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CLINICAL INVESTIGATION

Human immunodeficiency virus-related retinalmicroangiopathy and systemic cytomegalovirus disease association

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Abstract
Purpose To determine whether there is a significant association between human immunodeficiency virus (HIV)-related retinal microangiopathy and systemic cytomegalovirus (CMV) disease in HIV-infected patients.
Methods Participants in this single-center, cross-sectional, retrospective study were 383 HIV-infected patients assessed for ocular manifestations before the beginning of antiretroviral therapy. The presence of HIV-related retinal microangiopathy, the presence of systemic CMV disease, laboratory data, and demographic information were determined by referring to medical records. The significance of any association between HIV-related retinal microangiopathy and systemic CMV disease was determined by use of the Chi-squared test and by multivariate analysis.
Results HIV-related retinal microangiopathy was present in 85 patients, and was significantly associated with systemic CMV disease both by use of the Chi-squared test ($P = 0.006$) and by multivariate analysis ($P = 0.045$, odds ratio 2.03, 95 % confidence interval 1.02–4.06 adjusted for CD4+ cell count and plasma HIV-RNA level).
Conclusions These findings indicate that microangiopathy may be involved in the development of CMV disease in HIV-infected patients. Thus, detection of the presence of HIV-related retinal microangiopathy is important in the management of HIV-infected patients.

Keywords Microangiopathy · Cotton-wool spots · Cytomegalovirus · Human immunodeficiency virus · Acquired immune deficiency syndrome

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Introduction

Human immunodeficiency virus (HIV)-related retinal microangiopathy, which is manifested as cotton-wool spots, intraretinal hemorrhage, or both, is the most common ocular complication of HIV infection [1]. Many studies show that it reflects the severity of HIV-infection, e.g., lower CD4+ cell counts and higher plasma HIV-RNA levels [2, 3]. Histological results are indicative of damage of microvessels around cotton-wool spots, e.g., loss of pericytes, microaneurysm formation, thickened vascular walls, swelling of endothelial cells, and thickening of the vascular basement membrane [4, 5]. Several hypotheses have been proposed to explain the pathogenesis of HIV-related retinal microangiopathy:

1. immune complex disease;
2. direct damage of HIV to retinal vascular endothelium; and
3. hemorheologic abnormalities [1].

Theories about the pathogenesis of HIV-related retinal microangiopathy are not conclusive, however.

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The presence of HIV-related retinal microangiopathy is important, because it is reported to be a high risk factor for the development of cytomegalovirus (CMV) retinitis [6–9]. CMV infection causes a variety of end organ diseases in HIV-infected patients. A pathology report published by Holland et al. [6] indicates that all 16 acquired immune deficiency syndrome (AIDS) patients with retinal cotton-wool spots had systemic CMV disease. However, the association between HIV-related retinal microangiopathy and end organ CMV diseases other than CMV retinitis has not been proved statistically.

The purpose of this study was to determine, by means of a cross-sectional study, whether there is a significant association between the presence of HIV-related retinal microangiopathy and the presence of systemic CMV disease.

Materials and methods

Subjects and study design

This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital. This was a cross-sectional chart-review study. We reviewed the medical records of 383 consecutive HIV-infected patients who were examined for ocular manifestations at the Tokyo Metropolitan Komagome Hospital before initiation of antiretroviral therapy (ART). The patients were examined between January 2000 and December 2009, and all 383 patients began the ART after evaluation and treatment of their complications. Diagnosis and treatment of AIDS were made by HIV specialists in the Department of Infectious Diseases.

We obtained the following information from medical records:

- ocular manifestations and presence of systemic CMV disease before the commencement of ART;
- demographic information (age, sex, and ethnicity); and
- laboratory data at the time of ocular assessment.

The stage of HIV disease was determined from the patients' medical records on the basis of the 2008 CDC criteria [10].

Ocular manifestations

The physicians at the Department of Infectious Diseases referred all the patients to our department before the initiation of ART, where they underwent a complete ophthalmologic examination. Patients were categorized into 6 groups on the basis of their ocular manifestations. Patients with intraocular diseases were classified into Groups A and B; patients in Group A had HIV-related intraocular findings [1] whereas those in Group B had intraocular findings but not HIV-related intraocular findings. Patients with extraocular findings without intraocular findings were placed in Group C. Patients without any abnormal intraocular or extraocular findings were placed in Group D.

Group A was further subdivided into 2 groups; patients in Group A1 had only HIV-related retinal microangiopathy and patients in Group A2 had other HIV-related intraocular findings either with or without HIV-related microangiopathy. HIV-related retinal microangiopathy was regarded as present when cotton-wool spots or intraretinal hemorrhage or both were detected. HIV-related retinal microangiopathy was differentiated from early CMV retinitis by lack of progressive enlargement over 1–2 weeks and resolution over 4–6 weeks [11]. Group B was also subdivided into 2 groups; patients in Group B1 had retinal hemorrhage or cotton-wool spots, e.g., diabetic retinopathy and hypertensive retinopathy, and patients in Group B2 had no retinal hemorrhage or cotton-wool spots but had other intraocular findings, e.g., lattice degeneration, glaucoma. Because of the difficulty of making a definitive diagnosis of HIV-related retinal microangiopathy for the patients in Groups A2 and B1, they were excluded from the statistical analysis.

Systemic CMV disease

The presence of systemic CMV disease was determined by physicians of the Department of Infectious Diseases. Diagnosis of gastrointestinal disease was based on histological evidence of tissue destruction with the presence of viral inclusion bodies. Diagnosis of CMV neurologic disease was based on amplification of the DNA of CMV in cerebrospinal fluid by use of the Amplicor CMV test by polymerase chain reaction (PCR; Roche Diagnostic Systems, Branchburg, NJ, USA), and exclusion of other intracranial diseases by magnetic resonance imaging.

Laboratory data

The CD4+ cell count, CD8+ cell count, and plasma HIV-RNA level were used as markers of HIV infection. The CD4+ cell count and CD8+ cell count were measured by use of specific monoclonal antibodies and fluorescence-activated cell-sorter analysis. Plasma HIV-RNA level was measured by use of the Roche Amplicor HIV Monitor assay based on reverse transcription PCR (Roche Molecular Systems, Tokyo, Japan).

Statistical methods

The significance of any association between the presence of systemic CMV disease and the presence of HIV-related

retinal microangiopathy, laboratory data, and demographic information were determined by use of Mann–Whitney's *U* tests for numerical data and Chi-squared tests for categorical data. We also determined the significance of the association between the presence of HIV-related retinal microangiopathy and the presence of systemic CMV disease by multivariate logistic regression analysis. Age, sex, ethnicity, a decrease in CD4+ cell count <50 cells/μl, and an increase in plasma HIV-RNA level $>1.0 \times 10^6$ copies/ml were defined as explanatory variables, if each factor was associated with the presence of systemic CMV disease in the univariate logistic regression ($P < 0.20$). The odds ratio (OR) and 95 % confidence intervals (CI) were calculated. All statistical analysis was conducted by use of the R package for statistical analysis, ver. 2.14. *P* values <0.05 were regarded as statistically significant.

Results

Ocular manifestations (Table 1)

Categorization of patients on the basis of their ocular manifestations is summarized in Table 1. HIV-related retinal microangiopathy was detected in 85 patients (Group A1). Other HIV-related intraocular findings were detected in 58 patients (Group A2). There were 23 patients with CMV retinitis in Group A2. Eight patients were categorized into Group B1, 19 patients were categorized into Group B2, and 3 patients were categorized into Group C. Two-hundred and ten patients had no abnormal intraocular or extraocular findings (Group D). As mentioned in the "Materials and methods" section, 66 patients (17 %) were excluded because of their ocular manifestations, 58 patients from Group A2 and 8 patients from Group B1. Finally, 317 patients were analyzed statistically.

