

Cumulative incidence of macular edema in non-infectious uveitis indicates an early therapeutic window

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Abstract

Purpose: Uveitis-associated macular edema (UME) is a significant cause of visual impairment in non-infectious uveitis (NIU). However, the UME incidence remains unclear. Here, we evaluated the cumulative incidence of UME.

Methods: Medical records of patients registered with a uveitis diagnosis code between 2010 and 2024 were assessed to validate uveitis diagnoses of the patient registry of the North Denmark Region, a region of 600 000 inhabitants. Positive predictive values (PPV) were calculated for uveitis diagnosis and subtypes. The data from medical records were used to estimate prevalence, incidence and cumulative incidence of UME. The group differences were analysed by chi-squared test and cox proportional-hazards model.

Results: A total of 1476 medical records were reviewed. The PPV for a uveitis diagnosis was 92.2% (95% CI: 90.7–93.5) and 88.4% (95% CI: 86.8–90.0) for uveitis subtypes. Among 1218 patients with NIU, 6.9% had UME at referral. During follow-up, 8.3% of the NIU patients developed UME with an incidence rate of 1.4 per 100 person-years (95% CI: 1.3–1.7) and a cumulative incidence of 10.7% (95% CI: 8.5–13.5). A higher incidence of UME was observed for patients with bilateral uveitis, systemic disease, intermediate uveitis, posterior uveitis and panuveitis ($p < 0.001$). A substantial increase in the cumulative incidence of UME was observed in the first 2 years post-referral.

Conclusion: The high PPV supported the registry's reliability for uveitis research. UME was frequently present at the first uveitis clinic visit. NIU patients were at heightened risk of UME within the first 2 years after referral, indicating an early time window with a critical need for inflammation management.

KEYWORDS

Danish registry, epidemiology, incidence, macular edema, non-infectious uveitis, uveitis, uveitis-associated macular edema, validation

1 | INTRODUCTION

Uveitis comprises a sight-threatening group of disorders resulting from inflammation in the uveal tract, which includes the iris, ciliary body, choroid and associated ocular structures. In the Western World, uveitis is a common cause of blindness (Ghadiri et al., 2023; Xue et al., 2023). The pathogenic mechanisms underlying

uveitis are heterogeneous, but uveitis is broadly categorized as either infectious or non-infectious uveitis (NIU). Uveitis can be further classified based on the primary anatomical site of inflammation: anterior uveitis is the most common subtype, followed by posterior uveitis and panuveitis and intermediate uveitis as the least common (García-Aparicio et al., 2021). NIU may be associated with an underlying systemic autoimmune condition or

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occur as isolated ocular disease. NIU is a broad group of heterogeneous conditions, and a significant proportion of cases have an idiopathic aetiology (Tran et al., 1994).

Uveitic-associated macular edema (UME) is a sight-threatening complication where inflammation-driven disruption of the blood–retinal barrier results in the accumulation of intraretinal and/or subretinal fluid, potentially leading to central vision loss (Massa et al., 2019). The management of UME is often associated with significant challenges. Long-lasting resolution of UME may be difficult to achieve, and the retreatment is often necessary due to the recurrent nature of the condition. UME is often recurrent, and multiple therapeutic approaches may be required for successful resolution. UME may be refractory with incomplete response or resistance to available therapies (Massa et al., 2019).

Studying the epidemiology of UME may elucidate specific time windows in the course of NIU that are critical for the clinician to provide adequate therapy. Despite the potential to cause severe vision loss, the knowledge about the epidemiology of UME is limited, particularly in European populations (Koronis et al., 2019; Massa et al., 2019). Most of the currently available epidemiologic data on UME is based on small cohorts outside of Europe (Koronis et al., 2019; Massa et al., 2019). Although previous studies have reported on prevalence, there is very limited knowledge about the incidence of UME. Furthermore, very little is known about associations between systemic diseases and UME (Koronis et al., 2019; Massa et al., 2019).

