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Anxiety and Depression in Patients With Retinitis Pigmentosa

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Abstract

Purpose: Retinitis pigmentosa (RP) is a chronic progressive disease with no curative treatments. Understanding the variables involved with improving patients' quality of life is important in managing this population. The literature investigating the relationship of anxiety and depression with RP relies on the analysis of smaller subset populations of patients with RP, and no study has quantified the effect size of the potential association. This study aims to elucidate and quantify the association between RP, anxiety, and depression. **Methods:** A retrospective case-control study was conducted of 6 093 833 medical records within the University of North Carolina Hospital and outpatient clinic system from July 1, 2004, to August 30, 2019. Patients with a diagnosis of RP, anxiety, and depression were identified within the Carolina Data Warehouse for Health by *International Classification of Diseases*, Ninth and Tenth Revision codes. **Results:** From the base population of 6 093 833 patients' medical records, 690 patients were diagnosed with RP, 253 065 with anxiety, and 232 541 with depression. Patients with RP have an odds ratio, adjusted for sex and age, of 4.915 (95% CI, 4.035-5.987) for having comorbid anxiety, 5.609 (95% CI, 4.622-6.807) for comorbid depression, and 4.130 (95% CI, 3.187-5.353) for comorbid anxiety and depression. **Conclusions:** Patients with RP have a higher prevalence of anxiety and depression, with increased odds of approximately 5 to 6 times for also carrying a diagnosis of anxiety or depression and about 4 times for carrying diagnoses of anxiety and depression compared with the general population.

Keywords

retinitis pigmentosa, anxiety, depression, mental health, retina

Introduction

Retinitis pigmentosa (RP), characterized by progressive photoreceptor and pigment epithelial cell dysfunction, is the most common group of inherited retinal disorders.[1] RP is estimated to affect 1 in every 4000 people in the United States and similarly worldwide.[2,3] RP is associated with varying presentations and disease progressions but classically is characterized by nyctalopia due to loss of rods, followed by peripheral then finally central vision loss due to cone and retinal pigmented epithelium degeneration.[2,3] Making an early diagnosis of RP can be difficult because of the gradual onset of disease. Symptoms that would prompt formal evaluation, such as central vision loss, do not occur until later stages of the disease. Difficulty with daily tasks may not arise in patients with a central field reduction as limited as 50° in diameter from the normal 180°.[4] The classic pattern, however, presents with symptoms as early as adolescence followed by an exponential decline that results in most patients becoming legally blind by age 40.[3,5-8]

Our growing understanding of RP has linked multiple genotypes to the disease, and there are ongoing studies into the discovery of a cure. Currently, however, there is no standard for treatment. High-dose vitamin A was proposed to slow the progression of the disease, but a Cochrane review found no such relationship.[9,10] The chronicity, progression, and lack of treatment options make it important to understand the implications for the patient. Quality of life measures can be used to assess the potential influences for the patient. Various studies have reported on the quality of life aspects tied to the difficulties of performing daily tasks and social functioning associated with RP.[11-13] Another important component included in quality of life is mental health, because a diagnosis such as anxiety or depression has been shown to have negative implications.[14,15]

Higher levels of anxiety and depression have shown to be associated with various ocular pathologies. The importance of identifying the relationship between RP, anxiety, and

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depression is highlighted in its comparison to other ocular pathologies. Glaucoma, for example, was found to have a dramatic increase for comorbid anxiety and depression.[9-15] In a Japanese study comparing glaucoma and RP, patients with RP were found to have a higher prevalence of depression.[16] The higher prevalence compared with patients with glaucoma, for whom reported odds ratios (ORs) were as high as 10.6 for anxiety and 12.3 for depression vs those without glaucoma, shows the importance of investigating the relationship for patients with RP.[17] Small subsets of patients with RP studied in France, Korea, Greece, and Sweden have reported a potential relationship between RP and depression. Possibly because of variations in the base study populations, the presence of increased risk, variance in the reported rate, and presence of influencing patient characteristics are conflicting.[18-24] Similarly, investigations on the relationship between RP and anxiety have also produced conflicting reports on the association.[19,20]

Although it is important to identify the presence or absence of an association between RP with anxiety and depression, the magnitude or effect size of the difference is equally significant. To our knowledge, there has been no quantification of the effect size of the association between RP, anxiety, and depression. In this study, we aim to elucidate the presence or absence of an association between RP with anxiety and depression. Additionally, if an association is present, we aim to quantify the effect size, represented as an OR, of the association.