Systemic CMV disease

Among the 317 patients analyzed statistically, 43 (14 %) had systemic CMV disease. Forty one patients had gastrointestinal disease, 1 had encephalitis, and 1 had both peripheral neuropathy and gastrointestinal disease. No patient had any other type of systemic CMV disease.

Characteristics of the patients (Table 2)

The clinical characteristics of the 317 patients are summarized in Table 2. The median age was 42 years (range 18–75 years), 294 (93 %) were men, and 298 (94 %) were Japanese. Thirteen patients were at stage 2 of HIV infection and 304 patients were at stage 3 of HIV infection (AIDS). Median CD4+ cell count was 48 cells/μl (range 1–379 cells/μl). Median CD8+ cell count was 460 cells/μl (range 9–5,041 cells/μl). Median plasma HIV-RNA level was 2.6×10^5 copies/ml (range 7.6×10^2–6.7×10^8 copies/ml). There were no significant differences between the age, sex, ethnicity, clinical stage of HIV infection, and laboratory data of the 317 patients included in the study and those of the 66 excluded patients. However, the CD4+ cell count of the 23 patients with CMV retinitis was significantly lower than that of the 317 patients included (median 18 cells/μl, range 1–195 cells/μl, $P = 0.004$). The plasma HIV-RNA level of the 23 excluded patients was slightly higher than that of the 317 included patients (median 4.2×10^5 copies/ml, range 1.0×10^5–1.1×10^7 copies/ml, $P = 0.090$).

HIV-related retinal microangiopathy was significantly associated with systemic CMV disease ($P = 0.006$). CD4+ cell count was significantly lower for patients with systemic CMV disease than for patients without systemic CMV disease ($P = 0.003$). CD8+ cell count was slightly lower for patients with systemic CMV disease than for patients without systemic CMV disease, although the difference was not significant ($P = 0.052$). The plasma HIV-

Table 1 Patients' categorization on the basis of ocular manifestations

Category	Ocular manifestation	Number of patients
Group A	With HIV-related intraocular findings	
A1	HIV-related retinal microangiopathy	85
A2	Other HIV-related intraocular findings with/without HIV-related retinal microangiopathy	58
Group B	With intraocular findings that were not related to HIV infection	
B1	Retinal hemorrhages or cotton-wool spots	8
B2	Without retinal hemorrhages or cotton-wool spots	19
Group C	With extraocular findings without intraocular findings	3
Group D	Without abnormal intraocular and extraocular findings	210
Total		383

HIV human immunodeficiency virus

Table 2 Baseline characteristics of the 317 patients

Characteristic	Patients ($n = 317$)	Systemic CMV disease		P value
		Yes ($n = 43$)	No ($n = 274$)	
Age (years), [median, (range)]	42 (18–75)	43 (27–65)	41 (18–75)	0.31[a]
Male sex [n, (%)]	294 (93 %)	40 (93 %)	255 (93 %)	0.99[b]
Japanese [n, (%)]	298 (94 %)	38 (88 %)	260 (95 %)	0.09[b]
CDC clinical stage [n, (%)][c]				0.15[b]
Stage 1	0 (0 %)	0 (0 %)	0 (0 %)	
Stage 2	13 (4 %)	0 (0 %)	13 (5 %)	
Stage 3 (AIDS)	304 (96 %)	43 (100 %)	261 (95 %)	
Retinal microangiopathy [n, (%)]	85 (22 %)	19 (44 %)	66 (24 %)	0.006[b],**
CD4 count (cells/μl), [median, (range)]	48 (1–379)	26 (4–377)	52 (1–379)	0.003[a],**
CD8 count (cells/μl), [median, (range)]	460 (9–5041)	361 (75–1818)	465 (9–5041)	0.052[a]
Plasma HIV-RNA level (copies/ml), [median, (range)]	2.6×10^5 (7.6×10^2 – 6.7×10^8)	2.9×10^5 (5.6×10^3– 6.7×10^8)	2.5×10^5 (7.6×10^2– 9.1×10^7)	0.17[a]

CMV cytomegalovirus, *CDC* Centers for disease control and prevention, *AIDS* acquired immune deficiency syndrome

[a] Mann–Whitney U test

[b] Chi-squared test, ** $P < 0.01$

[c] Clinical staging of HIV-infected patients was performed on the basis of 2008 CDC criteria [10]

Table 3 Univariate and multivariate analysis between systemic CMV disease and possible explanatory variables

Variable	Univariate analysis			Multivariate analysis		
	OR	95 % CI	P value	OR	95 % CI	P value
Age per 1-year increase	1.01	0.98–1.04	0.39			
Male sex	0.99	0.28–3.51	0.99			
Japanese[a]	0.41	0.14–1.20	0.10	0.40	0.13–1.23	0.11
Retinal microangiopathy[a]	2.50	1.29–4.84	0.007**	2.03	1.02–4.06	0.045*
CD4+ count, <50 cells/μl[a]	2.44	1.22–4.89	0.011*	2.01	0.98–4.13	0.057
Plasma HIV-RNA, $>1.0 \times 10^6$ copies/ml[a]	2.57	0.97–6.80	0.057	2.08	0.77–5.61	0.15

OR odds ratio, *CI* confidence interval

* $P < 0.05$, ** $P < 0.01$

[a] Explanatory variables associated with presence of systemic CMV disease in univariate analysis ($p < 0.20$) were included in the multivariate logistic regression model (as mentioned in the "Materials and methods" section)

RNA level was not significantly associated with presence of systemic CMV disease ($P = 0.17$).

Multivariate analysis between systemic CMV disease and each factor (Table 3)

We used multivariate logistic regression analysis to determine whether HIV-related retinal microangiopathy is an independent risk factor for the presence of systemic CMV disease. In univariate analysis, P values were <0.20 for associations between systemic CMV disease and ethnicity ($P = 0.10$), HIV-related retinal microangiopathy ($P = 0.007$), a decrease in CD4+ cell count <50 cells/μl ($P = 0.011$), and an increase in plasma HIV-RNA level $>1.0 \times 10^6$ copies/ml ($P = 0.057$). Age ($P = 0.39$) and sex ($P = 0.99$) were not significantly associated with the presence of systemic CMV disease. Ethnicity, HIV-related retinal microangiopathy, a decrease in CD4+ cell count <50 cells/μl, and an increase in plasma HIV-RNA level $>1.0 \times 10^6$ copies/ml were defined as explanatory variables in the multivariate logistic regression model. HIV-related retinal microangiopathy was independently associated with systemic CMV disease (OR 2.03, 95 %CI 1.02–4.06, $P = 0.045$). The association between a decrease in CD4+ cell count <50 cells/μl and systemic CMV disease was suggestive but not significant (OR 2.01, 95 %CI 0.98–4.13, $P = 0.057$). Ethnicity and an increase in plasma HIV-RNA level $>1.0 \times 10^6$ copies/ml were not significantly associated

with systemic CMV disease in the multivariate analysis ($P = 0.11$, $P = 0.15$, respectively). Co-linearities between the explanatory variables were low.

