Congenital collagenopathies increased the risk of inguinal hernia developing and repair: analysis from a nationwide population-based cohort study

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Abstract

Introduction: The aim of this study is to explore whether male patients diagnosed of congenital collagen diseases had higher risk of occurrence inguinal hernia than patients who do not had these diseases.

Method: Data were collected from National Health Insurance Research Database (NHIRD) of Taiwan retrospectively. 1801 male patients who diagnosed of congenital collagen disease by using ICD-9 CM diagnostic code was the study cohort, and in the other hand, after propensity score matching, 6493 man without congenital collagen disease were enrolled as control group. The primary endpoint was receiving inguinal hernia repair during observation period.

Result: During median 133.9 months follow-up period, the risk of inguinal hernia in collagen cohort was significantly higher than the control group (HR = 2.237, 95% CI:1.646–3.291, $p < 0.001$). Furthermore, this phenomenon also presented in patient younger than 18 (HR:3.040 95% CI: 1.819–5.083, $p < 0.001$) and in age 18–80 (HR: 1.909, 95% CI: 1.186–3.073, $p < 0.001$).

Conclusion: Asian men, regardless of age, with congenital collagen disease are at the risk of developing inguinal hernia. Detailed physical examination and well patient education should be performed while facing these patients.

Introduction

Inguinal hernia repair, being executed over 20 million times annually, is one of the most common surgical procedure all over the world[1, 2]. In the recent days, the surgical techniques of treating inguinal hernias is increasing. In addition to traditional open approach, laparoscopic approaches, including transperitoneal, extraperitoneal or even single port, are becoming accepted and executed by surgeon in current era. Previous study demonstrated less recurrent rate in laparoscopic approach than in open approach without mesh repair.[3] Sigle-incision laparoscopic extraperitoneal repair may provide more advantages including less pain and better cosmetic outcome.[4] New techniques, including microsurgical assist[5] or transinguinal peritoneal approach[6] have been added to traditional open hernia repair nowadays. In some techniques, hernia sac is not routinely removed and sent for microscopic examination, however, though the incidence is low, malignancy including colon-rectal carcinoma or prostate adenocarcinoma may be found occasionally.[7] Thus, debate is ongoing around the necessity of regular microscopic examination of the hernia sac.

In traditional concept, the etiology of an inguinal hernia can be divided into congenital and acquired origins. The congenital type is caused by patent processus vaginalis, a invagination site of peritoneum, which should have closed during embryo development.[8] It was the most popular type of pediatric hernia, while the need of secondary repair was not low.[9] Acquired type is related to a weakening or dehiscence of fascial structure accompanying with loss of abdominal wall strength, which let hernia sac drop out easily.[10] Several factors including mechanical strain, previous operation and intra-abdominal

pressure also attribute to hernia formation.[11] If these risk factors still presented after initial inguinal hernia repair, the patient had a higher risk of contralateral inguinal hernia.[12]

Recent studies are focusing on the biology level of the cause of hernia. The molecular which had been studied the most was collagen, the main protein of forming extracellular matrix (ECM). Collagens are a huge family of protein which are important of tissue scaffolding, cell adhesion, cell migration and tissue repair.[13] Collagen itself could be classified into several types, whereas type I, III, IV and V collagens distribution disorder had been proved to related to hernia formation in previous studies. Type I collagen is related to strength fascia or mature scar while type III collagen is characteristic for less cross-link and unstable collagen, which synthesized during early wound healuing.[14] Once tissue were injured, fibroblast gathered initially and preferentially produced type III collagen.[15] Decreasing in the amount of type I collagen and increasing in the amount of type III collagen, while lowering type I/III collagen ratio, reduce tensile strength and may a factor contributing to hernia.[14, 16, 17] Besides, merely increased in type III collagen gene expression will eventually leading to hernia development.[18] Type V collagen, which is important for filbrilogenesis, may also be an important contributor in development of inguinal hernia disease. Previous study had shown the turnover of type V collagen persistently altered with patient with an inguinal hernia.[19] Furthermore, patients with inguinal hernia or incisional hernia was found to characterized with Type IV turnover increase.[20]

There are several kinds of congenital connective tissue disease which bring about collagenopathies including Ehlers-Danlos syndrome (EDS), Osteogenesis imperfecta, chondrodystrophy and osteodystrophies. Our hypothesis is that patient with these congenital connective tissue diseases have quantitative or qualitative defects in collagen, which have strong relation with the development of inguinal herniation. Several published case reports had shown the relationship of connective disease and all kinds of hernia[21–23], however, in best of our knowledge, high-level clinical evidence linking collangenopathy and inguinal hernia was lacking. In this study, we investigate the relationship between congenital collagenopathy and inguinal hernia by conducting the nationwide population-based cohort study of Taiwan.