The Danish National Patient Registry offers long-term longitudinal health data and holds the potential to generate valuable insights into the epidemiology of UME. Despite promising potential, the registry data has not previously been validated for research purposes in the field of uveitis. More specifically, the accuracy in the assignment of a correct uveitis diagnosis (ICD-10) has not been evaluated. In this study, we validated the accuracy of uveitis diagnosis codes within the registry and assessed the epidemiology of UME.

2 | METHODS

2.1 | Setting

The Danish healthcare system gathers data primarily for administrative and quality control purposes across multiple national databases (Ørskov et al., 2023). All registry information is linkable to each permanent resident of Denmark through their unique personal identification number (CPR). At Danish hospitals, it is mandatory for doctors to register the diagnosis code. Following a hospital visit, each patient is registered with one primary discharge diagnosis (known as ‘A diagnosis’) and up to 20 secondary discharge diagnoses (‘B diagnosis’) that are registered using the 10th revision of WHO’s International Statistical Classification of Disease and Related Health Problems (ICD-10) by the examining doctor.

Approval from The Department of Research of the North Denmark Region was obtained before data collection. The study adhered to the tenets of the Declaration of

Helsinki and complied with the General Data Protection Regulation.

2.2 | Study population

The study population consisted of a total of 1476 uveitis patients ranging in age from 0 to 100 years, each assigned and registered with a unique uveitis ICD-10 code and seen at The Department of Ophthalmology at a hospital in the North Denmark Region between January 1st, 2010 and January 1st, 2024. The population of the North Denmark Region is approximately 600 000 people.

In Denmark, ophthalmological patients are usually initially examined by a private practice ophthalmologist, who refers patients with severe cases to hospital-based care. Therefore, the 1476 patients included in this study represented the patient group with severe cases of uveitis. The patients were identified through the patient registry of the North Denmark Region.

The following uveitis ICD-10 codes were included: DH200 acute and subacute anterior uveitis, DH201 chronic anterior uveitis, DH209 anterior uveitis unspecified, DH208 other anterior uveitis, DH300 focal posterior uveitis, DH309 posterior uveitis unspecified, DH308 other posterior uveitis, DH301 disseminated posterior uveitis, DH302 intermediate uveitis and DH441E panuveitis (Table 1).

2.3 | Medical records review

For each patient, every medical record was reviewed by two independent researchers to collect all information of interest. Data were anonymized. The medical records for each individual patient were assessed to determine whether the diagnosis code registered matched the medical record. The medical records from the Department of Ophthalmology were considered sufficient to verify the diagnosis of uveitis, as the ophthalmological examinations were carried out by ophthalmological experts at the department. Uveitis cases were considered infectious based on the clinician’s assessment of clinical examination and diagnostic investigations. Uveitis cases were considered non-infectious if there was no information on infectious pathology. In case of diagnostic uncertainty, cases were considered non-infectious if there were no

TABLE 1 The specific validated ICD-10 codes for uveitis.

| ICD-10 code | Description |
|-------------|-------------------------------------|
| DH200 | Acute and subacute anterior uveitis |
| DH201 | Chronic anterior uveitis |
| DH209 | Anterior uveitis unspecified |
| DH300 | Focal posterior uveitis |
| DH309 | Posterior uveitis unspecified |
| DH308 | Other posterior uveitis |
| DH301 | Disseminated posterior uveitis |
| DH302 | Intermediate uveitis |
| DH441E | Panuveitis |

positive tests confirming an infectious cause. In case of remaining uncertainty about the uveitis diagnosis, the case was assessed by a third reviewer, an experienced uveitis specialist. Data on age, sex, ophthalmological findings, ICD-10 codes for uveitis, HLA-subtype, history of pulmonary or rheumatologic systemic disease, presence of UME and treatment were noted for each patient.

UME cases were included only if they were associated with NIU, whereas those with any other probable cause were excluded. If the medical records did not provide sufficient information on the presence of UME, the optical coherence tomography (OCT) of each individual patient was reviewed. In the case of disagreement between the researchers on the presence of UME, an experienced uveitis specialist was consulted. UME was considered prevalent if present at the first visit to the uveitis clinic and incident if it was diagnosed after the first visit.

