

出國報告（出國類別：海報發表）

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# 摘 要

參與泛太平洋尿控學術會議之『海報發表』，由台灣、日本、韓國、大陸 4 個國家聯合舉辦的討論會議，藉由來自不同國家的婦女泌尿科醫師的報告中，彼此進行交流討論而獲得不同想法。與世界各地針對間質性膀胱炎的專家討論與意見交流，了解最新研究成果，可供本研究團隊對於台灣地區與世界其他地區相關資訊差異的後續研究，可作為日後台灣地區制定治療間質性膀胱炎準則的重要參考資訊。

# (第四十三屆國際尿控協會年度會議)

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# 本 文

## 目的

參與 PPCS 海報發表與各國做學術上的交流，不同方向的實驗研究讓我們對 IC 有更突破性的見解，並讓各國了解 IC 在台灣的現況、研究及未來方向。

## 過程

從103年蒐集資料、實驗、整理、分析到結論，一整個年度的成果最後能在國際會議上發表並與其他國做交流實屬不易。以下報告發表一至發表四。在發表過程中，對於其他不同切入點可以看見衍生出的成果，並讓我們思考其他可能性。

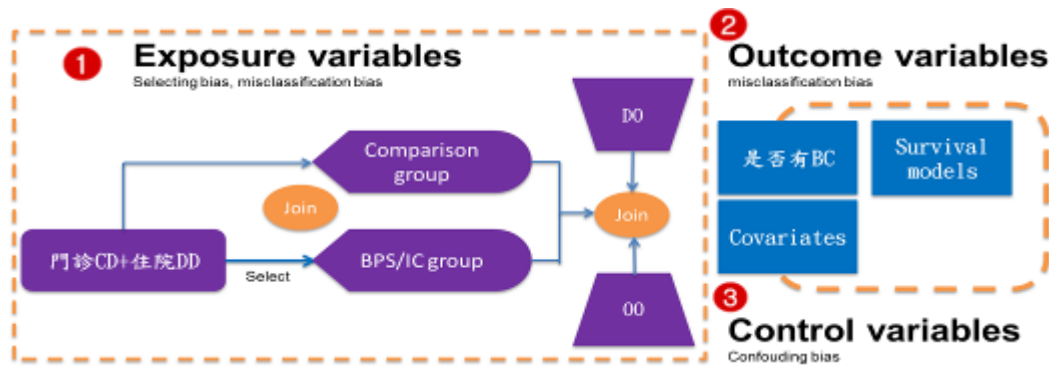
## 發表一：Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS) is not Related to Bladder Cancer: A Nationwide Population-based, Propensity Score – Matched Cohort Study

### Purpose

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a highly prevalent debilitating chronic condition characterized by bladder pain and urinary symptoms such as frequency, urgency, and nocturia. Previous study reported that patients with IC/BPS during the 3-year follow-up period showed increased risk of bladder cancer than healthy controls. However, a potential detection bias may exist when elevated risk for bladder cancer within three years immediately following an IC/BPS diagnosis. There should be noted that it is also common for IC/BPS to coexist with either unexplained medical conditions, such as fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome or confusable diseases during diagnosis of IC/BPS, such as urolithiasis and urinary tract infection. Therefore, we re-examined the risk of bladder cancer in a large population based cohort of individuals with a new diagnosis of IC/BPS to assess a potential detection bias.

### Materials and Methods

We performed a retrospective cohort study of Longitudinal Health Insurance Database 2000 with newly diagnosis of IC/BPS from 2002 through 2010. After limiting our sample to patients with IC/BPS diagnosis (ICD-9 code 595.1 at least once during the study period), we identified an IC/BPS cohort. We then excluded patients with diagnosis of bladder cancer (ICD-9 codes, 180-189) before IC/BPS diagnosis. The primary outcome was the event of bladder cancer, determined by the record with ICD-9 codes, 180-189 after the entry dates. We defined the logit of predicted probability of bladder cancer as a propensity score using the following baseline characteristics: sex, age, date of diagnosis, comorbidity, and smoking status. Subjects with IC/BPS were matched on a one-to one basis with subjects with non-IC/BPS. We used chi-square tests to evaluate associations between events of bladder cancer and patient-level covariates (age, sex, comorbidity, smoking status). Next, we compared primary outcome (events of bladder cancer) between IC/BPS and non-IC/BPS cohort using multiple logistic regression. Analyses were performed using SPSS version 22.



