

Dry Eye Syndrome Risks in Patients With Fibromyalgia

A National Retrospective Cohort Study

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Abstract: The coexistence of fibromyalgia (FM) and dry eye syndrome (DES) has been previously reported. However, there are few studies on how patients with FM may develop concomitant DES. Patients with chronic widespread pain, like FM, chronic fatigue syndrome, and irritable bowel syndrome (IBS), was concerned for the rheumatic or psychosomatic disorders which might adequately reflect the long-term risk of DES.

We retrieved data on FM patients from the National Health Insurance Research Database of Taiwan covering the years 2000 to 2011. Our FM population consisted of 25,777 patients versus 103,108 patients in the non-FM group: the overall incidence of DES in these populations was 7.37/10,000 and 4.81/10,000, respectively.

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Male FM patients had a higher incidence of DES, with a 1.39-fold DES risk for males and a 1.45-fold for females after adjustment for confounding factor. Notably, FM patients aged ≤ 49 years had an elevated 80% risk of DES compared with the non-FM group. Without comorbidities, FM patients had an approximately 1.40-fold risk of DES than those without FM. The additive effects of FM and IBS or FM and sleep disturbance were pointed out that the risk for DES would be elevated when the FM patients with IBS or sleep disturbance.

FM patients have a higher incidence of DES than that of non-FM patients. They carry long-term DES risks from a relatively young age, particularly those with psychiatric problems. Risk stratification for a timely psychiatric medication intervention and risk modifications are not intended.

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Abbreviations: aHR = adjusted hazard ratio, CFS = chronic fatigue syndrome, DES = dry eye syndrome, FM = fibromyalgia, IBS = irritable bowel syndrome, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LASIK = Laser-Assisted in situ Keratomileusis, NHIRD = National Health Insurance Research Database, RA = rheumatoid arthritis.

INTRODUCTION

Dry eye syndrome (DES) is a common multifactorial problem in the tears and ocular surface of ophthalmologic patients.¹ A previous study determined that the cause may be due to the repression of osmolality in tear film layers following ocular surface inflammation.² Fibromyalgia (FM) is a chronic problem characterized by chronic widespread pain, sleep disturbance, and fatigue.^{3,4} Considered a rheumatic disorder similar to Sjögren syndrome, FM has overlaps with DES.^{5,6} In a previous study, DES was reported in 20% to 35% of FM patients, which might have been due to coexistence.¹ Based on our research, few hospital-based studies have shown that the association of DES and FM exists without any comorbidities.^{6,7} Another case-control study was demonstrated that the DES severity would be one of surrogate marker of FM patients, even following relative treatments.⁸ The other articles indicate that patients with chronic pain syndrome, including FM, exhibit psychosomatic symptoms and have high rates of concomitant diseases; both conditions are highly correlated to DES.⁴

The population of Taiwan consists of approximately 23 million people. The National Health Insurance (NHI) system was established in 1995 and covers 99.6% of the general population.⁹ We hypothesized that psychosomatic disorders such as FM could be related to the risk of DES, and that through a population-based cohort study we could determine the long-term risk of DES by comparing FM and non-FM patients. We used the National Health Insurance Research Database (NHIRD) to explore the prevalence of DES and the associated risk of FM in the general population.

METHODS

NHIRD and Patient Identification

All health care records registered between January 1, 2000 and December 31, 2011 were retrieved from the NHIRD. The NHIRD is managed by the National Health Research Institute, which encrypts any individual identification information in the data before any analyses are conducted. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012).

Patients repeatedly diagnosed with FM (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 729.1) over 3 times within 3 months, according to the criteria listed in the ICD-9-CM, were selected. Each health record had a scrambled identification number and contained information such as the patient's date of birth, date of hospital visit, sex, type of visit (admission or outpatient), diagnosis, and procedure codes. And the control group was selected that these patients were not ever diagnosed with FM within 3 months from 2000 to 2011 and were matched 4:1 to FM group cases on these attributes, including age, gender, and index year. To estimate the DES incidence rate, we included patients who were admitted to a hospital or who visited an outpatient department with a major diagnosis of DES. The overall and age-specific incidence rates (per 10,000 persons) were calculated with an adjusted hazard ratio (aHR) for the period between 2000 and 2011.

