautions should be taken during therapeutic and diagnostic colonoscopy in older patients and in those with several comorbidities. Prevention is better than a cure. If CP occurs, we should choose an adequate treatment for patients. Some CPs may be treated safely without the need for surgery, but some may require surgical intervention. In certain conditions, surgery could save the lives of patients with CP.

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原　著

大腸鏡後病患死亡風險因子分析

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目的　大腸鏡後產生之大腸破裂 (CP) 被認為是下消化道內鏡檢查最嚴重的併發症之一。本篇研究使用全民健康保險研究資料庫 (NHIRD) 來評估台灣因大腸鏡檢查產生大腸破裂後死亡的發生率和危險因子分析。

方法　本篇為回朔性的研究文章，從全民健康保險研究資料庫 (NHIRD) 收集了從 2000 年至 2010 年、共 10 年的數據。使用皮爾森卡方檢定 (Pearson chi-square test) 以及費雪精確檢定 (Fisher's exact test) 對變量進行了分析，並以 Kaplan-Meier 分析法來比較大腸鏡後產生大腸破裂之病患的存活率。

結果　共有 307 名大腸鏡後產生大腸破裂之病患納入本篇研究之研究組，而對照組中則有 103,505 名大腸鏡後未產生大腸破裂之病患。在大腸鏡後 30 天內產生大腸破裂之機率為 0.3% (307/103812)。這些被診斷為 CP 的人在 30 天內的總死亡率為 3.91% (12/307)。由多變量分析的結果顯示男性、老年人、患有合併症的病患 (例如糖尿病、末期腎病、中風和憩室炎) 以及在接受大腸鏡瘜肉切除術之患者的 CP 後死亡風險增加。

結論　根據本篇以全民健康保險研究資料庫 (NHIRD) 進行的全國性回顧性研究中，男性、老年人、合併症患者以及大腸鏡瘜肉切除術後均與 CP 術後死亡風險之增加有相關性，因此在這些病患如發生 CP 則應考慮採取更積極的外科手術治療以期降低死亡率。

關鍵詞　死亡率、大腸鏡後大腸破裂、全民健康保險研究資料庫、回顧性研究。