2.4 | Statistical analysis

Stata 18 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. To evaluate the validity of the uveitis diagnoses in the patient registry of the North Denmark Region, the positive predictive value (PPV) was calculated. The PPV was calculated for the uveitis diagnosis in general and at the subtype level. The confidence interval values were estimated using the Wilson score method.

The calculations for the prevalence of UME were performed on all NIU patients with a validated uveitis diagnosis, with further stratification by sex, uveitis anatomical subtype, HLA-B27 subtype and history of an associated systemic disease. The incidence and cumulative incidence of UME in the NIU population were estimated for a 12-year follow-up period. The cumulative incidence was assessed using the Aalen Johansen Estimator, taking death into consideration as a competing risk.

To compare the characteristics of the NIU population, a chi-squared test of independence was carried out. First, the prevalent group was compared with the incident group. Second, these groups were compared with the patient group that never developed UME, respectively. A significance level of $p < 0.001$ was used for all statistical tests.

Using the cox proportional-hazards model, the characteristics for the incident UME cases were compared, and the results were presented as hazard ratios (HR) with 95% confidence intervals (CIs).

3 | RESULTS

3.1 | Validation

Among 1476 patients, uveitis diagnosis was confirmed for 1361 patients, corresponding to a PPV of 92.2% (95% CI: 90.7–93.5) for the total uveitis population (Table 2).

Among the 1476 patients with a registered uveitis diagnosis, the following subtypes were identified: 1273 cases of anterior uveitis, 50 cases of intermediate uveitis, 134 of

TABLE 2 Validation of the overall and subtype diagnoses of uveitis.

| Strata | No. of patients | Verified | PPV ^a (95% CI) |
|----------------------|-----------------|----------|---------------------------|
| Overall diagnosis | | | |
| Uveitis | 1476 | 1361 | 92.2 (90.7–93.5) |
| Subtype diagnosis | | | |
| Overall | 1476 | 1304 | 88.4 (86.6–89.9) |
| Subgroups | | | |
| Anterior uveitis | 1273 | 1162 | 91.3 (89.6–92.7) |
| Intermediate uveitis | 50 | 38 | 76.0 (62.6–85.7) |
| Posterior uveitis | 134 | 87 | 64.9 (56.5–72.4) |
| Panuveitis | 19 | 17 | 89.5 (68.6–97.1) |

^aPositive predictive value.

posterior uveitis and 19 cases of panuveitis (Table 2). For subtypes in general, the PPV was 88.4% (95% CI: 86.8–89.9). For anterior, intermediate, posterior and panuveitis, the PPVs were 91.3% (95% CI: 89.6–92.7), 76.0% (95% CI: 62.6–85.7), 64.9% (95% CI: 56.5–72.4) and 89.5% (95% CI: 68.6–97.1), respectively (Table 2).

3.2 | Baseline characteristics of the NIU population

Of the 1361 patients with a verified uveitis diagnosis, 1218 were diagnosed with NIU (Table 3). Of the 1218 patients, 579 (47.5%) were men and 639 (52.5%) were women, with a mean age of 49.6 years (± 19.4 SD) (Table 3). A total of 873 patients (71.7%) were of working age (18–65 years). Systemic disease was present in 203 patients (16.7%), with 62 patients (5.1%) presenting with ankylosing spondylitis and 48 patients (3.9%) presenting with sarcoidosis. The patients were classified as sarcoidosis-associated uveitis if sarcoidosis was verified by biopsy and the clinical presentation was consistent with sarcoidosis-associated uveitis.

Among the NIU patients, UME was prevalent in 84 cases (6.9%) at referral.

A total of 94 patients (8.3%) developed UME during follow-up. In all cases, UME appeared while the patients were under active treatment for uveitis. Finally, 1040 patients (85.4%) did not develop UME at any time during the follow-up period (Table 3).