Identification of FM and DES Patients, and Medication Used

FM patients and their related healthy controls were tracked from health insurance benefit requests made before December 31, 2011. The occurrence of FM was determined by repeated diagnoses referring to ICD-9-CM code 729.1. This would exclude FM patients who had been diagnosed before the entry date as follows: Polymyositis (ICD-9-CM, 710.4), Polymyalgia rheumatic (ICD-9-CM, 725), Degenerative disc disease (ICD-9-CM, 722.52), and Osteoarthritis (ICD-9-CM, 715). DES was identified according to ICD-9-CM code 370.33. Diseases overlapping with FM were also identified according to the following ICD-9-CM codes: cancer (ICD-9, 140–208), chronic fatigue syndrome (CFS) (ICD-9-CM, 780.71), irritable bowel syndrome (IBS) (ICD-9-CM, 564.1), depression (ICD-9-CM, 296.2x–296.3x, 300.4, 311.x), anxiety (ICD-9-CM, 293.84, 300.0x, 300.10, 300.2x, 300.3, 300.5, 300.89, 300.9, 308.x, 309.81), sleep disturbance (ICD-9-CM, 307.4, 327, 780.5), Sjögren syndrome (ICD-9-CM, 710.2), rheumatoid arthritis (RA) (ICD-9-CM, 714), systemic lupus erythematosus (ICD-9-CM, 710.0), and thyroid diseases (ICD-9-CM, 193, 226, 240–246 & A-CODE, A156). Treatment was identified for any of the following drugs used: tramadol, antidepressants (amitriptyline, fluoxetine, duloxetine, milnacipran, and meclobemide), tropisetron, pramipexole, and pregabalin. The annual risk of DES was determined using the cumulative incidence rates of DES in the FM and non-FM groups for the period between 2000 and 2011; this figure was obtained by dividing the number of cases with DES by the number of existing FM patients.

Statistical Analysis

We used SAS 9.2 software (SAS; Cary, NC) to perform the statistical analyses. The overall and age- and sex-specific incidence rates (5-year age categories) were calculated from sex-specific population sizes for the period between 2000 and

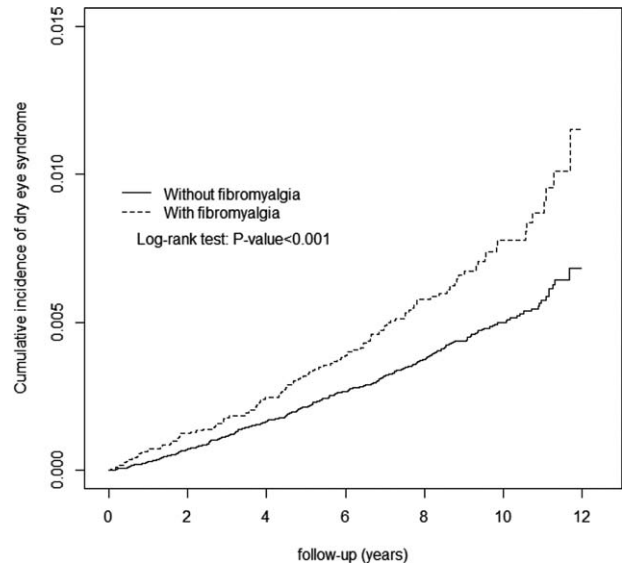


FIGURE 1. Cumulative incidence of dry eye syndrome for patients with (dashed line) or without (solid line) fibromyalgia.

2011. Statistical testing of the cumulative incidence rate was estimated using the log-rank test. The synergistic effect was determined using an additive interaction *P* value.

RESULTS

Baseline Difference Between FM Patients and the Control Group

FM was identified in 25,777 patients in the NHIRD, in addition to a control group of 103,108 non-FM patients matched by age and sex, corresponding to a 1:4 ratio. The mean age was 47.6 ± 15.3 years in FM patients and 47.1 ± 15.5 years in non-FM patients, but the stratified age groups were without significance difference. Baseline comorbidities were identified from a literature review and listed the comorbidities as coexisting subsequent complications would be mentioned, such as 2.5% of FM patients also having a pre-existing overall malignancy. FM patients were also diagnosed with sleep disturbance (22.2%), anxiety (11.1%), depression (4.98%), IBS (4.35%), and CFS (0.26%). The rates for rheumatoid diseases, such as Sjögren syndrome (0.03%), RA (0.11%), systemic lupus erythematosus (0.07%), and thyroid diseases (4.85%), were similar to the rates in the control group (Table 1).