Method

2.1 Database

We conducted a national cohort study retrospectively from Taiwan's National Health Insurance Research Database (NHIRD), which is regulated and maintained by the Data Science Centre of the Ministry of Health and Welfare (MOHW) of Taiwan. The NHIRD is the database of National Health Insurance (NHI) program in Taiwan, which included over 23 million Taiwanese, almost all of Taiwan's residents. Thus, the database could be regarded as the medical record of entire Taiwan population. In this database, the clinical diagnosis of the patients were determined according to International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). This study was approved by the Institutional Review Board of E-Da Hospital (EMRP-106-063) and Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20180308)

conducting in accordance with the Declaration of Helsinki. As this work is a retrospective, case control study gathering data from NHIRD, informed consent for study participation was not needed, approving by the Institutional Review Board.

2.2 Inclusion and Exclusion criteria

The subjects of this study were selected by using NHIRD data for the period from January 1, 2003 to December 31, 2013. All patients with the diagnosis of congenital collagen disease as Collagen group. It was established by ICD-9-CM code including 756.51, 756.59, 756.83, 756.89, 756.4 which represented for Osteogenesis imperfecta, Albright syndrome, Ehlers-Danlos syndrome, Amyotrophia congenita, Chondrodystrophy respectively. The index day was 2003/01/01. We excluded female patients, patients who was born after index day, patients who was died before index day, and patients receive hernia repair before 2003/01/01.

On the other hand, we randomly sampled 50000 active civilians as the general population. After excluding those included in our experimental cohort and those who had hernia repair before 2003/01/01, we used propensity score-matched (1:4) analysis by age and comorbidities including Charlson Comorbidity Index (CCI) score, Chronic Obstruction Pulmonary Disease (COPD), prostate disease and obese.

All the included patients were followed until their withdrawal record presented in the NHI or the end of our study period, December 31, 2013. The flow chart of selection criteria is shown in Fig. 1.

2.3 Study outcomes and covariates

The primary outcome of our study is accepting inguinal hernia repair. The diagnosis of hernia was confirmed by both ICD-9 CM code of a hernia (550.xx to 553.xx) and the surgical procedure code that included for inguinal hernia (53.00 to 53.05)[12, 24, 25]. In Taiwan, the cost of hernia repair, including both traditional open approach and laparoscopic assist, were fully covered by National Health Insurance. Thus, all the medical records were subjected to a detailed evaluation to ensure the diagnosis and the treatment were appropriated. Follow up time was defined as the time from beginning of inclusion, 2003/01/01, to receiving hernia repair or the end of the research.

In our study, patients' demographic data, including age and baseline comorbidities, were recorded. These baseline comorbidities that may be the potential risk factors of h in prior studies and possibly have affected our result were examined. During analysis, we assessed several independent variables as comorbidities, including prostate disease (ICD-9-CM code 600.x, 601.x, 602.x) [12]; obesity (ICD-9-CM code: 278.00, 278.01)[26] and **Chronic obstructive pulmonary disease (COPD) (ICD-9-CM code: 491.x-496.x, 501.x-504.x)**, which was reported as a risk factor for hernia repair[12, 27]. Comorbidities identified by an ICD-9 code within the NHIRD database before admission were included as comorbidities.

2.4 Statistical analysis

The baseline characteristics of the two groups (congenital collangen disease cohort and general population) were analyzed using descriptive statistics. The Kaplan – Meier (KM) curve was used to estimate the cumulative incidences of receiving hernia repair for the two groups, and the difference between two groups was estimated with log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CI) were calculated using chi-squared, and multivariable-adjusted Cox proportional hazards models were used to test the association between these two groups. SPSS version 25 software (IBM, Chicago, IL, USA) was used for the statistical analysis. A P value less than 0.05 was considered statistically significant.