The incidence of UME in the NIU population was 1.4 per 100 person-years (95% CI: 1.3–1.7) yielding a cumulative incidence of 10.7% (95% CI: 8.5–13.5). Moreover, the largest increase in cumulative incidence of UME occurred within the first 2 years of follow-up in the hospital (Figure 1).

No statistically significant differences were identified between the prevalent and the incident cases in terms of laterality, uveitis subtype and the presence of systemic disease ($p > 0.001$).

Developing UME were found to be associated with bilateral uveitis, systemic disease as well as intermediate

TABLE 3 Baseline characteristics of the non-infectious uveitis population.

| Baseline characteristics | Total (n = 1218) | Prevalent UME (n = 84) (6.9%) | Incident UME (n = 94) (8.3%) ^a | No UME (n = 1040) (85.4%) |
|--------------------------|------------------|-------------------------------|---|---------------------------|
| Age (years), mean ± SD | 49.6 (±19.4) | 53.3 (±18.4) | 52 (±19.9) | 49.1 (±19.5) |
| Sex | | | | |
| Male | 579 (47.5%) | 43 (51.2%) | 48 (51.1%) | 488 (46.9%) |
| Female | 639 (52.5%) | 41 (48.8%) | 46 (48.9%) | 552 (53.1%) |
| Laterality | | | | |
| Unilateral | 858 (70.4%) | 35 (41.7%) | 36 (38.3%) | 787 (75.6%) |
| Bilateral | 360 (29.6%) | 49 (58.3%) | 58 (61.7%) | 253 (24.4%) |
| Subtype | | | | |
| Anterior | 1060 (87%) | 46 (54.8%) | 69 (73.4%) | 945 (90.9%) |
| Intermediate | 51 (4.2%) | 13 (15.5%) | 12 (12.8%) | 26 (2.5%) |
| Posterior | 79 (6.5%) | 16 (19.0%) | 10 (10.6%) | 53 (5.1%) |
| Panuveitis | 28 (2.3%) | 9 (10.7%) | 3 (3.2%) | 16 (1.5%) |
| HLA-B27 | | | | |
| Yes | 179 (14.7%) | 13 (15.5%) | 17 (18.1%) | 149 (14.4%) |
| No | 1039 (85.3%) | 71 (84.5%) | 77 (81.9%) | 891 (85.6%) |
| Systemic disease | | | | |
| Yes | 203 (16.7%) | 17 (20.2%) | 24 (25.5%) | 152 (15.6%) |
| No | 1015 (83.3%) | 67 (79.8%) | 70 (74.5%) | 888 (84.4%) |
| Type of systemic disease | | | | |
| Ankylosing spondylitis | 62 (5.1%) | 4 (4.8%) | 4 (4.3%) | 54 (5.2%) |
| Sarcoidosis | 48 (3.9%) | 8 (9.5%) | 8 (8.5%) | 32 (3.1%) |

^aPercentage of the total excluding the prevalent cases.