Methods

This study is a retrospective, case-control study of patients within the University of North Carolina Hospital (UNCH) and outpatient clinic system who were diagnosed with RP, anxiety, and depression.

Sample

Certain *International Classification of Diseases*, Ninth (ICD-9) and Tenth Revision (ICD-10) codes within the medical records were used to determine the presence of RP (ICD-9: 362.74; ICD-10: H35.5), general anxiety disorder (ICD-9: 300; ICD-10: F41.x), and major depressive disorder (ICD-9: 311, 296.2x, 296.3x; ICD-10: F32.x, F33.x). ICD-9 and ICD-10 codes have set criteria, and studies have shown adequate accuracy between ICD codes and medical record–supported diagnoses.[25,26] Additionally, using ICD-9 and ICD-10 codes are an easily standardized method for identifying patients of interest and can be easily replicated for future comparison studies.

Data were stored and accessed from the Carolina Data Warehouse for Health between July 1, 2004, and August 30, 2019. Patients with a diagnosis of RP were considered the exposure group and compared with the general population without RP. During the study period, patients with or without a diagnosis of RP were categorized for having a diagnosis of anxiety, depression, or both at any point in their medical record. Patients were also stratified by sex and by age group (< 18 years, 18-64 years, ≥ 65 years). Age group stratifications were based on predetermined categories within the database.

Table 1. Baseline Patient Characteristics.

Demographic	Count (% of total population)[a]
Diagnosis	
With RP	690 (0.01)
Without RP	6 093 143 (99.99)
Sex	
Female	3 275 095 (53.7)
Male	2 818 738 (46.3)
Age group, y	
<18	778 448 (12.8)
18-64	3 599 032 (59.1)
≥65	1 716 353 (29.2)

Abbreviation: RP, retinitis pigmentosa.
[a]Percentages may not total 100 because of rounding.

Secondary Analysis

The average age of diagnosis for RP is 35 years, thus additional analysis was completed with patients stratified to age groups of younger than 35 years and 35 years and older.[3,5-8] In addition, ORs were recalculated with temporal data that required the mental health diagnosis to occur after the diagnosis of RP. In both cases, patients were stratified by sex and age.

Statistical Analysis

The χ^2 test of homogeneity and Fisher-exact test were used to determine a statistical significance between binomial proportions. Multiple logistic regression analysis was used to calculate the effect size of an association, through ORs, and determine the associated 95% CI. *P* values of less than .05 were considered to be statistically significant. Adjusted ORs were determined for sex and age. Age stratification was collected dichotomously to standardize ORs. Thus, ORs with age stratification were compared against those not in the designated age group. SPSS 26 (IBM) was the statistical software used for analysis.

Results

As shown in Table 1, the study queried 6 093 833 medical records, and 3 275 095 (53.74%) were of female patients. A total of 690 patients were diagnosed with RP, of whom 371 were female (53.7%), 253 065 (4.15%) were diagnosed with anxiety, and 232 541 (3.82%) with depression. Table 2 shows that the control population of individuals without a diagnosis of RP had a prevalence of anxiety of 4.15%, a prevalence of depression of 3.81%, and a prevalence of comorbid anxiety and depression of 2.90%.

Anxiety

A total of 122 patients (17.68%) diagnosed with RP were found to have comorbid anxiety. The χ^2 test of homogeneity determined that there was a statistical difference between the

Table 2. Number of Patients With Retinitis Pigmentosa With and Without Anxiety, Depression, and Comorbid Anxiety and Depression.

	Count (% of total population)[a]	
Diagnosis	With RP	Without RP
With anxiety	122 (0.002)	252 943 (4.2)
Without anxiety	568 (0.009)	5 840 200 (95.8)
With depression	129 (0.002)	232 412 (3.8)
Without depression	561 (0.009)	5 860 731 (96.2)
With anxiety/depression	65 (0.001)	171 132 (2.9)
Without anxiety/depression	504 (0.008)	5 728 211 (94.0)

Abbreviation: RP, retinitis pigmentosa.
[a]Percentages may not total 100 because rounding.

