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Pars Plana Vitrectomy in Hereditary ATTR Amyloidosis (ATTRv): a series of 267 patients

Inês da Silva Morais

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Pars Plana Vitrectomy in Hereditary ATTR Amyloidosis (ATTRv): a series of 267 patients

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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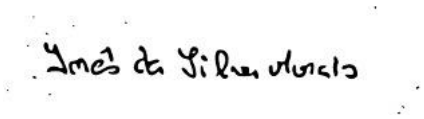

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DEDICATIONS

Dedico a presente dissertação a um conjunto de pessoas que são muito importantes para mim e que me têm ensinado a ser cada vez mais uma pessoa melhor e a ter um gosto especial pela vida.

Aos meus pais e irmã, por me apoiarem incondicionalmente e por serem o meu porto de abrigo.

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RESUMO

Introdução: A amiloidose hereditária por transtirretina (ATTRv), patologia com uma elevada incidência em Portugal, tem um atingimento sistémico, frequentemente com um predomínio neuropático. Cerca de 10% dos pacientes apresentam envolvimento ocular, sendo a amiloidose vítrea uma das possíveis manifestações a motivar diminuição da acuidade visual. Considerando que a transtirretina (TTR), proteína envolvida na patogénese, é produzida pelo epitélio pigmentado da retina e do corpo ciliar mesmo após tratamento com transplante hepático, existe uma produção contínua de TTR a nível ocular. A vitrectomia via pars plana (PPV) é atualmente o único tratamento da amiloidose vítrea. Assim, o intuito desta investigação é determinar quais são os benefícios e complicações decorrentes desta técnica no tratamento de doentes ATTRv com opacidades vítreas.

Métodos: Foi realizado um estudo retrospetivo no Centro Hospitalar Universitário de Santo António (CHUdSA) que incluiu 267 doentes com ATTRv, com mutação V30M, submetidos a PPV por amiloidose vítrea entre 1 de Janeiro de 2010 e 31 de Dezembro de 2020. Foram considerados apenas doentes com um seguimento de pelo menos 3 meses desde a última cirurgia. As indicações cirúrgicas foram miodesopsias incapacitantes e/ou perda de mais de 2 linhas na acuidade visual. A PPV foi realizada com o sistema CONSTELLATION®, 23 gauge.

Resultados: O estudo incluiu 267 doentes, entre os quais 54,9% eram do género feminino. O tempo médio de *follow-up* pós-operatório foi de 4,7 [4,16-5,42] anos. A percentagem de falecimento foi de 27,4 % e o tempo médio decorrido da cirurgia até à morte foi de 9,32 anos. A melhor acuidade visual corrigida aumentou, em média, de 0,38 no pré operatório para 0,89 no pós-operatório, no primeiro olho ($p<0.001$). A presença de glaucoma no pré-operatório foi associada a menor ganho na acuidade visual (0,41 vs 0,58) ($p<0.001$). No pré-operatório 39,1% apresentavam glaucoma e 2,6% apresentavam angiopatia retiniana. Ao longo do seguimento, 68,5% e 21,7% dos doentes desenvolveram de novo glaucoma ou angiopatia retiniana, respetivamente.

Foi verificado que 57% dos doentes foram operados ao 2º olho, com um ganho na melhor acuidade visual corrigida de 0,52 no pré-operatório para 0,89 no pós operatório ($p<0.001$). Doentes que realizaram transplante hepático necessitaram mais frequentemente de cirurgia ao 2º olho (59,6% vs 38,7%). O tempo médio de cirurgia entre os dois olhos foi de 3 anos.

Conclusão: A PPV em doentes com ATTRv consiste numa cirurgia eficaz no tratamento de amiloidose vítrea, com um considerável ganho na acuidade visual. Tendo em conta as possíveis complicações pós-operatórias, um *follow-up* a longo prazo é necessário para a deteção de novas complicações ou o agravamento de complicações prévias.

Palavras-Chave: Amyloid; Amyloidosis; Vitrectomy; Vitreous Body; Hereditary Transthyretin Amyloidosis

ABSTRACT

Introduction: Hereditary Transthyretin Amyloidosis (ATTRv), a pathology with a high incidence in Portugal, is characterized by a systemic involvement with a frequent neuropathic predominance. Around 10% of patients have ocular involvement, with vitreous amyloidosis being one of the possible manifestations associated with decreased vision. Considering that thansthyretin (TTR), a protein involved in pathogenesis, is produced by the retinal and ciliary pigment epithelium even after treatment with liver transplant, there is a continuum of TTR production at the ocular level. Pars Plana Vitrectomy (PPV) is currently the only treatment for vitreous amyloidosis. Therefore, the purpose of this investigation is to determine what benefits and complications arise from the use of this technique in the treatment of ATTRv patients with vitreous opacities.

Methods: A retrospective study was conducted at Centro Hospitalar Universitário de Santo António (CHUdSa) that included 267 patients with ATTRv amyloidosis with the V30M mutation who underwent PPV for vitreous amyloidosis between January 1, 2010 and December 31, 2020. Only patients with a *follow-up* of at least 3 months since the last surgery were considered. Indications for surgery were disabling myodesopsia and/or 2 lines loss in visual acuity. PPV was performed with 23-gauge vitrectomy with CONSTELLATION® system.