Discussion

HIV-related retinal microangiopathy is significantly associated with lower CD4+ cell count and higher plasma HIV-RNA levels [2, 3]. The presence of HIV-related retinal microangiopathy reflects the stage of HIV disease and poor patient survival [12, 13]. It is also reported that lower CD4+ cell count and higher plasma HIV-RNA levels are important risk factors indicative of poor patient survival and the development of opportunistic infections [14–18]. Our logistic regression results indicate that HIV-related retinal microangiopathy is significantly associated with systemic CMV disease even after adjustment for CD4+ cell count and plasma HIV-RNA level. To the best of our knowledge, this is the first study to demonstrate a significant association between HIV-related retinal microangiopathy and systemic CMV disease.

We suggest two possible causes for the significant association between retinal microangiopathy and systemic CMV disease. First, patients who have HIV-related retinal microangiopathy are most likely also to have systemic microangiopathy; second, the systemic microangiopathy may facilitate the development of systemic CMV disease.

Similar ocular findings (cotton-wool spots and retinal hemorrhages) are also found in patients with other systemic diseases, for example diabetes mellitus, systemic hypertension, and systemic inflammatory disease [19–21]. For these patients detection of retinal microangiopathy is important in management of the systemic disease. For example, diabetic retinopathy is a significant predictor of diabetic nephropathy [22]. Similar associations may be present for HIV-related retinal microangiopathy and systemic vascular damage in HIV infected patients. Geier et al. [23] report that the severity of the ocular microangiopathic syndrome is significantly associated with the severity of cerebral hypoperfusion. The results of their study and ours indicate there are significant associations between HIV-related retinal microangiopathy and systemic vascular damage. Although many reports indicate that HIV-infected patients are at high risk of developing systemic vascular diseases, e.g., cardiovascular disease, stroke, and renal disease [24–27], there have been very few investigations of the significance of the association between HIV-related retinal microangiopathy and systemic vascular diseases [23]. Further evaluation of the associations between HIV-related retinal microangiopathy and systemic vascular diseases are needed.

Our results support previous findings [6, 7, 9] that HIV-related retinal microangiopathy is a risk factor for development of CMV retinitis. Although the cause of the significant association between HIV-related retinal microangiopathy and CMV retinitis has not been definitively shown, many researchers hypothesize that damage to the retinal microvasculature may facilitate invasion of CMV from vessels into retinal tissue [4, 6, 28, 29]. The same mechanism is possible for systemic microangiopathy and systemic CMV disease. However, the involvement of microangiopathy and CMV in the development of gastrointestinal diseases may be different from that in the development of neural diseases. In our study, gastrointestinal and neural diseases were combined as systemic CMV diseases. This is one limitation of our study; further studies are needed to examine each factor separately.

It has often been reported that a decrease in CD4+ cell count <50 cells/μl is a significant risk factor for development of CMV disease [9, 18, 30, 31]. In addition, at least three studies have shown that a high plasma HIV-RNA level is associated with CMV disease [31–33]. Among our participants, the association between a decrease in CD4+ cell count <50 cells/μl and systemic CMV disease was only suggestive, and an increase in plasma HIV-RNA level $>1.0 \times 10^6$ copies/ml was not associated with systemic CMV disease in the multivariate analysis. There are other limitations to our study. Our participants were HIV-infected patients who required initiation of ART, and few patients had high CD4+ cell count and low plasma HIV-RNA level. Therefore, the significance of the association between the CD4+ cell count and systemic CMV disease, and plasma HIV-RNA levels and systemic CMV disease, may have been underestimated in our study. In addition, we excluded patients with CMV retinitis because of the difficulty of detecting the presence of HIV-related retinal microangiopathy after the development of CMV retinitis. The 23 patients with CMV retinitis who were excluded had low CD4+ cell count and slightly high HIV-RNA level. This exclusion may have also affected the statistical results of these associations. Thus, we believe our results are in agreement with those from previous studies that show a significant association between systemic CMV disease and low CD4+ cell count and high HIV-RNA level [9, 18, 31–33]. To investigate the precise significance of the association between the presence of HIV-related retinal microangiopathy, CD4+ cell count, plasma HIV-RNA level, and presence of CMV disease, additional longitudinal studies are needed which investigate these associations among stage 1 or 2 HIV-infected patients, i.e., before the AIDS stage.

CD4+ cell count and plasma HIV-RNA levels are important indicators of the need to begin ART or prophylaxis against opportunistic diseases. Our study shows that HIV-related retinal microangiopathy that can be easily detected by ophthalmologists, could be another clinical

indicator of the need for systemic treatment that may inhibit the development of systemic CMV disease.

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ORIGINAL PAPER

Predictive factors for comorbid psychiatric disorders and their impact on vision-related quality of life in patients with high myopia

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Abstract To determine the incidence of depression and anxiety disorders in patients with high myopia as well as the factors that would predict the development of psychiatric complications and their impact on vision-related quality of life (VR-QoL). Two hundred and five patients with pathologic myopia (axial length ≥26.50 mm) were studied. Incidence of depression and anxiety disorders was determined using the Hospital Anxiety and Depression Scale (HADS). VR-QoL was determined by the 25-item National Eye Institute Visual Function Questionnaire. Incidence of depression was 22.0 % and incidence of anxiety disorder was 25.9 %. Absence of children was the only factor significantly associated with the presence of depression, and a past history of cataract surgery was the only factor significantly associated with the presence of anxiety disorder. Factors which decreased the VR-QoL were in order of importance—anxiety disorder, decreased visual acuity in the best eye, depression, and being female. Responses of the subjects to two HADS statements 'I can laugh and see the funny side of things' and 'I can enjoy a good book or radio or television program' identified 82.2 % of depressed patients, and 'I get sudden feelings of panic' and 'I can sit at ease and feel relaxed' identified 71.7 % of patients with anxiety disorder. Twenty-two to 26 % of highly myopic patients had psychiatric disorders which had a strong negative impact on their VR-QoL. Two statements from the HADS questionnaire can be used to screen highly myopic patients for depression or anxiety disorders.

Keywords High myopia · Depression · Anxiety · Vision-related quality of life

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Introduction

Recent studies have shown that psychiatric disorders, such as depression and anxiety disorders, often develop as comorbidities in cases of chronic and non-chronic somatic illnesses, e.g., cardiac infarction, rheumatoid arthritis, and malignancies [1–3]. Earlier studies also demonstrated that such psychiatric

complications have a negative impact on health-related quality of life (HR-QoL) [4–6]. This is important because it has been established that the HR-QoL score is an effective rating scale to assess the medical care from a patient's perspective [7].

High myopia is a major cause of irreversible blindness worldwide especially in East Asian countries [8–10]. In fact, myopic macular degeneration is the leading cause of blindness in Japan as found in the Tajimi study [11, 12], and the second most important cause of blindness in China [13]. Takashima et al. [14] previously evaluated HR-QoL in patients with high myopia using a self-rating questionnaire, and reported that scores of the HR-QoL subscales were significantly lower than those of a control group. Although it was concluded that these low scores were attributed to disability and handicap caused by the visual disturbances due to high myopia, we assume that comorbid psychiatric disturbances might also be associated with HR-QoL through vision-related QoL (VR-QoL).

The VR-QoL questionnaire is a subtest of the HR-QoL questionnaire that is specific for ocular diseases [15]. The impact of comorbid depression and anxiety disorders in patients with chronic ocular diseases, such as age-related macular degeneration, and glaucoma, on VR-QoL has been reported [16–18]. However, to the best of our knowledge, a PubMed search using the words 'high myopia' and vision-related quality of life', 'high myopia and depression' and 'high myopia and anxiety' did not return any studies investigating the impact of comorbid depression and anxiety disorders on VR-QoL in patients with high myopia. Because highly myopic patients are often visually impaired during their most productive years, the associated psychiatric disorders would much more affect their social ability, and add a greater burden to family members and community, than those of age-related macular degeneration or glaucoma.

The Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), is a standard instrument for diagnosing psychiatric disorders [19]. However, because this instrument is designed to be administered by a trained mental health professional, it might be impossible for ophthalmologist to assess mental health in clinical practices. Therefore, several screening tools have been developed for a non-specialist to detect a patient's psychological distress. While most of screening tools are developed on the assumption that the subjects would be physically healthy, the 14-item self-administered questionnaire from the Hospital Anxiety and Depression Scale (HADS), that can simultaneously evaluate both depression and anxiety disorder on two orthogonal axes, is well accepted to screen psychiatric disorders in patients with somatic illness [20, 21]. Compared with diagnoses made with the SCID, optimal compromise between sensitivity and specificity for HADS diagnoses is achieved most frequently at a cut-off score of $\geq$8 for both depression and anxiety disorder subscales, giving sensitivities and specificities for both subscales of approximately 80 % [22].

The purpose of this study was to estimate the prevalence of depression and anxiety disorders in patients with high myopia using the HADS, and to determine the factors associated with the development of psychiatric complications and their impact on VR-QoL. Our findings allowed us to develop a simple algorithm to screen depression and anxiety disorders in patients with high myopia.

Methods

Subjects

This research adhered to the tenets of the Declaration of Helsinki, and the procedures were approved by the Ethics Committee of Tokyo Medical and Dental University. Written informed consent was obtained from all patients.

Patients with high myopia who were examined in the High Myopia Clinic in Tokyo Medical and Dental University, Tokyo, Japan, between September and October 2010, were studied. Generally, high myopia can be defined as spherical equivalent >6.00 diopters (D) or axial length $\geq$26.50 mm. However, a previous study suggests that the definition of high myopia based on axial length is more appropriate than the one based on refraction [23]. This is because axial elongation, in addition to myopic pathology, is a factor associated with ocular comorbidities resulting from high myopia. Therefore, in our study, the eyes were classified as being high myopia when their axial lengths were $\geq$26.50 mm. For controls, 72 emmetropic eyes (refractive error $<\pm$3D) of 72 subjects were examined. All the emmetropic participants were current or former staff members of the Tokyo Medical and Dental University, and all volunteered.

Patients who had serious systemic disorders such as cognitive disturbance, mental disability or limb deficiency, or severe disabilities such as complete hemiplegia or total leg paralysis caused by spinal injury, and patients who had visual impairment due to other causes than high myopia, who were scheduled for eye surgery, or were <20 years old, were all excluded from our study. However, patients who were receiving treatment for systemic illnesses such as hypertension, diabetes mellitus, cardiac infarction or rheumatism, or patients who has a past history of treatment for ocular comorbidities resulting from high myopia were not excluded. None of the patients had undergone refractive surgery.

Self-reporting questionnaire

The provided HR-QoL questionnaire had three subcategories. The first was on the socio-demographic characteristics of the individual, e.g., age, gender, family, marital status, presence of children, occupation, educational background, mental disability, and systemic complications. The second category comprised 14 questions on the HADS which was used to screen for depression and anxiety disorders in patients with somatic illnesses. And the third category was the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) which was used to assess VR-QoL.

Hospital Anxiety and Depression Scale (HADS)

The Japanese version of HADS is a reliable, validated, widely used self-reporting scale designed to screen for clinically significant depression and anxiety disorders in patients with somatic illnesses [20, 21]. It is a 14-item questionnaire; seven items relate to depression (HADS-D) and seven items relate to anxiety (HADS-A). To grade the questionnaire, a 4-point Likert scale was used—0 representing absence of symptoms to 3 representing maximum symptoms. A scale of 0–21 was used to classify HADS-D and HADS-A. The following cut-off scores have been commonly used in other studies—total score ≤ 7 is classified as a non-case; 8–10 classified as a possible case; and 11–21 classified as a probable case. According to Bjelland et al. [22] an optimal balance between sensitivity and specificity is achieved when a case is defined by a score ≥ 8 on both the HADS-A and HADS-D; we used a score ≥ 8 as clinically significant distress for statistical analysis.

National Eye Institute 25-item Visual Function Questionnaire (NEI-VFQ25)

The NEI-VFQ25 is a reliable, validated, widely used self-reporting questionnaire designed to evaluate a patient's VR-QoL [15, 24]. It consists of 12 subscales—one general health-related scale and 11 vision-related scales (general vision, near vision, distance vision, driving vision, peripheral vision, color vision, ocular pain, vision-associated role limitations, dependency, social functioning, and mental health). A 5-point Likert scale was used to answer the questionnaire and each subscale ranged from 0 (worst state) to 100 (best state). A composite score was obtained from the following subscales—general vision, near vision, distance vision, vision-associated role limitations, dependency, social functioning, and mental health. The seven subscales composite score is mainly used in the Japanese version of the NEI-VFQ25 and was used in this study.

Reliability and validation of the subscales of the HADS and the NEI-VFQ25

The internal consistency and reliability of the two subscales and seven subscales of HADS and the composite score of the NEI-VFQ25 were assessed using Cronbach alpha coefficients.

Statistical analyses

The results of the questionnaires are shown by summary statistics. The patients were classified into two groups according to the HADS-D or HADS-A cut-off score of ≥ 8. The socio-demographic and clinical characteristics and the NEI-VFQ25 scores were compared between the two groups using Mann–Whitney's U tests, χ^2 tests, or Fisher's exact probability tests.

To estimate the predictive factors and their contribution for the development of depression or anxiety disorders, a multivariate logistic regression analysis was performed. In addition, to determine the impact of depression and anxiety disorders on the seven subscales composite score of the NEI-VFQ, a multiple linear regression analysis was performed. The explanation variables were selected based on the external

clinical judgment led by referring to the previous literatures, or on the statistical significance in univariate screening. In both analyses, an appropriate number of explanation variables were included, and if the variables seemed to confound with each other, only one variable was selected.

Finally, to simplify the task for ophthalmologists to detect psychiatric disorders in patients with high myopia, the items in the HADS which were critical for screening for depression and anxiety disorders, were identified by a Classification and Regression Tree Analysis (CART) [25] similar to that performed by Augustin et al. [16]. First, an impurity index was calculated from the collected data for all HADS items. Then, the CART was constructed by dividing the subsets of data into two groups using the HADS item having the lowest impurity index. Repeatedly, an impurity index was calculated for all HADS items at each branch and the two groups were split again into two subgroups using the HADS item with the lowest impurity index. The HADS items resulting in minimum impurity indices, consequently enabling the best detection of depression or anxiety disorders accurately, were selected.

All decimal BCVA units were converted to the logarithm of minimum angle of resolution (LogMAR) for statistical purpose. A spherical equivalent was used for the calculations of refractive error. The spherical equivalent was defined as a sphere plus half of the cylindrical refraction. Data analyses were performed using the SPSS 12.0 software (SPSS, Chicago, IL, USA) or R version 2.10.1. A P value <0.05 was considered to be statistically significant.

Ophthalmic examinations

All the participants had a comprehensive ocular examination including measurement of the refractive error (spherical equivalent), axial length with the intraocular (IOL) master (Carl Zeiss Meditec, Dublin, CA, USA), fundus biomicroscopy, visual field examination, and optical coherence tomography (OCT) (Cirrus; Carl-Zeiss Meditec, Germany).