Risk of DES Adjusted for Age, Sex, and Comorbidities

Among the 25,777 FM patients identified in the NHIRD, the overall crude risk of DES was 1.53 compared with the healthy (non-FM) control group; after adjustment for age, sex, and morbidities, the aHR was 1.43. When we stratified by sex, the crude risk of DES in males was 1.56 and the aHR was 1.45. In females, the crude risk was 1.48 and the aHR was 1.39. Table 2 shows that the incidence rate in female FM patients was higher than in male FM patients. In the group stratified by age, the FM patients aged ≤ 49 years had a significantly higher risk of DES, and the incidence rate of DES in FM patients aged < 65 years was higher than in non-FM groups (Table 2). The risk of DES in FM patients aged < 65 years were demonstrated on

TABLE 1. Comparisons in Demographic Characteristics and Comorbidities in Patient With and Without Fibromyalgia

	Fibromyalgia		P-Value
	No (N = 103,108)	Yes (N = 25,777)	
Gender			0.99
Women	53,897 (52.3)	13,474 (52.3)	
Men	49,211 (47.7)	12,303 (47.7)	
Age stratified			0.99
≤34	23,200 (22.5)	5800 (22.5)	
35–49	37,636 (36.5)	9409 (36.5)	
50–64	27,101 (26.3)	6772 (26.3)	
65+	15,171 (14.7)	3796 (14.7)	
Age, mean ± SD*	47.1 ± 15.5	47.6 ± 15.3	<0.001
Comorbidity			
Cancer	1979 (1.92)	644 (2.50)	<0.001
Chronic fatigue Syndrome	136 (0.13)	68 (0.26)	<0.001
Irritable bowel syndrome	2992 (2.90)	1121 (4.35)	<0.001
Depression	3047 (2.96)	1283 (4.98)	<0.001
Anxiety	6042 (5.86)	2851 (11.1)	<0.001
Sleep disturbance	13,464 (13.1)	5710 (22.2)	<0.001
Sjögren syndrome	20 (0.02)	7 (0.03)	0.23
Rheumatoid arthritis	106 (0.10)	29 (0.11)	0.59
Systemic lupus erythematosus	76 (0.07)	18 (0.07)	0.84
Thyroid disease	4049 (3.93)	1250 (4.85)	<0.001
Chi-Square Test			
* t-test.			

TABLE 2. Comparison of Incidence Densities of Dry Eye Syndrome and Hazard Ratio Between With and Without Fibromyalgia by Demographic Characteristics and Comorbidity

	Fibromyalgia						Crude HR [‡] (95% CI)	Adjusted HR [§] (95% CI)
	Event	No PY	Rate [†]	Event	Yes PY	Rate [†]		
All	319	663,463	4.81	123	166,835	7.37	1.53 (1.24, 1.88)***	1.43 (1.16, 1.76)***
Gender								
Women	214	359,760	5.95	84	90,568	9.27	1.56 (1.21, 2.00)***	1.45 (1.12, 1.87)**
Men	105	303,704	3.46	39	76,267	5.11	1.48 (1.02, 2.13)*	1.39 (0.96, 2.01)
Stratify age								
≤49	130	402,526	3.23	64	101,731	6.29	1.94 (1.44, 2.61)***	1.80 (1.33, 2.44)***
50–64	103	171,920	5.99	40	42,645	9.38	1.57 (1.09, 2.26)*	1.48 (1.03, 2.15)*
65+	86	89,018	9.66	19	22,460	8.46	0.88 (0.53, 1.44)	0.81 (0.49, 1.34)
Comorbidity								
No	217	536,000	4.05	66	113,580	5.81	1.43 (1.09, 1.89)*	1.43 (1.09, 1.89)*
Yes	102	127,463	8.00	57	53,255	10.7	1.31 (0.95, 1.81)	1.39 (1.00, 1.92)*

CI = confidence interval, HR = hazard ratio, PY = person year.