## Results

After adjusted with propensity score-matching, we identified 1642 patients with diagnosis of IC/BPS and 1642 patients with non-IC/BPS cohort. There is no statistically significant association between comorbidity and bladder cancer except urolithiasis ( $P < 0.001$ ) and urinary tract infection ( $P = 0.03$ ). During the study period, 20 (1.2%) IC/BPS patients and 30 (1.8%) non-IC/BPS patients were diagnosed as having bladder cancer. Chi-square test showed no difference of bladder cancer incidence between IC/BPS and non-IC/BPS cohort ( $p = 0.2$ ) (Table 1). Moreover, the multiple logistic regressions estimating the risk of bladder cancer showed no significant association among IC/BPS, sex, urolithiasis, and urinary tract infection except age ( $B = 0.02$ ,  $p = 0.005$ ) (Table 2).

Table 1

			Bladder Cancer		Total
			No	Yes	
IC/BPS	No	Count (Percentage)	925198 (99.7%)	2528 (0.3%)	927726 (100%)
	Yes	Count (Percentage)	1664 (98.8%)	20 (1.2%)	1684 (100%)
Total		Count (Percentage)	926862 (99.7%)	2548 (0.3%)	929410 (100%)

Table 2

			Bladder Cancer		Total
			No	Yes	
IC/BPS	No	Count (Percentage)	1612 (98.2%)	30 (1.8%)	1642 (100%)
	Yes	Count (Percentage)	1622 (98.8%)	20 (1.2%)	1642 (100%)
Total		Count (Percentage)	3234 (98.5%)	50 (1.5%)	3284 (100%)

## Conclusions

Our results imply us that IC/BPS is not related to bladder cancer. The detection bias from previous study may be the results of either an inadequate matching non-IC/BPS cohort or poor controlled confounding factor.

<Table1> Chi-square tests between IC/BPS & non-IC/BPS cohort

			Bladder Cancer		Total
			No	Yes	
IC/BPS	No	Count (Percentage)	1612 (98.2%)	30 (1.8%)	1642 (100%)
	Yes	Count (Percentage)	1622 (98.8%)	20 (1.2%)	1642 (100%)
Total	Count (Percentage)	3234 (98.5%)	50 (1.5%)	3284 (100%)	

<P value=0.2>

<Table 2> Multiple logistic regression of factors influencing incidence of bladder cancer

	B value	P value
IC/BPS	-0.23	0.447
Age*	0.02	0.005*
Sex	0.59	0.056
Urolithiasis	14.44	0.999
Urinary tract infection	0.69	0.999

## 發表二 : The Prevalence of Non-bladder Condition in patients with ketamine abuse and IC/BPS

### Purpose

Recreational ketamine abuse cause lower urinary tract symptoms including dysuria, urinary frequency, urgency, urge incontinence and hematuria. Several reports showed denuded epithelial inflammation of the bladder and petechial hemorrhage. As with similarly presenting interstitial cystitis, several studies investigated the pathophysiology as purinergic neurotransmission of ketamine induced uropathy. A recent study found that patients with IC/BPS often have other non-bladder conditions such as irritable bowel syndrome (IBS), fibromyalgia (FM), migraine headaches, and depression. These IC/BPS patients with comorbid disease seem to be more severe pain than without. The aim of this study is to investigate if prevalence of non-bladder condition in ketamine induced uropathy compared to ketamine abusers without bothering lower urinary tract symptoms (LUTS) and IC/BPS patients.

### MATERIALS AND METHODS

This was a retrospective cross-sectional study. Of 32 patients who were admitted due to severe lower urinary tract symptoms with recreational ketamine abuse history more than one year and 27 female age-matched IC/BPS patients who were compatible with AUA/SUFU criteria including unpleasant sensation (pain, pressure, discomfort) perceived to be related to bladder with duration >6 weeks were included. All of patients with ketamine induced uropathy and IC/BPS patients were assessed by cystoscopic hydrodistension and all of them have different severity of glomerulations or post-dilated hemorrhage. Moreover, we collected 44 ketamine abusers without LUTS with the duration than one year of their ketamine abuse. The definition of ketamine abusers without bothering LUTS was 1.no pelvic pain (VAS pain score=0) 2.mild LUTS (ICSI+ICPI <6). All these three groups completed measures of pain severity (Visual Analog Scale), bladder symptom severity (IC Symptom Index, IC Problem Index) and non-bladder condition as medical history questionnaire including FM, IBS, allergic history and depression. These data were analyzed using point bi-serial correlation for ANOVA and chi-square to evaluate symptoms and comorbid disease in these three patient' s groups.