Table 3. Estimated Odds Ratio Between Retinitis Pigmentosa and Anxiety.[a]

Characteristic	Adjusted odds ratio	95% CI
RP[b]	4.915	4.035-5.987
<18 y[c]	3.964	1.226-12.818
18-64 y[c]	3.721	2.840-4.876
≥65 y[c]	7.696	5.693-10.403
Female[d]	4.999	3.903-6.401
Male[d]	4.781	3.442-6.642

Abbreviation: RP, retinitis pigmentosa.
[a]All *P* values are less than .001.
[b]Adjusted for age and sex.
[c]Adjusted for sex.
[d]Adjusted for age.

prevalence of anxiety in patients diagnosed with RP compared with the control group with a *P* value of less than .001. Table 3 displays the various calculated ORs pertaining to anxiety. Multivariable logistic regression models determined patients with RP, compared with patients without RP, had an OR of 4.915 (95% CI, 4.035-5.987; $P<.001$) for comorbid anxiety when adjusted for age and sex. When comparing patients with RP to those without, patients with RP who were younger than 18 years had an OR of 3.964 (95% CI, 1.226-12.818; $P<.001$), between age 18 and 64 years had an OR of 3.721 (95% CI 2.840-4.876; $P<.001$), and aged 65 years and older had an OR of 7.696 (95% CI, 5.693-10.403; $P<.001$) for comorbid anxiety and adjusting for sex. When adjusting for age and comparing against women without a diagnosis of RP, women with RP had an OR of 4.999 (95% CI, 3.903-6.401; $P < .001$) for comorbid anxiety. Similarly, when comparing men without RP to those with RP, men with RP had an OR of 4.781 (95% CI, 3.442-6.642; $P < .001$).

Depression

A total of 129 (18.70%) RP patients were diagnosed with comorbid depression. The difference in the prevalence of depression in this population compared with the control population was found to be statistically significant using the χ^2 test of homogeneity, with *P* less than .001. Table 4 presents the adjusted ORs related to depression. Calculated odds were determined for patients with a diagnosis of RP compared with patients without a diagnosis of RP. Patients with RP were determined to have an OR of 5.609 (95% CI, 4.622-6.807; $P<.001$) for comorbid depression when adjusted for age and sex. Patients with RP between age 18 and 64 years had an OR of 4.66 (95% CI, 3.590-6.048; $P<.001$), and aged 65 years and older, an OR of 7.522 (95% CI, 5.600-10.105; $P<.001$) for comorbid depression when adjusted for sex. Patients with RP younger than 18 had a CI that accepted the null hypothesis. Adjusting for age, women with RP, compared with women without RP, had an OR of 5.865 (95% CI, 4.607-7.468; $P<.001$) and men with RP, compared to men without RP, had an OR of 5.190 (95% CI, 3.747-7.188; $P<.001$) for comorbid depression.

Table 4. Estimated Odds Ratio Between Retinitis Pigmentosa and Depression.[a]

Characteristic	Adjusted odds ratio	95% CI
RP[b]	5.609	4.622-6.807
<18 y[c]	2.941	0.404-21.414
18-64 y[c]	4.660	3.590-6.048
≥65 y[c]	7.522	5.600-10.105
Female[d]	5.865	4.607-7.468
Male[d]	5.190	3.747-7.188

Abbreviation: RP, retinitis pigmentosa.
[a]All *P* values are less than .001.
[b]Adjusted for age and sex.
[c]Adjusted for sex.
[d]Adjusted for age.

Anxiety and Depression

Among patients diagnosed with RP, 65 (9.42%) had comorbid anxiety and depression. The difference of this compared with the control group was statistically significant, with a *P* value of less than .001 according to the χ^2 test of homogeneity. OR calculated for comorbid anxiety and depression are found in Table 5. Patients with RP were compared with patients without RP and were determined to have a 4.130 (95% CI, 3.187-5.353; $P<.001$) OR for a diagnosis of both anxiety and depression when adjusted for sex and age. Patients with a diagnosis of RP who were between ages 18 and 64 years had a 3.012 OR (95% CI, 2.103-4.314; $P<.001$), and patients aged 65 years and older had an OR of 6.925 (95% CI, 4.739-10.121; $P<.001$). No patients younger than 18 years were found to have a diagnosis of RP and comorbid anxiety and depression. ORs for comorbid anxiety and depression comparing women with a diagnosis of RP to women without a diagnosis of RP and men with a diagnosis of RP to men without a diagnosis of RP were completed with adjustments for age. Women with a diagnosis of RP were determined to have an OR of 6.274 (95% CI, 4.560-8.633; $P < .001$) while men with a diagnosis of RP were found to have an OR of 2.315 (95% CI, 1.467-3.653; $P < .001$).

Table 5. Estimated Odds Ratio Between Retinitis Pigmentosa and Comorbid Anxiety and Depression.