* P < 0.05.

** P < 0.01.

*** P < 0.001.

† Incidence rate, per 10,000 person-years.

‡ Relative hazard ratio

§ Multivariable analysis including age, gender, and comorbidities of cancer, chronic fatigue syndrome, irritable bowel syndrome, depression, anxiety, sleep disturbance, Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and thyroid disease.

|| Patients with any one of the comorbidities cancer, chronic fatigue syndrome, irritable bowel syndrome, depression, anxiety, sleep disturbance, Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and thyroid disease were classified as the comorbidity group.

age ≤ 49 years had a crude risk of 1.94 and an aHR of 1.80 after adjustment for sex and comorbidities; for patients aged 50 to 64 years, the crude risk was 1.57 and the aHR was 1.48. FM patients without comorbidities had a significantly higher risk of DES compared with the control group (Table 2).

Medication Intervention and the Risk of DES in the FM and Control Groups

FM patients with a psychiatric disorder, such as anxiety or depression, are typically prescribed an antianxiety drug or antidepressant. We tried to survey psychiatric drugs use that would affect the risk of DES, whose crude risk of tramadol use was 0.74 and aHR was 0.53 (Table 3). Moreover, the tropisetron and pramipexole use were shown that there were no event of FM group, and pregabalin use was not prescript for FM patients in NHIRD of Taiwan. Psychiatric medication such as antidepressant use would be shown that insignificantly increased crude risk for DES as 2.18-fold which was observed a comparison of medication used in FM with no medication used in FM patients (Table 3). However, most FM patients were shown to have a significantly increased risk of DES without any psychiatric or analgesia medication used, the crude risk was 1.57 and aHR was 1.51 for DES (Table 3).

Joint Effects of FM and Comorbidities

The synergistic interaction effects between FM and comorbidities such as IBS, anxiety, and sleep disturbance were examined. Patients with FM and one of these comorbidities had an increased risk of DES compared with the control group. The joint effects of FM/IBS, FM/sleep disturbance, and FM/anxiety were shown to significantly increase the risk of DES, but the additive risks were unclear. Patients with both FM/IBS and FM/sleep disturbance showed the additive effect, with increased DES risks of 3.47 and 2.26, respectively (Table 4).

This study investigated the prevalence and long-term DES risk in FM patients by using a nationwide database representing $>99.6\%$ of the general population of Taiwan and spanning 12 years. We found that the incidence rate of DES was 3.23 to 6.29/10,000 for patients aged ≤ 40 years. The results show a significant association between the risk of DES and FM patients, but the causal relationship remains unclear. To investigate that relationship, a prospective cohort study in a clinical setting is necessary.

Medication intervention in FM patients with depression and anxiety, although low, was still substantially higher than that in the non-FM group. Patients with FM, particularly females, carry long-term DES risks in middle age (≤ 65).

DISCUSSION

Based on our research, this study was the first to comprehensively investigate the long-term risk of DES and its relative complications in FM patients by using a population-based database. The reported incidence of FM in Taiwan has grown each year, probably because of increased recognition of the disease and other environmental influences. This increasing trend was clearly evident until 2000. Since 2000, the overall DES incidence among people aged ≤ 49 years has ranged from 3.23/10,000 to 6.29/10,000.

In a previous study on chronic widespread pain syndrome, which has overlaps with CFS and FM, there were no significant associations between DES and age, salivary gland atrophy, or Sjögren syndrome. Our results show that patients aged ≤ 64 years have a higher prevalence of DES. Although exposure and environmental factors are not recorded in the NHIRD, the present study demonstrated the significant association between DES and FM when we adjusted for comorbidities.

In the present study, we found that the overall incidence rate of DES was 7.37/10,000 in the FM population, and 4.81/10,000 in the control group. The age-specific incidence rate was highest among those 50 to 64 years (9.38/10,000) in the FM population. Moreover, the incidence rate was highest among those aged >65 years (9.66/10,000) in the control group; this group is the most vulnerable to DES.