### RESULTS

There is no difference in age between ketamine abuser without bothering LUTS and ketamine induced uropathy. Age-matched IC/BPS showed more severe LUTS than ketamine induced uropathy and ketamine abusers without bothering LUTS (ICSI: 13.00 vs



9.72 vs 1.11,  $p < 0.001$ ; ICPI: 11.73 vs 7.13 vs 0.27,  $p < 0.001$ ). More severe pain perception in IC/BPS and ketamine induced uropathy groups were found than ketamine abuser without bothering LUTS (VAS pain: 5.40 vs 4.16 vs 0,  $p < 0.001$ ). There is no difference in IBS and FM between these three groups. However, ketamine induced uropathy had more severe depression and allergy history than age-matched IC/BPS and ketamine abuser without bothering LUTS (Depression: 53.1% vs 7.4% vs 9.1%,  $p < 0.001$ ; Allergy: 62.5% vs 37% vs 25%,  $p = 0.004$ ).

## CONCLUSION

Subjective symptom scores, three day voiding diary parameters, and anesthetic bladder capacity in patients with KIC seem more severe compare to those with IC/BPS. Compare to age matched IC/BPS, there were no differences in non-bladder condition between KIU and IC/BPS patients.

<Table1> Age and subjective symptoms between three groups using ANOVA

	Ketamine abusers without bother LUTS (N=44)	Ketamine induced uropathy (N=32)	Age-matched IC/BPS (N=27)	P value
Age	26.81 ± 3.7	26.58 ± 4.4	26.54 ± 2.4	0.98
VAS Pain	0.00 ± 0.0	4.16 ± 2.8	5.40 ± 2.9	<0.001
ICSI	1.11 ± 1.2	9.72 ± 6.8	13.00 ± 3.0	<0.001
ICPI	0.27 ± 0.7	7.13 ± 5.5	11.73 ± 2.7	<0.001

<Table 2> Comorbid disease between three groups using chi-square

	Ketamine abusers without bother LUTS (N=44)	Ketamine induced uropathy (N=32)	Age-matched IC/BPS (N=27)	P value
IBS	1 (2.3%)	1 (3.1%)	2 (7.4%)	0.53
FM	1 (2.3%)	3 (9.4%)	2 (7.4%)	0.39
Depression	4 (9.1%)	17 (53.1%)	2 (7.4%)	<0.001
Allergy	11 (25%)	20 (62.5%)	10 (37%)	0.004

### 發表三 : Pain Perception, Functional Bladder Capacity, Anesthetic Bladder Capacity and Comorbid Disease in Interstitial Cystitis / Bladder Pain Syndrome

#### Objective

The purpose of this study was to examine association between functional, anesthetic bladder capacity and non-bladder conditions in a physician diagnosed of women with IC/BPS.

#### Methods

Of 175 female patients who were compatible with AUA/SUFU criteria including unpleasant sensation (pain, pressure, discomfort) perceived to be related to bladder with duration >6 weeks were included. All of IC/BPS patients were assessed by cystoscopic hydrodistension and all of them have different severity of glomerulations. These patients were assessed by validated questionnaire including O'Leary-Sant Symptom (ICSI) and Problem Index (ICPI) was used to objectify subjective symptoms. Pelvic Pain and Urgency/Frequency (PUF) questionnaire and VAS pain and urgent score were also completed. Validated voiding diary and anesthetic bladder capacity during 2-minutes hydrodistension were also measured. All patients completed medical history questionnaire for non-bladder condition. Symptomatic duration was also asked. We separated IC/BPS patients into two groups: pure IC/BPS and IC/BPS with comorbid disease. These data were analyzed using independent T test.

#### Results

There is no association between symptomatic duration and symptom, voiding diary parameter, and anesthetic bladder capacity. There is no difference between ICSI, ICPI, PUF, urgent score and comorbid disease. However, systemic IC/BPS showed more severe pain perception than pure IC/BPS ( $6.00 \pm 2.61$  vs  $4.90 \pm 3.04$ ,  $P=0.02$ ). According to validated voiding diary, the mean value of daytime frequency, daytime average voided volume, nocturnal frequency, and nocturnal average voided volume are  $14.58 \pm 6.91$ ,  $103.74 \pm 61.9$  ml,  $3.92 \pm 1.86$ ,  $101.96 \pm 83.53$  ml. Systemic IC/BPS showed more day-time voiding volume than pure IC/BPS ( $120.38 \pm 51.3$  ml vs  $102.87 \pm 63.1$  ml,  $P=0.05$ ). However, there is no significant association between daytime, night-time frequency and comorbid disease. During cystoscopic hydrodistension, there is no difference between anesthetic bladder capacity and comorbid disease. Multiple linear regression model revealed more severe pain predicted systemic type IC/BPS ( $B=0.02$ ,  $P=0.04$ ).