Characteristic	Adjusted odds ratio	95% CI	*P*
RP[a]	4.130	3.187-5.353	<.001
<18 y[b]	0.000	NA	NA
18-64 y[b]	3.012	2.103-4.314	<.001
≥65 y[b]	6.925	4.739-10.121	<.001
Female[c]	6.274	4.560-8.633	<.001
Male[c]	2.315	1.467-3.653	<.001

Abbreviations: NA, not applicable; RP, retinitis pigmentosa.
[a]Adjusted for age and sex.
[b]Adjusted for sex.
[c]Adjusted for age.

Table 6. Estimated Odds Ratio of Anxiety and Depression for Patients With Retinitis Pigmentosa.

Age, y	Adjusted odds ratio[a]	95% CI	*P*
Anxiety			
<35	3.773	2.268-6.275	<.001
≥35	5.176	4.178-6.412	<.001
Depression			
<35	1.694	0.747-3.844	<.001
≥35	6.402	5.230-7.836	<.001
Anxiety and depression			
<35	0.760	0.188-3.075	.001
≥35	4.875	3.734-6.365	<.001

[a]Adjusted for sex.

Secondary Analysis

Stratification by age groups of younger than 34 years and 35 years and older resulted in 987 941 women (30.2% of female population) and 929 269 males (33.0% of male population) younger than 35 years. Age 35 years was chosen as a cutoff because this is the average age of diagnosis of RP. The prevalence of anxiety in those younger than 35 years was 3.5% compared with 4.4% in those older than 35 years. Depression was present in 2.5% of those younger than 35 years, whereas 4.2% of those older than 35 years were found to have comorbid depression. The presence of comorbid anxiety and depression was found in 2.1% of those younger than 35 years and 3.2 for those older than 35 years. The χ^2 test of homogeneity found the difference between the prevalence of anxiety or depression among the age groups to be statistically significant ($P<.001$). The Fisher exact test determined the presence of a statistical significance between the age groups for those with comorbid anxiety and depression ($P<.001$). The calculated ORs for these groups are found in Table 6.

When adjusted for sex, patients with RP younger than 35 years had a 3.773 OR (95% CI, 2.268-6.275; $P<.001$) for having anxiety when compared with those without RP; for depression alone and anxiety and depression together, the ORs were found to accept the null hypothesis because their 95% CI contained the value of 1. Patients with RP 35 years and older had an OR, adjusted for sex, of 5.176 (95% CI, 4.178-6.412; $P<.001$) for having anxiety, 6.402 (95% CI, 5.230-7.836; $P<.001$) odds of having depression, and 4.875 odds (95% CI, 3.734-6.365; $P<.001$) of having both anxiety and depression.

When accounting for the sequence of the mental health diagnosis in relation to the diagnosis of RP and adjusting for sex and age, patients with RP compared with those without have a 2.059 OR (95% CI, 1.561-2.717; $P<.001$) for having anxiety and a 2.649 OR (95% CI, 1.978-3.547; $P < .001$) for having depression (Table 7).

Table 7. Estimated Odds Ratio of Anxiety and Depression for Patients With Retinitis Pigmentosa.[a]

Disease	Adjusted odds ratio[b]	95% CI
Anxiety	2.059	1.561-2.717
Depression	2.649	1.978-3.547

[a]All *P* values are less than .001.
[b]Adjusted for age and sex.

Conclusions

This study finds a statistically significant difference in the prevalence of anxiety and depression in individuals diagnosed with RP compared with those without RP. This finding alone, although controversial among previous studies, has been reported in the past.[18-24] To further understand the implications of this difference, further analysis was completed to calculate the effect size or magnitude of this difference. This value is presented in terms of increased odds of patients with RP to have a diagnosis of anxiety by 4.9-fold, depression by 5.6-fold, and both anxiety and depression by 4.1-fold when compared with those without RP.

Among the other studies that also found an association, the prevalence of depression and anxiety in the individuals diagnosed with RP did not always align with those found in this study.[19,20] This discrepancy may be partly explained by the differences in baseline prevalence of the disease in the smaller subset population, in ages between studies, and in requirements of the diagnosis.[18,27-29] Our sample size from patients seen at the UNCH system is several orders of magnitudes larger than previously published studies. As a large referral center that provides care for multiple surrounding areas and states, UNCH also serves as a safety net health care organization for North Carolina. Thus, our population may contain a set of patients who are more diverse racially, ethnically, and socioeconomically. Furthermore, our overall population prevalence for anxiety and depression is consistent with current epidemiological literature at 4.2% and 3.8%, respectively.[14,15]