The incidence rate of DES reflects the risk and duration of the disease, and provides an adequate estimate of the disease burden in both FM and control groups. FM patients who do not undergo a significant induction period might not continue their medical follow-up, which could lead to an increased risk of DES. The high adherence by FM patients to long-term treatment, combined with the relatively high incidence rate of DES between 2000 and 2011, might account for the lower incidence rate of DES observed in younger age groups.

A previous study presented the depression, pelvic pain, IBS, and chronic widespread pain syndrome were similar provided the large effect size for estimating the risk of DES among the British female population. The recent study was

TABLE 3. Incidence, Hazard Ratio of Dry Eye Syndrome Compared Among Fibromyalgia Patients With and Without Treatment and Nonfibromyalgia Controls

Variables	N	Event	PY	Rate [†]	Crude HR [‡] (95% CI)	Adjusted HR [§] (95% CI)
Nonfibromyalgia controls	103,108	319	663,463	4.81	1 (Reference)	1 (Reference)
Fibromyalgia						
Without Treatments	23,471	113	149,966	7.54	1.57 (1.27, 1.94) ^{***}	1.51 (1.21, 1.87) ^{***}
Treatment with tramadol	1622	4	11,136	3.59	0.74 (0.27, 1.97)	0.53 (0.20, 1.44)
Treatment with antidepression	634	6	5384	11.1	2.18 (0.97, 4.90)	1.67 (0.74, 3.77)
Treatment with tropisetron	32	0				
Treatment with pramipexole	18	0				

CI = confidence interval, HR = hazard ratio, PY = person year. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[†] Incidence rate, per 10,000 person-years.

[‡] Relative hazard ratio.

[§] Multivariable analysis including age, gender, and comorbidities of cancer, chronic fatigue syndrome, irritable bowel syndrome, depression, anxiety, sleep disturbance, Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and thyroid disease.

TABLE 4. Cox Proportional Hazard Regression Analysis for the Risk of Dry Eye Syndrome-Associated Fibromyalgia With Joint Effect of Comorbidity

Variables		Event	PY	Rate [†]	Adjusted HR [‡] (95% CI)
Fibromyalgia	Irritable bowel syndrome				
No	No	298	646,758	4.61	1 (Reference)
No	Yes	111	160,244	6.93	1.49 (1.20, 1.86) ^{***}
Yes	No	21	16,705	12.6	2.39 (1.54, 3.73) ^{***}
Yes	Yes	12	6592	18.2	3.47 (1.95, 6.19) ^{***}
Fibromyalgia	Anxiety				
No	No	292	630,112	4.63	1 (Reference)
No	Yes	105	149,187	7.04	1.51 (1.21, 1.89) ^{***}
Yes	No	27	33,351	8.10	1.46 (0.98, 2.16)
Yes	Yes	18	17,648	10.2	1.95 (1.21, 3.13) ^{**}
Fibromyalgia	Sleep disturbance				
No	No	263	590,939	4.45	1 (Reference)
No	Yes	86	133,664	6.43	1.43 (1.12, 1.83) ^{**}
Yes	No	56	72,525	7.72	1.48 (1.11, 1.98) ^{**}
Yes	Yes	37	33,172	11.2	2.26 (1.60, 3.20) ^{***}

CI = confidence interval, HR = hazard ratio, PY = person year.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

[†] Incidence rate, per 10,000 person-years.

[‡] Adjusted for age and sex.

disclosed that the patients with chronic pain syndromes were coexisted the higher proportion of DES, and the study was also pointed out that the several estimated parameters, like Ocular Surface Disease Index (OSDI) rather than the objective ocular surface signs. The NHIRD was not included the further individual clinical examination among these low to moderate severity DES patients.¹⁰

The level 4 severity of DES, which was paid for ophthalmic preparations by specialist peer review of Taiwan NHI system, mentioned that DES medication use was followed 5 criteria; Schirmer test without anesthesia was less than 2 mm/5 min; Tear film break-up time was present as immediate; Staining of the cornea and conjunctiva, and amount of mucus mentioned the severe epithelium damage, inflammation and ulcer, even keratosis, etc.; Ever used local antiinflammatory drug; and Visual function test was less than 0.6. In this population-based approaching, the majority weakness was involved in 2 parts; The measurable fashions were not involved in the population-based cohort study. However, the recent study was shown that chronic pain syndromes are commonly associated with severity of DES symptoms.¹⁰ We considered that early symptoms of DES might facilitate for discovery the clues in understanding the discrepancy between widespread pain syndromes, like FM. The further approaching which based on prospective cohort study design would be helped to pivotal a clue of relationship between chronic pain and DES.