	Pure IC/BPS	Systemic IC/BPS	P value
VAS Pain	4.90 ± 3.04	6.00 ± 2.61	0.02*
VAS Urgency	6.44 ± 2.38	7.02 ± 2.06	0.12
ICSI	13.04 ± 3.46	13.20 ± 3.58	0.78
ICPI	11.57 ± 2.93	12.17 ± 3.44	0.28
PUF	19.44 ± 5.74	20.17 ± 6.09	0.47

<Table1> Subjective symptoms between pure and systemic IC/BPS using independent T test

	Pure IC/BPS	Systemic IC/BPS	P value
Day-time frequency	14.46 ± 6.44	14.00 ± 7.51	0.69
Night-time frequency	2.52 ± 2.64	1.91 ± 1.60	0.06
Day-time voiding volume	102.87 ± 63.1	120.38 ± 51.2	0.05*
Night-time voiding volume	111.35 ± 78.2	129.80 ± 97.2	0.21
Anesthetic bladder capacity (2 min)	594.49 ± 173.4	605.89 ± 187.7	0.70

<Table2> Objective findings between pure and systemic IC/BPS using independent T test

### Conclusions

It is also demonstrated from evidence of voiding diary that systemic IC/BPS showed as same as day-time and night-time frequency to pure IC/BPS. Moreover, even systemic IC/BPS showed more pain than pure IC/BPS, there is no difference in anesthetic bladder capacity during cystoscopic hydrodistension.

Systemic IC/BPS showed more severe pain perception than pure IC/BPS but not lower urinary tract symptoms. However, systemic IC/BPS did not showed smaller anesthetic bladder capacity than pure IC/BPS.

## 發表四：A Cohort study for Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS) and Hysterectomy in Taiwan

### Purpose

IC/BPS is a chronic disease of uncertain etiology that is characterized by urgency, frequency, and suprapubic pain related to bladder filling. Because the symptoms of IC/BPS usually similar to diseases of Gynecology, which are often indications of hysterectomy. Gynecologists may therefore recommend hysterectomy for patients with IC/BPS. Previous study reported that the incidence of hysterectomy in IC/BPS female are higher than general public female. To clarify if such phenomenon present in Taiwan area, we investigate the risk of hysterectomy in a large population based cohort of female individuals with a new diagnosis of IC/BPS. Then provide reference for Gynecologists in surgical decision.

### Materials and Methods

We performed a retrospective cohort study of Longitudinal Health Insurance Database 2000 with newly diagnosis of female IC/BPS from 2002 through 2013. After limiting our sample to female patients with IC/BPS diagnosis (ICD-9 code 595.1 at least once within the study period), we identified an IC/BPS cohort. We then excluded female patients who had been received hysterectomy (ICD-9 procedures codes, 68.4、68.41、68.49、68.51、68.59) before IC/BPS diagnosis. The primary outcome was the event of hysterectomy, determined by the record with ICD-9 procedures codes, 68.4、68.41、68.49、68.51、68.59 after the entry dates. We defined the logit of predicted probability of hysterectomy as a propensity score using the following baseline characteristics: age, date of diagnosis, comorbidity. Subjects with IC/BPS were matched on a one-to one basis with subjects with non-IC/BPS. We used Chi-square tests to evaluate associations between events of hysterectomy and patient-level covariates (age, comorbidity). Next, we compared primary outcome (events of hysterectomy) and hazard ratio (*HR*) between IC/BPS and non-IC/BPS cohort using multiple logistic regression and Cox regression. Analyses were performed using SPSS version 22.