The ocular comorbidities specific to high myopia included the visual field defects due to pathologic myopia, and three fundus lesions—myopic choroidal neovascularization (myopic CNV), severe chorioretinal atrophy, and myopic tractional maculopathy (MTM).

The kinetic visual fields were measured for each eye by Goldmann perimetry with the refractive errors corrected by disposable soft contact lenses. The findings were quantified in a grid system similar to that used by Kwon et al. [26]. The grid consisted of 100 equal sectors that lay within the V4 isopters. The visual field value ranged from 0 to 100 with 0 indicating a total loss of vision and 100 represents a normal visual field within the V4 isopters. Highly myopic patients with >10 % defect in the visual field (a visual field value <90) were defined to have significant myopic visual field defects, as we have reported [27].

A myopic CNV included all phases CNV—active phase, scar phase, and atrophic phase. Myopic chorioretinal atrophy was divided into diffuse atrophy and patchy atrophy [28]. Severe chorioretinal atrophy was defined as diffuse chorioretinal atrophy occupying the entire posterior fundus or as patchy chorioretinal atrophy when the atrophy was 3 times larger than the disc area. MTM was defined according to Panozzo and Mercanti [29] based on the OCT findings. The MTM included retinal thickening (foveal thickness >200 μm), macular retinoschisis, retinal detachment, and lamellar macular holes.

Results

A total of 250 patients with high myopia were studied. Among those patients, 45 were excluded—18 because they failed to fill out the questionnaires properly, five because they had difficulties in filling out the questionnaires by themselves due to cognitive disorders, 14 because of a history of mental disorders, and eight because of visual impairments not due to high myopia. Finally, 205 patients met our inclusion criteria. As controls, 72 emmetropic subjects (spherical equivalent of refractive error $<\pm 3$D) were also studied. Comparison of socio-demographic and clinical characteristics factors of those 205 patients and controls are summarized in Tables 1 and 2. Comparisons between highly myopic patients and emmetropic subjects showed that there were no significant differences between the two groups with regard to age, gender and other sociodemographic variables apart from education (Mann–Whitney's U tests and χ^2 tests).

Table 1 Comparison of sociodemographic characteristics between patients with high myopia and control group

Sociodemographic variables	High myopia	Control	*P* value
Age (years), median (IQR)	60 (49–68)	60 (45–65)	0.495
Gender, *n* (%)			
Male	69 (33.7)	26 (36.1)	0.775
Female	136 (66.3)	46 (63.9)	
Living arrangements, *n* (%)			
Living alone	31 (15.1)	16 (22.2)	0.236
Living with someone else	163 (79.5)	56 (77.8)	
Unanswered	11 (5.4)	0 (0.0)	
Marital status, *n* (%)			
Married	149 (72.7)	56 (77.8)	0.867
Unmarried, widowed or divorced	45 (22.0)	16 (22.2)	
Unanswered	11 (5.4)	0 (0.0)	
Children, *n* (%)			
Present	148 (72.2)	48 (66.7)	0.113
Not present	46 (22.4)	24 (33.3)	
Unanswered	10 (4.9)	0 (0.0)	
Education, *n* (%)			
High school or less	85 (41.5)	18 (25.0)	0.039*
College	119 (58.0)	54 (75.0)	
Unanswered	1 (0.5)	0 (0.0)	
Employment status, *n* (%)			
In employment	92 (44.9)	40 (55.6)	0.119
Unemployed or retired	113 (55.1)	32 (44.4)	
Systemic complication, *n* (%)			
Present	78 (38.0)	24 (33.3)	0.475
Not present	127 (62.0)	48 (66.7)	

IQR interquartile range

* $P < 0.05$

In patients with high myopia, the median HADS-D score was 4.0 (interquartile range 2.0–7.0) and the median HADS-A score was 5.0 (interquartile range 3.0–8.0). The Cronbach alpha value for HADS-D was 0.78, while the Cronbach alpha value for HADS-A was 0.80. Both values exceeded the recommended values of 0.70, indicating adequate internal consistency. A HADS-D score ≥8 and HADS-A score ≥8 were observed in 22.0 % ($n = 45$) and 25.9 % ($n = 53$), respectively. Combined HADS-D and HADS-A score ≥8 was present in 13.7 % ($n = 28$) of 205 patients. As shown in Table 3, the median HADS-A score and prevalence of these psychiatric disorders in patients with high myopia were significantly higher than those of emmetropic subjects, except for the median HADS-D and combined HADS-D and HADS-A score of ≥8 (Mann–Whitney's *U* tests and χ^2 tests).

A comparison of the socio-demographic and clinical characteristics between patients with HADS-D and HADS-A of <8 and of ≥8 are shown in Tables 4 and 5. Univariate analyses showed that the depressed group tended to be younger ($P = 0.033$), had no children ($P = 0.002$), and had longer axial lengths ($P = 0.043$). However, a multivariate logistic regression analysis showed that the absence of children was the only factor significantly associated with the presence of depression (odds ratio [OR] 0.373; 95 % CI 0.174–0.802; $P = 0.012$), where the explanatory variables included age, gender, axial length, visual acuity in better eye, and presence of children. In addition, univariate analyses showed that the anxiety disorders group tended to have longer axial length ($P = 0.017$) and had a past history of cataract surgery ($P = 0.014$). However, a multivariate logistic regression analysis showed that a past history of cataract

Table 2 Comparison of eye characteristics between patients with high myopia and control group

Clinical variables	High myopia	Control	*P* value
Refractive error (D), median (IQR)	−11.0 (−14.3 to −5.7)	−0.25 (−2.0 to 0.9)	<0.001***
Axial length (mm), median (IQR)	29.9 (28.7–31.2)	24.1 (22.9–24.9)	<0.001***
LogMAR in the better eye, median (IQR)	0.0 (−0.1 to 0.1)	0.2 (0.2–0.3)	<0.001***
LogMAR in the worse eye, median (IQR)	0.2 (0.0–0.7)	0.3 (0.2–0.3)	<0.001***
Myopic CNV, *n* (%)			
Present			
Not present	123 (60.0)		
Severe chorioretinal atrophy, *n* (%)			
Present	41 (20.0)		
Not present	164 (80.0)		
Myopic traction maculopathy, *n* (%)			
Present	41 (20.0)		
Not present	164 (80.0)		
Significant visual field defects, *n* (%)			
Present	59 (28.8)		
Not present	73 (35.6)		
Not examined	73 (35.6)		
History of cataract surgery, *n* (%)			
Yes	65 (31.7)		
No	140 (68.3)		
History of vitreoretinal surgery, *n* (%)			
Yes	20 (9.8)		
No	185 (88.8)		

D diopter, *IQR* interquartile range, *LogMAR* logarithm of minimum angle of resolution, *CNV* choroidal neovascularization

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 3 Comparison of the HADS between patients with high myopia and control group

Variables	High myopia	Control	*P* value
Median HADS-D score, median (IQR)	4.0 (2–7)	4.0 (2–5)	0.134
Median HADS-A score, median (IQR)	5.0 (3–8)	3.5 (2–7)	0.038*
HADS-D score of ≥8, *n* (%)	45 (22.0)	8 (11.1)	0.044*
HADS-A score of ≥8, *n* (%)	53 (25.9)	9 (12.6)	0.019*
Combined HADS-D and HADS-A score of ≥8, *n* (%)	28 (13.7)	6 (8.3)	0.236

HADS-D Hospital Anxiety and Depression Scale-Depression, *IQR* interquartile range, *HADS-A* Hospital Anxiety and Depression Scale-Anxiety

* $P < 0.05$

surgery was the only factor significantly associated with the presence of anxiety disorder (OD 2.556; 95 % CI 1.315–4.969; $P = 0.006$, where the explanatory variables included age, gender, axial length, visual acuity in better eye, and past history of cataract surgery.