Results

Between January 1, 2003 to December 31, 2013, we identified 4941 patients who were diagnosed of congenital collagen disease by ICD-9-CM coding. Of these, 3140 patients met one or more exclusion criteria (Fig. 1): 100 patients were excluded because of receiving hernia surgery before, 295 patients died before enrollment, 1048 patients born after enrollment and 1697 patients were female. Finally, 1692 male patients with congenital collagen disease were included as “collagen group”. Meanwhile, 50000 alive civilians were randomly selected. Of these, 1460 were excluded because of repeat in collagen group and other 7873 patients were excluded due to female gender. Of the remaining 46007 patients, propensity score matching with age and comorbidities was performed to the collagen group at a ratio of 1 to 4. To the end, 6493 male civilians were enrolled as general population (control group). The algorithm of disposition for patients and civilians by inclusion and exclusion criteria is shown in Fig. 1.

In Table 1., we presented the baseline characteristic of collagen group and control group. Between these two groups, there were no significant differences in age and comorbidities related with inguinal herniation including Chronic Obstruction Pulmonary Disease (COPD)[28], prostate disease[29] and obesity[30]. The median age of patients in control group and collagen group were 13.41 (interquartile range, 5.50–30.50) and 13.42 (interquartile range, 5.35–30.47), respectively. As connective disease was a contribution factor of Charlson Comorbidity Index (CCI) score, the CCI score of collagen group was statistically higher than control group ($p < 0.001$).

Table 1
Basic characteristic collagen diseases group and control group in Asian adult male population

Variables	Control group (N = 6493)		Collagen group (N = 1692)		P value
	Median	IQR	Median	IQR	
Age	13.41	25.00	13.42	25.13	0.749
CCI score	0	0	0	0	< 0.001
Risk factors	N	(%)	N	(%)	
COPD	274	4.22%	62	3.66%	0.305
Prostate disease	88	1.36%	21	1.24%	0.715
Obesity	4	0.06%	2	0.12%	0.444

During a median follow-up period of 132.85 and 131.17 months in control group and collagen group, 1.3% and 3.0% of patients received hernia repair, respectively. In Table 2., we demonstrated that comparing with control groups, patients in collagen groups exhibited significant increasing risk of developing inguinal hernia (HR, 2.237; 95% CI: 1.646–3.291; $p < 0.001$). In Fig. 2, we demonstrated the cumulative incidence curves of both group for the cumulative probability of receiving hernia repair in the propensity score-matched cohort. In order to know while this tendency existed in both adult and child, we divided the patient into two groups by 18-year-old. In patient younger than 18, the incidence of receiving inguinal hernia repair were significantly higher in collagen group (0.9% vs. 2.6%; HR, 3.040; 95% CI: 1.819–5.083; $p < 0.001$). Similar tendency was also shown in patient older than 18 (2.0% vs. 3.6%; HR, 1.909; 95% CI: 1.186–3.073; $p = 0.008$). In Table 3., we demonstrated the incidence of developing both unilateral (1.22% vs 2.36%; $p < 0.001$) and bilateral (0.11% vs. 0.59%; $p < 0.001$) inguinal herniation were significantly higher in collagen group than in control group. Multivariable analysis using Cox regression models were performed, and the results are shown in Table 4. Age and collagen disease appeared as independent risk factors of developing inguinal hernia.

Table 2
The risk of collagen diseases group and control group in male adult civilians

	*No. cases	(%)	HR	95%CI	P value
All age					
Control group	86	(1.3%)	Ref.		
Collagen group	51	(3.0%)	2.237	1.646–3.291	< 0.001
Age < 18					
Control group	33	(0.9%)	Ref.		
Collagen group	26	(2.6%)	3.040	1.819–5.083	< 0.001
Age = 18 ~ 80					
Control group	53	(2.0%)	Ref.		
Collagen group	25	(3.6%)	1.909	1.186–3.073	0.008

Table 3
The incidence of developing unilateral, bilateral and all hernia between collagen group and control groups.

	Collagen disease	Control group	P value
All Hernia	3.01%	1.32%	< 0.001
Unilateral	2.36%	1.22%	< 0.001
Bilateral	0.59%	0.11%	< 0.001

Table 4
Multivariable analysis for risk of hernia of patient over 18-year-old

	HR	95%CI	P value
Collagen disease	1.907	1.185–3.070	> 0.01
Age	1.037	1.025–1.049	> 0.01
COPD	0.523	0.157–1.725	0.287
Prostate disease	1.162	0.509–2.653	0.722
Obesity	0.001	0.000-0.001	0.965