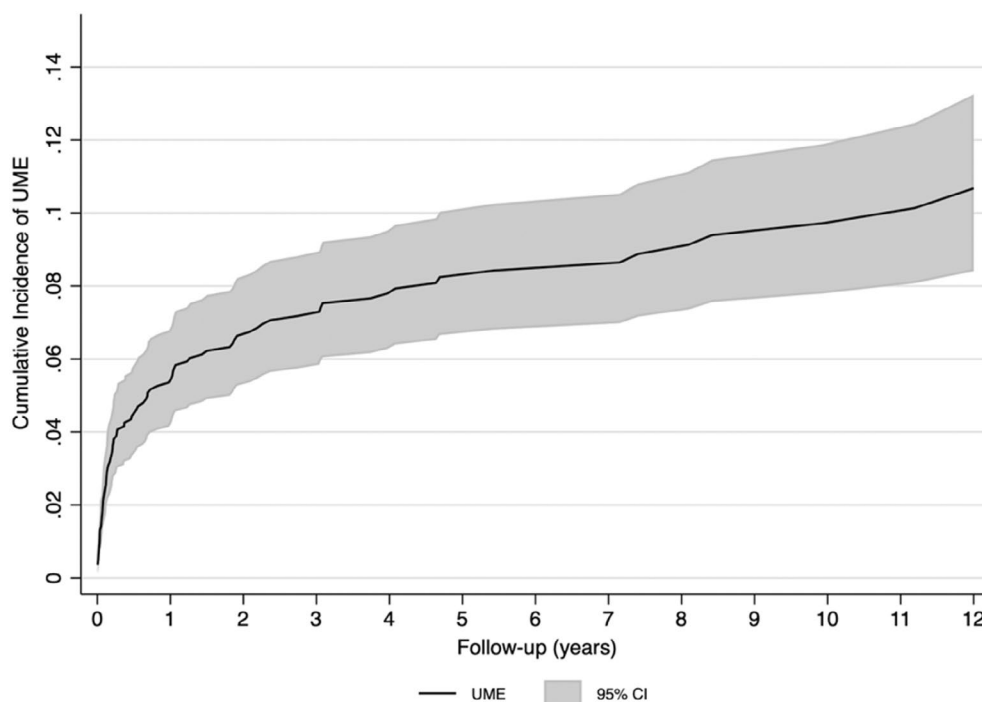


FIGURE 1 The cumulative incidence of uveitic macular edema in the non-infectious uveitis population with a 12-year follow-up. The largest increase in cumulative incidence occurred within the first 2 years. Confidence interval (CI): 95%.

uveitis, posterior uveitis and panuveitis when compared with the patients who did not develop UME ($p < 0.0001$).

Elevated hazard ratios (HR) of 4.4 (95% CI: 2.9–6.6), 3.2 (95% CI: 2.1–5.1) and 1.9 (95% CI: 1.2–2.9) were observed for bilateral uveitis, non-anterior uveitis and the presence of systemic disease, respectively (Table 4).

4 | DISCUSSION

4.1 | Registry validation

In this study, we first validated the uveitis diagnosis codes in the patient registry of the North Denmark

TABLE 4 Incidence rate and hazard ratio (HR).

| Strata | Events | Person time | Incidence rate (95% CI) | Risk % (95% CI) | HR (95% CI) |
|--------------------|--------|-------------|-------------------------|------------------|---------------|
| Laterality | | | | | $p < 0.001$ |
| Unilateral | 36 | 4768.0 | 0.8 (0.5–1.0) | 5.2 (3.7–7.2) | Reference |
| Bilateral | 58 | 1847.4 | 3.1 (2.4–4.1) | 23.7 (17.9–30.8) | 4.4 (2.9–6.6) |
| Subtype | | | | | $p < 0.001$ |
| Anterior | 69 | 5945.5 | 1.2 (0.9–1.5) | 8.9 (6.8–11.6) | Reference |
| Other ^a | 25 | 669.9 | 3.7 (2.5–5.5) | 25.9 (16.7–39.1) | 3.2 (2.1–5.1) |
| Systemic disease | | | | | $p < 0.001$ |
| Yes | 24 | 949.7 | 2.5 (1.7–3.8) | 19.3 (12.4–29.4) | 1.9 (1.2–2.9) |
| No | 70 | 5665.7 | 1.2 (0.9–1.6) | 9.2 (7.0–11.9) | Reference |

^aOther includes: Intermediate, posterior and panuveitis.

Region, and upon confirming the accuracy of the uveitis diagnosis codes in the patient registry, we then investigated the UME development and its characteristics in patients with NIU.

For patients in the registry with an assigned uveitis diagnosis, we identified an overall PPV of 92.2% (95% CI: 90.7–93.5) and an overall PPV at the subtype diagnosis level of 88.4% (95% CI: 86.8–90.0). A PPV of 60% and less is generally considered low, whereas a PPV of 80% and above is considered high (Johnsen et al., 2002; Thygesen et al., 2011). The high overall PPV in this study supports the use of the patient registry of the North Denmark Region for research in uveitis. Because the Danish registers have high validity and completeness (Schmidt et al., 2019), we would expect similar findings at a national level.