A comparison of the NEI-VFQ25 scores between the two groups is also shown in Table 6. We excluded the answers to the questions about driving from the analyses, because a previous study on the reliability, validity, and responsiveness of the Japanese version of the NEI VFQ-25, recommends that driving subscale could be optional, since it has a higher rate of missing data compared with that of other countries [24]. In our study, 55.1 % of the patients did not drive, simply because they were city inhabitants, and had few occasions to do so. Cronbach alpha value for the NEI-VFQ25 subscales and composite score demonstrated a moderately strong internal consistency and reliability

Table 4 Comparison of sociodemographic characteristics between patients with HADS-A and HADS-D scores of <8 and of ≥8

Sociodemographic variables	HADS-D (0–7; $n = 160$)	HADS-D (≥8; $n = 45$)	P value	HADS-A (0–7; $n = 152$)	HADS-A (≥8; $n = 53$)	P value
Age (years), median (IQR)	61 (49–70)	56 (48–61)	0.033*	60 (48–68)	59 (50–69)	0.897
Gender, *n* (%)						
Male	57 (35.6)	12 (26.7)	0.261	53 (34.9)	16 (30.2)	0.535
Female	103 (64.4)	33 (73.3)		99 (65.1)	37 (69.8)	
Living arrangements, *n* (%)						
Living alone	23 (14.4)	8 (17.8)	0.594	24 (15.8)	7 (13.2)	0.562
Living with someone else	128 (80.0)	35 (77.8)		118 (77.6)	45 (84.9)	
Unanswered	9 (5.6)	2 (4.4)		10 (6.6)	1 (1.9)	
Marital status, *n* (%)						
Married	120 (75.0)	29 (64.4)	0.099	109 (71.7)	40 (75.5)	0.981
Unmarried, widowed or divorced	31 (19.4)	14 (31.1)		33 (21.7)	12 (22.6)	
Unanswered	9 (5.6)	2 (4.4)		10 (6.6)	1 (1.9)	
Children, *n* (%)						
Present	123 (76.9)	25 (55.6)	0.002**	108 (71.1)	40 (75.5)	0.901
Not present	28 (17.5)	18 (40.0)		34 (22.4)	12 (22.6)	
Unanswered	9 (5.6)	2 (4.4)		10 (6.6)	1 (1.9)	
Education, *n* (%)						
High school or less	68 (42.5)	17 (37.8)	0.549	63 (41.4)	22 (41.5)	0.978
College	91 (56.9)	28 (62.2)		88 (57.9)	31 (58.5)	
Unanswered	1 (0.6)	0 (0.0)		1 (0.7)	0 (0.0)	
Employment status, *n* (%)						
In employment	67 (41.9)	25 (62.5)	0.103	67 (44.1)	25 (47.2)	0.697
Unemployed or retired	93 (58.1)	20 (12.5)		85 (55.9)	28 (52.8)	
Systemic complication, *n* (%)						
Present	61 (38.1)	17 (37.8)	0.966	54 (35.5)	24 (45.3)	0.208
Not present	99 (61.9)	28 (62.2)		98 (64.5)	29 (54.7)	

HADS-D Hospital Anxiety and Depression Scale-Depression, *HADS-A* Hospital Anxiety and Depression Scale-Anxiety, *IQRI* interquartile range

* $P < 0.05$, ** $P < 0.01$

within the cohort of patients with high myopia, with the exception of ocular pain (Table 6).

For the groups with depression or anxiety disorder, all subscale scores and composite score of the NEI-VFQ25 were significantly lower than those of the groups without depression or anxiety disorder. The results of the multiple linear regression analysis showed that the factors with significantly lower NEI-VFQ25 composite score, were in order of importance—presence of anxiety disorder ($\beta = -0.395$, $P < 0.001$), low visual acuity in the better eye ($\beta = -0.333$, $P < 0.001$), presence of depression ($\beta = -0.259$, $P = 0.001$), and female gender ($\beta = 0.158$, $P = 0.013$), where the explanatory variables included age, gender, the HADS-D and HADS-A scores and clinical variables, except the refractive error and visual acuity in the worse eye.

Finally, the results of CART analysis are shown in Figs. 1 and 2. The HADS-D item with the best detection accuracy for depression at the first dichotomy was item 2 'I can laugh and see the funny side of things'. Item 2 identified depression in 34 of 45 patients which represents 75.6 % of the total number of depressed patients, but misclassified 22 patients out of 160, which represents 13.8 % of the total number of non-depressed patients (Fig. 1).

Table 5 Comparison of clinical characteristics between patients with HADS-A and HADS-D scores of <8 and of ≥8

Clinical variables	HADS-D (0–7; $n = 160$)	HADS-D (≥8; $n = 45$)	P value	HADS-A (0–7; $n = 152$)	HADS-A (≥8; $n = 53$)	P value
Refractive error (D), median (IQR)	−10.8 (−14.2 to −5.0)	−11.4 (−15.3 to −8.5)	0.195	−11.3 (−14.6 to −7.8)	−9.3 (−13.9 to −3.9)	0.103
Axial length (mm), median (IQR)	29.9 (28.7–31.2)	30.5 (29.5–31.7)	0.043*	29.7 (28.5–30.9)	30.5 (29.6–31.5)	0.017*
LogMAR in the better eye, median (IQR)	0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.1)	0.286	0.0 (−0.1 to 0.0)	0.0 (−0.1 to 0.2)	0.146
LogMAR in the worse eye, median (IQR)	0.2 (0.0–0.7)	0.2 (0.0–1.0)	0.819	0.2 (0.0–0.7)	0.2 (0.0–1.0)	0.205
Myopic CNV, *n* (%)						
Present	64 (40.0)	18 (40.0)	0.594	61 (40.1)	21 (39.6)	0.948
Not present	96 (60.0)	27 (60.0)		91 (59.9)	32 (60.4)	
Severe chorioretinal atrophy, *n* (%)						
Present	29 (18.1)	12 (26.7)	1.000	28 (18.4)	13 (24.5)	0.339
Not present	131 (81.9)	33 (73.3)		124 (81.6)	40 (75.5)	
Myopic traction maculopathy, *n* (%)						
Present	32 (20.0)	9 (20.0)	0.206	31 (20.4)	10 (18.9)	0.811
Not present	128 (80.0)	36 (80.0)		121 (79.6)	43 (81.1)	
Significant visual field defects, *n* (%)						
Present	46 (28.8)	13 (28.9)	1.000	42 (27.6)	17 (32.1)	0.363
Not present	59 (36.9)	14 (31.1)		57 (37.5)	16 (30.2)	
Not examined	55 (34.4)	18 (40.0)		53 (34.9)	20 (37.7)	
History of cataract surgery, *n* (%)						
Yes	50 (31.3)	15 (33.4)	0.686	41 (27.0)	24 (45.3)	0.014*
No	110 (68.8)	30 (66.7)		111 (73.0)	29 (54.7)	
History of vitreoretinal surgery, *n* (%)						
Yes	14 (8.8)	6 (13.3)	0.791	13 (8.6)	7 (13.2)	0.325
No	146 (91.3)	39 (86.7)		139 (91.4)	46 (86.8)	

HADS-D Hospital Anxiety and Depression Scale-Depression, *HADS-A* Hospital Anxiety and Depression Scale-Anxiety, *D* diopter, *IQR* interquartile range, *LogMAR* logarithm of minimum angle of resolution, *CNV* choroidal neovascularization