Discussion

The etiology of developing inguinal hernias is complex and multi-factorial. In recent days, studies turned to focus on biological and genetic level, including the component of the extracellular matrix, the amount and ratio of different types of collagen and the genetic variant of related gene. Collagen, which effected the elasticity and resistance of transversalis fascia, could be classified into more than 30 types.[31] Different type of collagen had different characteristic and function. Type I collagen, which is the most abundant form of collagen throughout the body[32], is accounted for providing the tendon with its strength and mechanical durability[33]. During the healing process, a great amount of type III collagen would form at the wound site. The fibrils of type III collagen are thinner than type I.[34]Decreasing ratio of type I/ type III collagen had been shown to decrease strength and elasticity of tendon and fascia, therefore increase the possibility of developing inguinal hernia.[16, 17] Some congenital connective tissue disease lead to collagenopathy, causing quantitative or qualitative defects in collagen. However, to best of our knowledge, the direct relation between congenital collagen disease or connective tissue disease and risk of developing inguinal hernia had rarely been reported. In this study, we conducted the nationwide population-based cohort study of Taiwan to investigate the relationship between congenital collagenopathy and inguinal hernia.

In this propensity score-matched cohorts, we reported that a male patient with congenital collagenopathy did had higher rate of developing inguinal herniation. We examined the incidence of inguinal hernia was 2.237 times higher in male patients who was diagnosed of congenital collagen disease, comparing to general population. (HR: 2.237, 95% CI:1.646–3.291, $p < 0.001$). Multivariable analysis was performed to examine the effects of multiple independent variables. Our study showed age was also an independent variable. To diminish the effect of age, we divided the patient into two groups, age under 18 and age over 18. The risk of developing inguinal hernia were both significantly higher in collagen group of both age group, while the HR was 3.040 in patient younger than 18 (95% CI: 1.819–5.083, $p < 0.001$) and was 1.909 in patient who were in age 18 to 80 (95% CI: 1.186–3.073, $p < 0.001$).

Several possible mechanisms can explain this phenomenon. In most type of congenital collagenopathy, including Ehlers-Danlos syndrome (EDS), Osteogenesis imperfecta, chondrodystrophy and osteodystrophies, the main pathophysiology is alternations in genes involving collagen synthesis and processing of different type of collagen.[35–37] Ehlers-Danlos syndrome is an inherited connective tissue disorder characterized by defect in the synthesis of collagen causing progressive deterioration of collagens. Clinical presentation includes soft skin, skin fragile and, delayed wound healing, easy bruising, and joint hypermobility.[38] It could be classified into more than ten different subtypes, based on the defect of collagen metabolism and different gene mutation. An updated International Classification of EDS in 2017 identified 13 variants with mutations in 19 distinct genes.[39] It result in molecular or biochemical defect in collagen type I, III and V or/and related enzymes.[40] Osteogenesis imperfecta, the most common cause of congenital bone fragility, is a disease which leads to defect in type 1 collagen. Besides well-known mutation in the COL1A1 and COL1A2 genes, several other proteins have been described to involve in this disease.[41] The amount of the collagen may directly influence the possibility

of herniation development. Antonio Britto Casanova et al. reported that the total collagen amount was 17.3% lesser in patient with hernia comparing to control group. The decreasing tendency was more prominent in type I collagen than in type III collagen (23.7% vs. 6.4%).[34] Wagh et al. also suggested that decreasing the collagen amount in rectus sheath would lead to inguinal herniation. Thence, patient suffered from congenital collagen disease, which altered that quality and quantity of collagen may have higher risk of developing herniation. Furthermore, previous study had shown that hernia disease may be contributed by the imbalance between interstitial collagen and basement membrane.[34] This phenomenon could be resulted from inadequate turnover of type III, IV, V collagens. Thus, systemically poor quality of the ECM and collagen synthesis could be considered as a sign of hernia formation.[42]

In best of our knowledge, the most unique part of our study is that this is the first data directly reporting the risk of developing inguinal hernia among patients with collagenopathy. Another advantage of this study investigating the relationship between congenital collagenopathy and autoimmune diseases is that it is a large-scale nationwide population-based study. More than 99% of the total population of Taiwan was covered in the NHI system of Taiwan. Furthermore, Taiwan's NHIRD is among the few nationwide databases maintained by an Asian country.