PPVs for intermediate and posterior uveitis were 76.0% (95% CI: 62.6–85.7) and 64.9% (95% CI: 56.5–72.4), respectively. These findings indicate that diagnosing uveitis at the first visit to the uveitis clinic or in an acute setting can be challenging due to its plethora of different presentations, which may also evolve over time. A higher PPV of 91.3% (95% CI: 89.6–92.7) was found for anterior uveitis. As anterior uveitis is the most common subtype, one might argue that clinicians can be more inclined to use the diagnosis code for anterior uveitis when uncertain of the correct diagnosis at the subtype level. Furthermore, a significant limitation of the registry is that the diagnosis code is registered at the first visit to a public Danish hospital. While it is possible for clinicians to update a uveitis diagnosis in the registry, the diagnosis may not be adjusted in case of changes in clinical presentation over time. As a result, some cases may retain their initial diagnosis despite a progression or change in disease pattern. Therefore, there may be a discrepancy between the registered uveitis diagnosis and the actual type of uveitis, resulting in variation in PPV for the specific uveitis subtypes.

4.2 | Epidemiology of UME

We evaluated the prevalence and incidence of UME in a NIU population of 1218 patients with a verified uveitis diagnosis. Our study identified a prevalence of UME of 6.9% at referral to the hospital. Our results are similar to the observations by Xue et al. (2023), who reported

that 6.9% of 1946 NIU patients seen at their Chinese eye center had UME. However, Xue et al. reported on the frequency of UME, thereby including both prevalent and incident cases combined. This makes it difficult to directly compare their findings with ours, because we reported on incidence and prevalence separately. However, the fact that 6.9% of our NIU population presented with UME at the first visit to the uveitis clinic emphasizes the importance of performing OCT routinely for early detection and treatment of UME.

A cumulative incidence of UME of 10.7% and an incidence rate of 1.4 cases per 100 person-years (95% CI: 1.3–1.7) during a 12-year follow-up period was found. The largest increase in the cumulative incidence was observed within the first 2 years post-referral, indicating a time window where adequate anti-inflammatory therapy is crucial to prevent the formation of UME. These findings indicated that closer monitoring is crucial within the first 2 years after referral to ensure timely management of UME. Overall, our observations favour 3 months follow-up intervals rather than 6 months within the first 2 years after referral.

Uveitis patients are often observed within several months before the initiation of, for example, DMARD or TNF-alpha inhibitors. The cumulative incidence of UME in our study supports the initiation of early treatment instead of a watch-and-wait approach when, for example, DMARD or TNF-alpha inhibitors are indicated.

We are not aware of previous reports on the incidence of UME in a broad cohort of patients with NIU, making it challenging to directly compare our findings with others. A study conducted in the United States identified an incidence of UME of 5 cases per 100 person-years in patients with multifocal choroiditis with panuveitis in a small group of 33 patients (Thorne et al., 2006). However, this was a group of patients consisting exclusively of patients with multifocal choroiditis and panuveitis, which may differ from a general uveitis population. Some subtypes are more prone to develop UME, such as panuveitis (Massa et al., 2019). Therefore, it is not surprising that this is higher than the incidence rate we found when including all subtypes of uveitis in our study population.

Overall, patients prevalent with UME and patients developing UME during follow-up shared a number of characteristics, including sex, uveitis subtype, presence of HLA-B27 subtype and presence of systemic disease ($p > 0.001$). Among patients with UME, 58.3% of the

prevalent cases and 61.7% of incident cases presented with bilateral uveitis. These results differ from the patients not developing UME, where it was found that only 24.4% had bilateral uveitis ($p < 0.0001$). This is consistent with the findings from Xue et al. (2023) who found patients in their Chinese population to be more prone to develop UME in the case of bilateral uveitis.