### Results

After adjusted with propensity score-matching, we identified 1549 female patients with diagnosis of IC/BPS and 1549 female patients with non-IC/BPS cohort. There is statistically significant association between physician visit of comorbidity and hysterectomy including leiomyomata, adenomyosis, endometriosis, genital prolapse ( $p<0.005$ ) except age ( $p=0.209$ ) and physician visit of female genital organ pain or other symptoms ( $p=0.90$ ). During the study period, 28 (1.9%) IC/BPS female patients and 45 (3.0%) non-IC/BPS female patients received hysterectomy. Chi-square test showed no

significantly different incidence of hysterectomy between IC/BPS cohort and non-IC/BPS cohort ( $p=0.057$ ). But the multiple logistic regressions estimating the relative risk ( $RR$ ) of hysterectomy for non-IC/BPS cohort compare with IC/BPS cohort is 3.083 (95%  $CI=1.738-5.470$ ,  $p=0.000$ ) after controlling the age and comorbidity. The hazard ratio ( $HR$ ) of hysterectomy in non-IC/BPS cohort compare with IC/BPS is 1.749 (95%  $CI=0.997-3.069$ ,  $p=0.051$ ).

### Conclusions

Our results imply us that the relative risk of hysterectomy was lower, instead of higher, in IC/BPS female patient after IC/BPS diagnosed. The incidence of hysterectomy of IC/PBS female patient before IC/PBS diagnosed should be further investigated to clarify the relationship between IC/PBS and hysterectomy.

Table 1. Demographic characteristics of patients in IC/BPS cohort and non-IC/BPS cohort (n=2958)

variable	IC/BPS cohort(n=1479)	non-IC/BPS cohort(n=1479)
<b>Age (y/o)</b>		
Mean	48.31±15.32	48.31±15.32
<b>Leiomyomata</b>		
Mean physician visit (range)	1.22±3.45(0-36)	0.80±2.68(0-26)
<b>Adenomyosis</b>		
Mean physician visit (range)	0.40±2.14(0-27)	0.18±1.04(0-18)
<b>Endometriosis</b>		
Mean physician visit (range)	0.37±2.90(0-77)	0.08±0.85(0-26)
<b>Pelvic organ prolapse</b>		
Mean physician visit (range)	0.24±1.37(0-22)	0.04±0.59(0-12)
<b>female genital organ pain and other symptoms</b>		
Mean physician visit (range)	0.07±0.52(0-9)	0.01±0.25(0-9)
<b>Uterine or cervical or ovarian cancer</b>		
Mean physician visit (range)	0	0
<b>Vagina or vulvar cancer</b>		
Mean physician visit (range)	0	0

Mean physician visit = (Total number of outpatient visit + Total number of admission) / Total patient number

Table 2. Incidence and Risk of hysterectomy for patients by independent and confounding

variables by univariate analysis (n=2958)

variable	Hysterectomy (n,%)		p	RR
	no	yes		
<b>IC/PBS</b>				
no	1434(97.0%)	45(3.0%)	0.057	-
Yes	1451(98.1%)	28(1.9%)		
<b>age</b>	-	-	0.209	0.990
<b>Leiomyomata</b>	-	-	0.000*	1.156
physician visit				
<b>Adenomyosis</b>	-	-	0.000*	1.258
physician visit				
<b>Endometriosis</b>	-	-	0.001*	1.114
physician visit				
<b>Pelvic organ prolapse</b>	-	-	0.000*	1.181
physician visit				
<b>female genital organ pain and other symptoms</b>	-	-	0.766	0.884
physician visit				

Physician visit = Number of outpatient visit or admission, RR=Relative risk,  
\* indicates P<0.05

Table 3. Relative risk (RR) of hysterectomy in non-IC/BPS cohort compare with IC/BPS cohort (n=2958)

	non-IC/BPS cohort vs IC/BPS cohort, RR(95%CI)	p
<b>IC/BPS(no/yes)</b>	3.083(1.738-5.470)	0.000*
<b>age</b>	1.002 (0.984-1.021)	0.804
<b>Leiomyomata</b>	1.137 (1.093-1.183)	0.000*
Per one more physician visit		
<b>Adenomyosis</b>	1.230(1.154-1.311)	0.000*
Per one more physician visit		
<b>Endometriosis</b>	1.059(0.982-1.142)	0.138
Per one more physician visit		
<b>Pelvic organ prolapse</b>	1.196(1.074-1.332)	0.001*
Per one more physician visit		
<b>female genital organ pain and other symptoms</b>	1.011(0.495-2.065)	0.976

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Per one more physician visit

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Physician visit = Number of outpatient visit or admission; \* indicates P<0.05