There are several limitations in our study. First of all, this is a non-randomized analysis registered in the NHI database. We try to decrease the selection bias and cohorts' heterogenesity by using propensity score matching strategy. However, to some degree, selection bias was inevitable. Second, the database was extracted from NHI database by ICD-9CM coding system instead of medical records, misinterpretation of some data or misclassification of some diagnoses may become a bias if the coding system have not been well validated. Nevertheless, as we have combined the surgical procedure code, we may improve the accuracy of result while only patients recurved operation have surgical procedure code. Third, as this population-based study was a retrospective study, so further prospective studies are needed to fully understand the relationship between collagen disease and developing inguinal hernia.

In conclusion, this study demonstrated that Asian men with congenital collagen disease are at higher risk of developing inguinal herniation than those who did not owned those diagnosis. We should inform the possibility of inguinal hernia to specific patient owning these disease, also educate them about the symptoms and sign of incarcerated and strangulated hernias, which may lead to severe morbidity.

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Figures

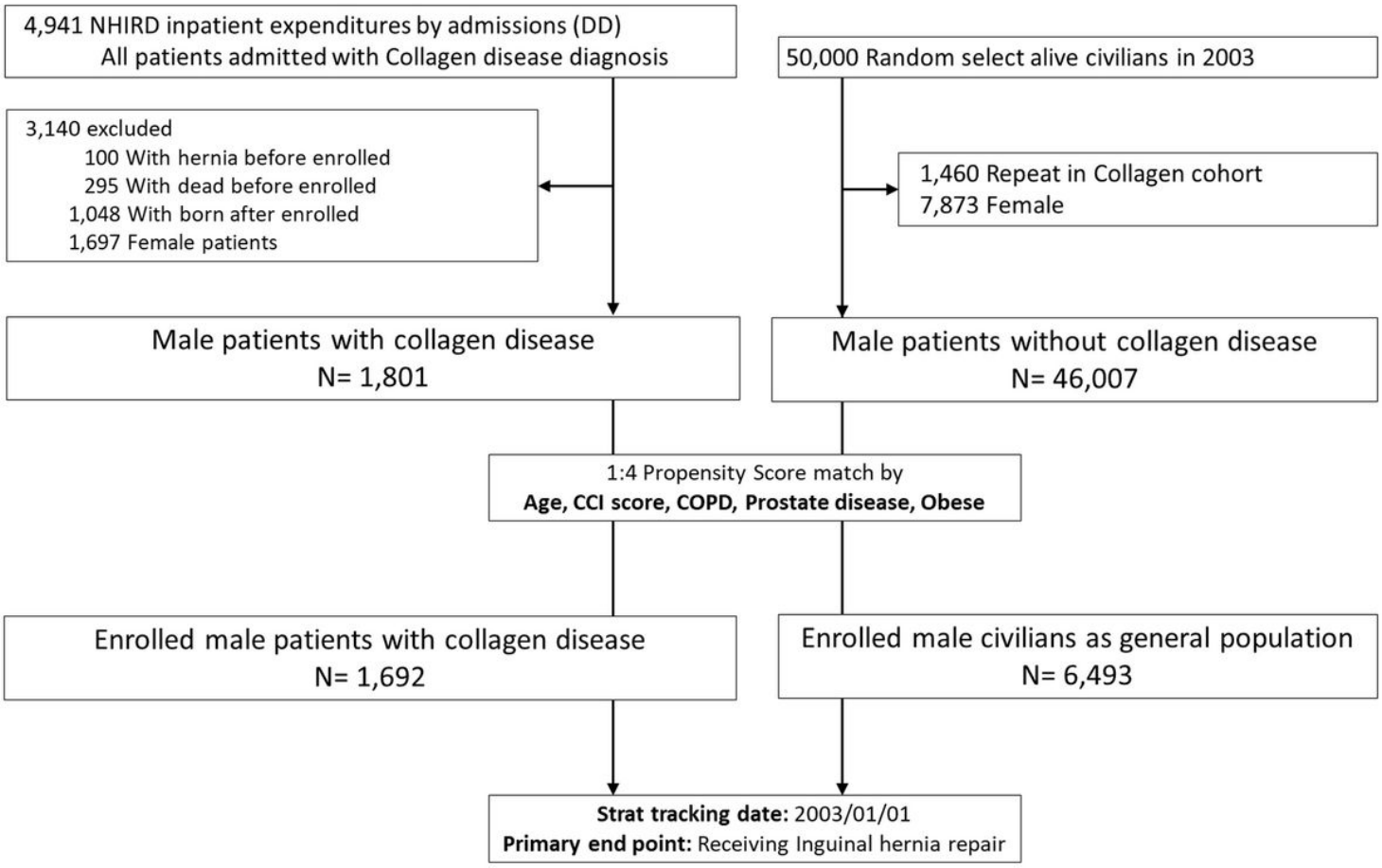

Figure 1

The flow chart shows the inclusion and exclusion criteria of our study.