* $P < 0.05$

Table 6 Comparison of NEI VFQ-25 subscales between patients with HADS-A and HADS-D scores of <8 and of ≥8

NEI VFQ-25 subscales	Cronbach alpha	HADS-D (0–7; $n = 160$)	HADS-D (≥8; $n = 45$)	P value	HADS-A (0–7; $n = 152$)	HADS-A (≥8; $n = 53$)	P value
General health	N/A	50 (50–50)	25 (25–50)	<0.001***	50 (50–50)	25 (25–50)	<0.001***
General vision	N/A	60 (60–80)	40 (40–80)	<0.001***	60 (60–80)	60 (40–80)	<0.001***
Ocular pain	0.65	75 (63–88)	63 (50–75)	<0.001***	75 (75–88)	50 (50–75)	<0.001***
Near activities	0.84	75 (58–75)	58 (40–67)	<0.001***	75 (58–77)	50 (42–67)	<0.001***
Distance activities	0.73	75 (58–83)	58 (48–58)	<0.001***	75 (58–83)	58 (50–67)	<0.001***
Social functioning	0.70	88 (75–88)	75 (72–88)	0.001**	88 (75–91)	75 (63–75)	<0.001***
Mental health	0.84	69 (50–81)	38 (23–69)	<0.001***	75 (56–88)	44 (31–56)	<0.001***
Role difficulties	0.84	75 (63–88)	50 (50–75)	<0.001***	75 (63–100)	63 (50–75)	<0.001***
Dependency	0.82	92 (75–100)	75 (58–83)	<0.001***	92 (75–100)	75 (58–83)	<0.001***
Color vision	N/A	100 (75–100)	75 (75–100)	0.011*	100 (75–100)	75 (75–100)	<0.001***
Peripheral vision	N/A	75 (50–75)	50 (25–50)	<0.001***	75 (50–75)	50 (25–50)	<0.001***
NEI-VFQ-25 (composite score)	0.93	74 (64–83)	60 (50–65)	<0.001***	76 (64–84)	61 (53–65)	<0.001***

Values are median (interquartile range)

HADS-D Hospital Anxiety and Depression Scale-Depression, *HADS-A* Hospital Anxiety and Depression Scale-Anxiety, *NEI-VFQ-25* 25-item National Eye Institute Visual Function Questionnaire, *N/A* correlations are not applicable because only one item in the subscale

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

At the second dichotomy, the HADS-D item enabling the best detection accuracy for depression was item 7 'I can enjoy a good book or radio or television program'. HADS-D item 7 together with HADS-D item 2 ultimately identified depression in 37 of 45 patients, which represents 82.2 % of the total number of depressed patients. However, it also misclassified 13 patients out of 160, which represents 8.1 % of the total number of non-depressed patients (Fig. 1). The sensitivity of the test was 82.2 % and the specificity was 91.9 %.

The HADS-A item with the best detection accuracy for anxiety disorder at the first dichotomy was item 7 'I get sudden feelings of panic'. Item 7 identified anxiety disorder in 24 (45.3 %) out of 53 patients with anxiety disorder, but misclassified two (1.3 %) out of 152 patients without anxiety disorder for all patients who answered 'sometimes' or 'most of the time' to the item 7. At this branch, the detection was finished because of the high detection accuracy for anxiety disorder.

At the second dichotomy branch for patients who answered 'never' and 'not often', the HADS-A item with the best detection accuracy for anxiety disorder was item 4 'I can sit at ease and feel relaxed'. The combination of HADS-A item 7 with HADS-A item 4 identified 14 patients to have anxiety disorder out of 179 patients who answered 'never' and 'not often' to the HADS-A item 7 in the previous dichotomy, but misclassified four (2.7 %) of 150 patients without anxiety disorder. Thus, HADS-A items 4 and 7 together identified 38 (71.7 %) of 53 patients with anxiety disorder, but misclassified six (3.9 %) of 152 patients without anxiety disorder. The sensitivity of the test was 71.7 %, and the specificity was 96.1 %.

Discussion

Our results showed that among 205 highly myopic patients, 22.0 % of them were possible and probable cases of depression, and 25.9 % of them were possible and probable cases of anxiety disorder. These prevalences were significantly higher than those of a similarly collected control group. However, among Japanese patients with somatic illnesses, higher prevalences have been reported when cut-off scores for HADS-A and HADS-D ≥ 8 were used. For example, in patients with malignant diseases, prevalences of depression and anxiety disorder were 49 and 46 %, respectively [30]. For patients with coronary artery disease, prevalence of depression and anxiety disorders were 24 and 42 %, respectively [31]. Therefore, it

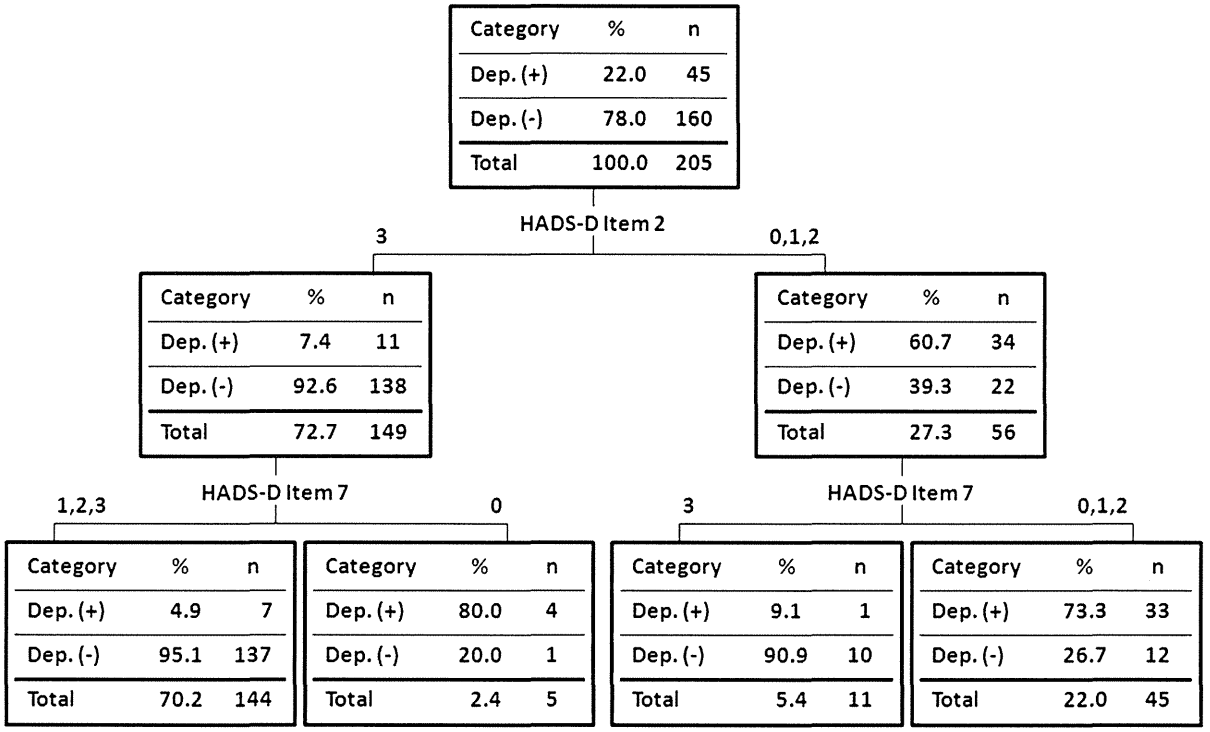

Fig. 1 Classification and regression tree for the prevalence of depression. *Dep. (+)* patients with HADS-D score of ≥8. *Dep. (−)* patients with HADS-D score of <8. Item 2 'I can laugh and see the funny side of things' (*0* hardly at all, *1* only a little, *2* not quite so much, *3* definitely as much). Item 7 'I can enjoy a good book or radio or television program' (*0* never, *1* not often, *2* sometimes, *3* most of the time)