Table 4. Hazard ratio of hysterectomy in non-IC/BPS cohort compare with IC/BPS cohort (n=2958)

	non-IC/BPS cohort vs IC/BPS cohort, <i>RR(95%CI)</i>	<i>p</i>
<b>IC/BPS(no/yes)</b>	1.749(0.997-3.069)	0.051
<b>age</b>	1.001(0.984-1.019)	0.867
<b>Leiomyomata</b>	1.115(1.076-1.156)	0.000
Per one more physician visit		
<b>Adenomyosis</b>	1.167(1.126-1.209)	0.000*
Per one more physician visit		
<b>Endometriosis</b>	1.006(0.981-1.032)	0.631
Per one more physician visit		
<b>Pelvic organ prolapse</b>	1.147(1.061-1.239)	0.001*
Per one more physician visit		
<b>female genital organ pain and other symptoms</b>	1.008(0.497-2.044)	.983
Per one more physician visit		

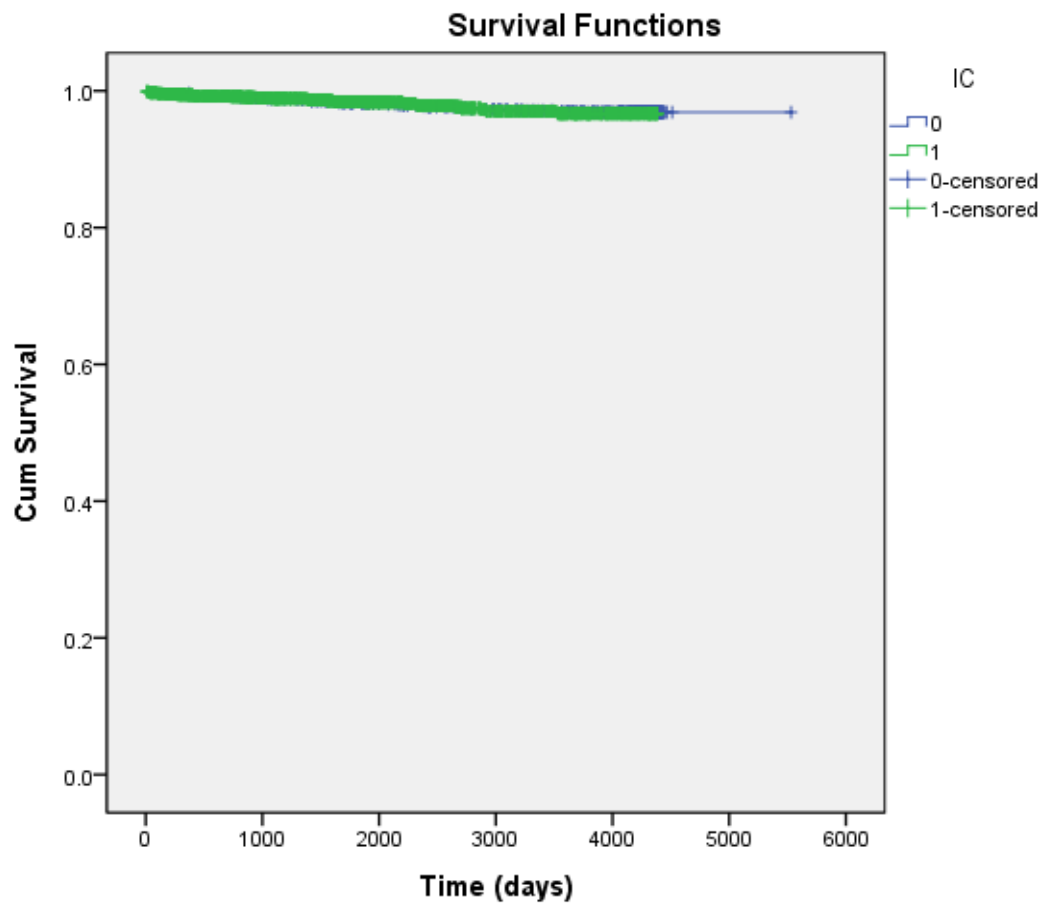
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HR=Hazard ratio; Physician visit = Number of outpatient visit or admission;

\* indicates P<0.05

Fig. 1 Cumulative incidence rate of hysterectomy in IC/BPS cohort and non-IC/BPS cohort





## 心得及建議

在這研究過程中累積出更多數據讓我們可以得到結論，這些結論讓我們了解如何給予病患更適合的治療，當現下單一的治療方式有限，整合的概念讓我們可以從多方面去了解病患的需求。

此行接收到更多元的資訊也將研究分享各國，期望能有所突破讓更多病患受惠，回院後亦將在院內之學術討論會、固定晨會、間質性膀胱炎學術討論會，與各科醫師討論交流，將此行豐碩的資料，將之發揚光大與經驗傳承，更能加速研究的成形，了解下一步的方向。

# 照片