The other weakness was focused on the different study design, like the FM patients could overestimate the sensation of ocular dryness which could be enlarged the prevalence of FM. Therefore, we demonstrate that the population-based cohort exhibited a similar phenomenon shown by the FM patients, who had a higher risk of DES than that of the non-FM group. After adjustment for possible DES risk factors, patients without any comorbidities have a significantly higher risk of DES compared

with FM and non-FM groups. Selection biases in cohort studies might include 3 parts such as healthy worker effect, diagnostic bias, and loss to follow-up. However, the national population-based study, which covered over 99% people of Taiwan, would be reduced the particular selection bias, like healthy worker effect and loss to follow-up. The diagnostic bias would be difficult to avoid in the cross-sectional and longitudinal study. Despite the bias is less of a problem in cohort studies compared with case-control studies, because FM and non-FM patients are enrolled before they develop the DES. In this present study, we had adjusted the confounding factors of NHIRD as possible as we can, and the bias forward to the null was equally distributed into FM and non-FM groups. Especially, the FM patients without any comorbidities were still existed 1.43-fold risk for DES. The estimation of hazard ratio for DES was relatively underestimated in this retrospective cohort study among the patients with FM and other similar disorders. Although the cause for this is unclear; one possible explanation could be the adverse effects of medication. However, we found that the use of antidepressant or anti-anxiety drugs does not significantly increase the risk of DES. The tramadol use would be repressed that the risk for DES of FM patients whether it was insignificant. We considered that the further study would be needed for disclose the tramadol use and DES risk of FM patients, even a comprehensive surveillance would be helped to disclose the pivotal clue of interaction among tramadol, DES, and FM.

In this population-based cohort, we found that the risk of DES in FM patients was significant at 1.43, and that the risk was greater among male than female patients (1.39 vs 1.45), which was consistency with the finding of a previous study.¹¹ A previous study investigating a cohort of chronic widespread pain patients revealed that the symptoms of DES and the signs for FM were reported in most of the patients, with the interpretation that they shared a similar genetic background; however,

we could not confirm this.^{4,12} Another study showed that because of inflammation, DES tends to develop during the 2nd complications after disease onset, or later might be associated with single nucleotide polymorphisms of the thrombospondin 1 gene.¹³

The progression of DES is particularly prevalent in patients with severe ophthalmologic problems related to essential medication use.^{14,15} However, FM patients generally existed the chance to survey the other disorders compared with the control group. Possible risk factors, such as Laser-Assisted in situ Keratomileusis, were existed less patients in the NHIRD which was not request for insurance benefits in the NHIRD. Providing evidence for disease association and causality would necessitate to doing cross-validation by another large-scale cohort study.^{16,17}

A study suggested that DES and FM might coexist in a subgroup of patients with chronic myalgia and myositis.¹ Patients in the FM group who had relative morbidity complications were shown to have a lower risk of DES than that of patients without morbidities. We suggested FM and DES would be existed the highly association, even if no comorbidities existence. To clarify the relationship between FM and DES, samples from the national biobank should be examined, and information such as exposure and environmental factors should be collected.^{18,19}

The current study has several limitations. First, the data extracted from the NHIRD describes only incidents at discharge: any possible associations between medical procedures and patient diagnosis could not be directly validated. Second, our study design and data access did not allow for the assessment of the severity of FM or DES; thus, we could not examine the effect of the severity of FM on the subsequent risk of DES. This evidence of current study might be restricted to Taiwan for the sake of feasibility expediency when we used the claim data in NHIRD. Another population-based prospective cohort study would be necessary to further clarify the association between FM and DES.

In conclusion, this nationwide insurance database study estimated the overall incidence rate of DES in FM and non-FM patients. For all age groups, male patients were at a higher risk of DES. We recommend the possible examination of DES would be performed in FM patients with ophthalmic problems, especially in younger and chronic FM patients.

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