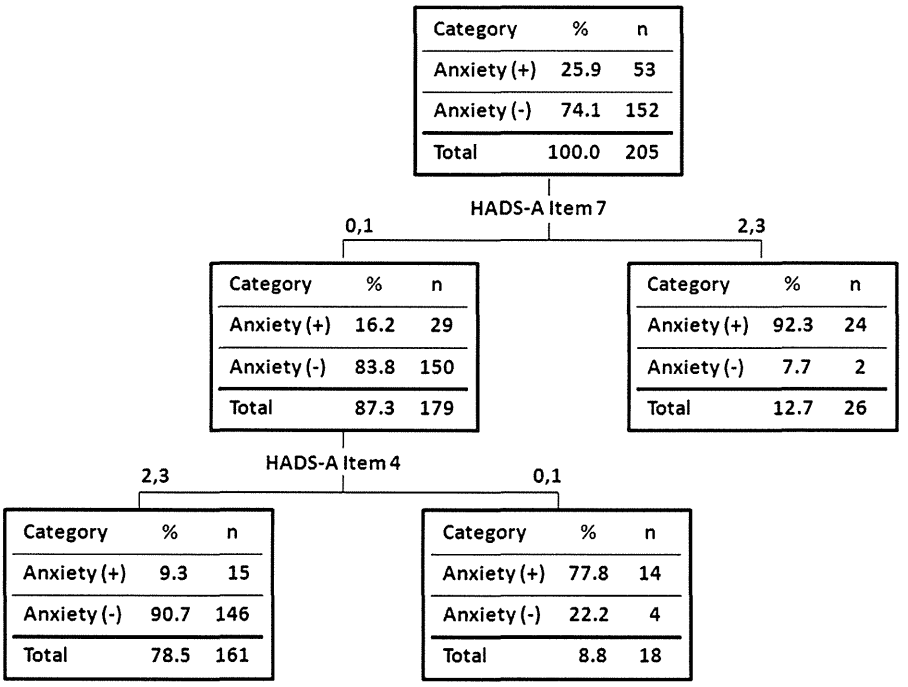

Fig. 2 Classification and regression tree for the prevalence of anxiety disorder. *Anxiety (+)* patients with HADS-A score of ≥8. *Anxiety (−)* patients with HADS-A score of <8. Item 7 'I get sudden feelings of panic' (*0* never, *1* not often, *2* sometimes, *3* most of the time). Item 4 'I can sit at ease and feel relaxed' (*0* hardly at all, *1* only a little, *2* not quite so much, *3* definitely as much)

could be considered that, in patients with high myopia, prevalences of depression and anxiety disorders were lower than those in life-threatening somatic illness, but higher than those in the general population. Similarly, in a study of monocular anophthalmic Korean patients, prevalence of depression and anxiety disorder were 28.4 and 29.9 %, respectively [32].

Multivariate logistic regression analysis showed that the absence of children was the only factor that was significantly associated with the presence of depression in patients with high myopia. In visually-impaired elderly individuals, the risk of depression was related to both an increase in age and a decrease in the visual acuity [33]. The association between depression and the severity of visual impairment was reported to be unclear in relatively younger individuals (40–50 years) [34]. Most of the patients in our study were between 40 and 50 years. This is probably one reason why the risk of depression was not significantly associated with visual acuity. Another reason might be because patients who were excluded from our study, due to missing data for the self-reporting questionnaires, could have potentially been patients with severe visual-impairment. Our result that the absence of children had about three times higher risk of depression seems to be confirmed by the general statement that social support from family and friends lowers the risk of depression for visually-impaired patients [35, 36]. Simultaneously, multivariate logistic regression analysis showed that a past history of cataract surgery was the only factor that was significantly associated with the presence of anxiety disorders in patients with high myopia. It is probably because, in patients with high myopia, the cataract surgery is performed at a relatively younger age, with not only the purpose of treating the cataract but also attenuating a patient's increasing anxiety caused by the deteriorating myopia.

The independent factors associated with lower VR-QoL were in order of importance—presence of anxiety disorder, decrease in the visual acuity in the better eye, presence of depression, and being female. These results are consistent with findings of previous studies on patients with macular telangiectasia and glaucoma where being female lowers the VR-QoL [37, 38]. Our results are also consistent with findings of studies on visually impaired patients with retinitis pigmentosa and age-related macular degeneration. The lower VR-QoL was associated with the presence of psychiatric disorders independently of the visual acuity status [39, 40]. Concerning a causal relationship between a lower VR-QoL and the presence of psychiatric disorders, both ways were considered, one whereby the lower VR-QoL due to the visual disturbances leads to development of psychiatric disorders and the one whereby development of psychiatric disorders due to visual disturbances leads to a lower VR-QoL, and they would have a negative impact on each other. In either way, in patients with high myopia, early detection of psychiatric problems may help preventing the deterioration of a patient's HR-QoL through the VR-QoL.

Because there are so few clinical clues to detect depression and anxiety disorders, it would be difficult for ophthalmologists to identify these psychiatric disorders in highly myopic patients during a routine ophthalmic examination. However, the use of HADS in clinical practice would enable screening for these psychiatric disorders and make an earlier treatment possible. This could possibly result in the enhancement of the VR-QoL. According to the CART analysis, we found that two HADS-D items—item 2 'I can laugh and see the funny side of things' and item 7 'I can enjoy a good book or radio or television program'—could help in screening patients, with a sensitivity of 82.2 %. Similar results were reported in a study conducted on patients with age-related macular degeneration [16]. The result was that 95 % of depressed patients could be identified using the same two items. In addition, our study showed that two HADS-A items—item 7 'I get sudden feelings of panic' and item 4 'I can sit at ease and feel relaxed'—could help identify 71.7 % of patients with anxiety disorders. As has been stated, anxiety disorders have the strongest impact on lowering VR-QoL. Therefore, using a reduced version of HADS-A in a routine examination, might be more efficient in detecting anxiety disorders in highly myopic patients.

There are some limitations to our study. First, this study was conducted in the High Myopia Clinic in our institute. Because of a limited number of highly myopic patients in general population, this study was conducted in a hospital-based manner. Thus, the results might not be representative of the myopic population. Second, the depression and anxiety disorders were not diagnosed using conventional diagnostic criterion such as SCID for the DSM-IV. They were diagnosed using the HADS self-reporting questionnaire, which is

fundamentally subjective. Finally, because all of the participants were Japanese patients with high myopia, comparable studies in other countries would be necessary in order to test the generalization of our results.

In conclusion, our results showed that 22.0–25.9 % of highly myopic patients were possible and probable cases of depression and anxiety disorders, and the presence of those psychiatric disorders was the major factor associated with the lowering of the VR-QoL for highly myopic patients. Moreover, our study revealed that the absence of children leads to about three times higher risk of depression, and a past history of cataract surgery leads to about 2.5 times higher risk of anxiety disorder. Finally, we developed a simpler algorithm, composed of only two statements from HADS-D, or only two statements from HADS-A, to screen possible to probable patients with depression or anxiety disorders, respectively.

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Conflict of interest The authors have no conflict of interest to disclose.

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