Among the UME patients in our study, 19% of the prevalent cases and 10.6% of incident cases had intermediate uveitis. Posterior uveitis accounted for 15.5% and 12.8% of prevalent and incident cases, respectively. This is statistically significantly different when compared with the patients not developing UME, where only 2.5% had intermediate uveitis ($p < 0.0001$) and 5.1% had posterior uveitis ($p < 0.0001$). Accorinti et al. found that UME was more common in patients with intermediate and posterior uveitis, which aligns with our findings (Accorinti et al., 2019).

A Swiss study stated that UME was less common in patients with anterior uveitis compared with intermediate, posterior and panuveitis (Massa et al., 2019). In comparison, we found that 90.8% of patients who did not develop UME had anterior uveitis. Among our patients with UME, 54.8% of the prevalent cases and 73.4% of the incident cases presented with anterior uveitis, indicating that patients with anterior uveitis are less susceptible to develop UME ($p < 0.0001$).

Finally, we found that among UME patients, 20.2% of the prevalent cases and 25.5% of the incident cases compared with 15.6% of the patients not developing UME presented with pulmonary or rheumatologic systemic disease. This indicates that NIU patients with associated systemic disease such as ankylosing spondylitis or sarcoidosis might be more prone to develop UME ($p < 0.0001$).

The abovementioned findings indicate that the patients who present with UME at first visit at the clinic and those who developed UME during follow-up have certain characteristics that differ from patients who never develop UME. Interestingly, these findings were further supported when we compared only the characteristics of the patients who developed UME during the follow-up period. Bilateral uveitis, intermediate uveitis, posterior uveitis, panuveitis and presence of systemic disease were all found to be associated with an increased rate of developing UME (HR, 4.4; [95% CI: 2.9–6.6]), (HR, 3.2; [95% CI: 2.1–5.1]) and (HR, 1.9; [95% CI: 1.2–2.9]). In this NIU population, these characteristics could potentially help identify patients at higher risk of developing UME.

4.3 | Strengths and limitations

This study utilized the unique infrastructure of the Danish healthcare system, especially the use of personal identification numbers to access patient information. This contrasts with other countries where centralized identification systems are not implemented (Erichsen et al., 2010). Minor differences between regions may be found due to private practice ophthalmological centers and clinicians between regions having different approaches. However, the Danish healthcare system is generally uniform across all regions due to regulatory and administrative bodies.

Moreover, the Danish healthcare system ensures free access to healthcare for all citizens, which could help ensure avoidance of bias in the composition of the study population due to inequality in healthcare access (Schmidt et al., 2019). In general, the criteria for referring patients with uveitis to a specialized hospital-based clinic are quite similar across the Danish regions.

A limitation of this study was that we did not calculate the negative predictive values, which would require us to have access to all patients in the registry to assess both the false negatives and the true negatives. As a result, this could possibly mean that we have not been able to include all patients diagnosed with uveitis in our study period (2010–2024), as some might not have been registered with a uveitis diagnosis code.

Our study population was initially 1476 patients, which gives a significant strength to our study. The size of the dataset is considered more than sufficient to assess the PPV, the epidemiology of uveitis, as well as the prevalence and incidence of UME. This is additionally supported by the routine performance of OCT imaging in our uveitis clinic. Given the risk of UME, patients presenting to the emergency service also undergo OCT at their first visit. Due to the routines of the department, the number of missed OCTs is considered minimal.

However, although the data from the North Denmark Region were used for the validation, future studies using the Danish National Patient Registry may be conducted on the uveitis population of the entire country.

5 | CONCLUSION

A PPV of 92.2% was identified for patients assigned a uveitis diagnosis code supporting the use of the patient registry of the North Denmark Region for research.

The prevalence of UME was 6.9% in patients with NIU at the first hospital visit and our finding emphasizes the importance of performing OCT routinely in uveitis patients. Patients with bilateral uveitis, intermediate uveitis, posterior uveitis and panuveitis were more susceptible to developing UME. The largest increase in cumulative incidence of UME occurred within the first 2 years post-referral, indicating an early time window where anti-inflammatory therapy is critical.

Given the high PPV for uveitis in this study, the Danish National Patient Registry may be used to evaluate treatment patterns in the management of UME.

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