Stratification of ORs provides additional insight into the potential patient characteristics that may be associated with higher odds of anxiety and depression. The increased odds for having a comorbid mental health diagnosis are more evident in patients aged 35 years and older when adjusting for sex. The difference in odds may be explained, in part, by various

aspects regarding the pathogenesis and progression of RP. Age 35 is the average age for patients to be diagnosed with RP, and this is most likely because of the progression of the disease to a point where the loss of central vision or function is observed.[3,30-32] Additionally, the prevalence of anxiety (15.2% of patients with RP), depression (17.8% of patients with RP), and both (9.1% of patients with RP) were higher, statistically significant by χ^2 test of homogeneity and Fisher exact test, in patients 35 years and older compared with those younger than 35 years. This is paradoxical to the decrease in the prevalence of anxiety and depression as the general population ages.[28,33] Women, compared with men while adjusting for age, also showed increased odds for having comorbid anxiety and depression, a consistent finding with literature reporting on the characteristics of anxiety and depression in the general population.[27]

Secondary analysis accounting for the sequence of the diagnosis, and with adjustments for sex, showed individuals with RP were found to still have double the risk of those without RP of developing a diagnosis of anxiety or depression. This value, however, most likely underestimates the true risk because of the difficulty of diagnosing RP in its early stages.

The increased in odds for patients with RP to have anxiety and depression suggest the potential for a higher risk of complications derived from the mental health disease. The general disease of depression and anxiety has also been shown to, independently, negatively affect a patient's quality of life,[14,15] which is derived from many facets of the patient's life; some aspects that depression or anxiety influence may directly hinder patients with RP. For example, patients with depression or anxiety tend to have decreased levels of physical activity, depression has been shown to reduce compliance with treatments, and reduced emotional health can lower incentive to pursue solutions to vision-related problems.[34-39] Increased levels of physical activity in patients with RP have been shown to be associated with better self-reported visual function and overall quality of life.[40] No cure currently exists for RP, but negative influences on a patient's compliance with treatments or desire to seek treatment can hinder not only the patient, but research towards finding the cure. RP-related visual impairments alone can negatively affect performance in daily activities, which can be further compounded by the presence of anxiety or depression.[41] These effects on daily activity can also result in a larger dependence on others for daily tasks, which may consequently further aggravate symptoms of depression.[23,35,41-45]

The cyclic nature and implications of anxiety and depression on patients with RP highlight the importance of whole-person care in patients with RP. Ophthalmologists and primary care physicians can collaborate and raise awareness about common mental health problems among patients with RP. Ophthalmology practices and primary care practices both can administer questionnaires as a screening tool for early detection of anxiety and depression, such as the Generalized Anxiety Disorder 7-item or 9-item Personal Health Questionnaire depression scale, both of which are validated and easily administered.[46-49] The 4-item Personal Health Questionnaire depression scale can also be used to screen both for anxiety and depression, and it has been shown to be feasible in ophthalmological practices.[46-49]

Findings in this study should be evaluated with the following limitations in mind. The retrospective nature of this study inherently hindered the ability to determine causation. The range of values within the 95% CI was, at times, relatively large, suggesting the sample size may have been too small; however, even the lower ends of the ORs were substantial.

Owing to limitations of our database, we used the age of the patient at the end of the study period, which might not have allowed enough time for a mental health diagnosis to occur among the younger patients. This aspect would most likely have decreased the effect size we ultimately found and caused our calculations to be more conservative. Thus, we felt it was an acceptable limitation.

Our findings further support the importance of the relationship between RP, anxiety, and depression. We were aware that our database would inhibit us from dose-adjusting our model for the effects of visual acuity, but previous work has shown that visual acuity does not explain the association of depression for patients with RP. Thus, we felt the study design still achieved our primary goal of identifying the association and quantifying its effect size between the general disease of RP, anxiety, and depression.[21] Furthermore, the establishment of a diagnosis was based on ICD-9 and ICD-10 codes, which may allow for the presence of some subjectivity when making the diagnosis. The population studied, however, included a wide network of patients who likely received these diagnoses from multiple providers. The diversity of individuals assigning the diagnoses helped to limit the influence of individual subjectivity. Last, the choice to use ICD-9 and ICD-10 codes provided an easily reproducible and standardized design.

In conclusion, we find patients with a diagnosis of RP to have a significantly increased prevalence of anxiety and depression, along with roughly 4- to 6-fold increased odds of having a diagnosis of anxiety and depression. Specifically, the population with the highest association are women aged 35 years and older.

Ethical Approval

All tenets of the Declaration of Helsinki were upheld throughout this study.

Statement of Informed Consent

This study was reviewed by the UNC institutional review board and deemed exempt from requiring consent.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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