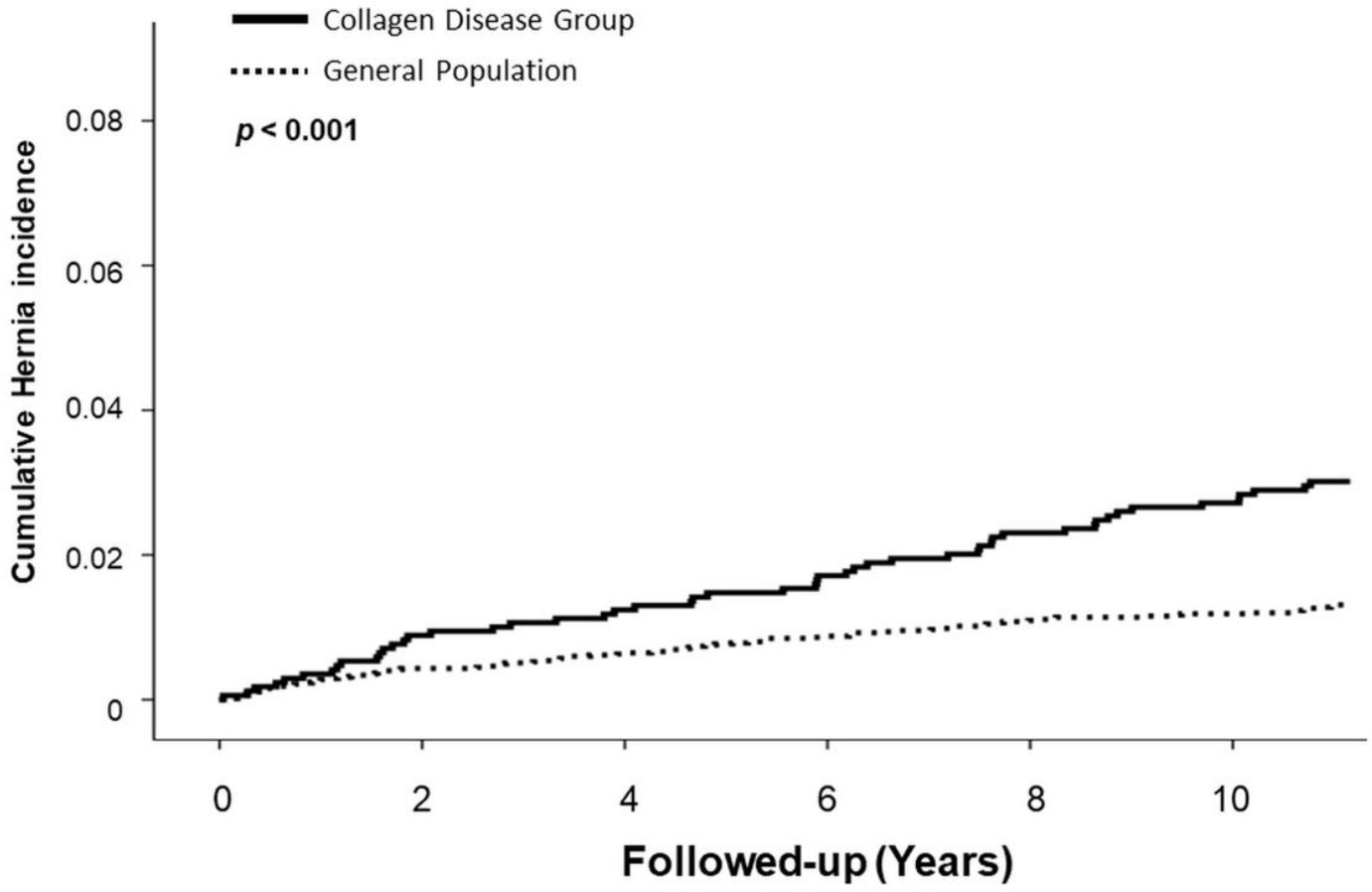

Figure 2

The cumulative incidence of hernia development. The solid line represent the collagen disease group while the dotted line represent general population.