Results: The study included 267 patients, among whom 54.9% were female. The *follow-up* period was 4.7 [4.16-5.42] years. The percentage of deaths was 27.4% and the mean time from surgery to death was 9.32 years. The Best Corrected Visual Acuity (BCVA) increased in average from 0.38 preoperatively to 0.89 postoperatively on the 1st eye ($p<0.001$). The presence of preoperative glaucoma was associated to a lower gain in visual acuity (0.41 vs 0.58) ($p<0.001$). Preoperatively, 39.1% of patients had glaucoma and 2.6% had retinal angiopathy. During *follow-up*, 68.5% and 21.7% developed new onset of glaucoma or retinal angiopathy, respectively.

It was observed that 57% of patients underwent surgery in the fellow eye, with a gain in BCVA from 0.52 preoperatively to 0.89 postoperatively ($p<0.001$). Patients with liver transplant required more often surgery in the fellow eye (59.6% vs 38.7%). The average time of surgery between the two eyes was 3 years.

Conclusion: PPV in patients with ATTRv is an effective surgery in the treatment of vitreous amyloidosis, with a considerable gain in visual acuity. Taking into account the possible postoperative complications, a long-term *follow-up* is necessary to detect new or further development of previous complications.

Keywords: Amyloid; Amyloidosis; Vitrectomy; Vitreous Body; Hereditary Transthyretin Amyloidosis

LIST OF ABBREVIATIONS

ABS: Age at Beginning of systemic Symptoms
ATTRwt: wild type ATTR
ATTRv: Hereditary Transthyretin Amyloidosis
BCVA: Best Corrected Visual Acuity
CHUdSA: Centro Hospitalar Universitário de Santo António
CNS: Central Nervous System
Met: Methionine
PPV: Pars Plana Vitrectomy
SD: Standard Deviation
TTR: Transthyretin
Val: Valine
Val30Met: Pathogenic variant in which a valine (Val) is replaced by methionine (Met) at the position 30

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INTRODUCTION

Amyloidosis defines a group of diseases in which deposition of insoluble fibrillar aggregates of proteins occurs, forming amyloid deposits in various organs or tissues and resulting in diverse clinical presentations.[1] Amyloid fibrils accumulate in the extracellular space. However, the presence of "intracellular inclusions" must also be considered when the fibrils originate from the intracellular space, leading to an expansion of the amyloid definition.[2] Amyloidosis can be divided into systemic and localized forms based on the location of amyloid deposits and the site of production. In localized forms, the production and deposit formation sites are the same, while in systemic forms, the site of production differs from the site(s) of deposition.[3] This group of diseases is also classified in regard to the amyloidogenic precursor protein involved.[4]

Considering the most recent information from the International Society of Amyloidosis Nomenclature Committee, the full number of known human amyloid fibril proteins is 42; 14 of which are only associated with systemic amyloidosis, 24 with local forms of amyloidosis, and 4 with both localized and systemic amyloidosis. [5] (Table I)

In ethnological terms, amyloidosis can be classified as primary or secondary, with primary localized forms being the most common.[6]

The formation of an amyloid fibril, which is made up of different protofilaments oriented in a β-sheet structure, occurs when a protein or peptide loses or fails to acquire a functional fold. As a result, the misfolded protein joins with other proteins or peptides of a similar type and aggregates into highly ordered fibrils. There are some characteristic histopathologic findings associated with amyloid fibrils, in particular, staining with thioflavin T and Congo red dye and the appearance of apple green birefringence when staining with Congo Red on polarized light microscopy. [5,7]

Ophthalmologic symptoms of various forms of amyloidosis can affect a wide range of ocular structures, including the retina and vitreous as well as eyelids, the orbit, and ocular appendages. (Table II) Primary systemic amyloidosis is commonly associated with palpebral cutaneous involvement. In contrast, localized amyloidosis is associated with periocular involvement in the absence of palpebral cutaneous involvement.[8]

There is a rare correlation between hereditary amyloidosis and orbital amyloidosis, a condition that can affect the lacrimal glands, orbital fat and extraocular muscles. The anterior chamber, iris, and lens may all be affected in hereditary amyloidosis. Decreased lacrimal gland function and the occurrence of qualitative changes in tears are associated with dry eye in ATTRv patients. Also, in addition to the detection of pupillary reflex changes caused by dysautonomia

associated with the disease, a very interesting phenomenon that occurs in ATTRv patients is the presentation of a jagged iris shape. [8]

Corneal involvement by amyloid can be associated with several amyloidosis, including primary localized, primary systemic and secondary localized corneal amyloidosis, however this does not occur in secondary systemic amyloidosis. The conjunctiva may also be affected in patients with amyloidosis, with preferential involvement of the superior fornix and tarsal conjunctiva.[8]

Finally, vitreous involvement is in most cases associated with ATTRv, which presents with myodesopsia and decreased visual acuity that initially affects one eye and can then evolve to the fellow eye.[8]

ATTRv results from a mutation in the TTR gene, located on chromosome 18 (18q12.1), which changes the encoded protein from tetramers to monomers that will aggregate and form extracellular amyloid deposits, predominantly in the peripheric and autonomic nervous system.[1,4,9,10] ATTRv has a high incidence rate in Portugal, where it was first identified.[11,12] The largest patient pool in the world is concentrated at CHUdSA, the national reference center for ATTRv.[13]

ATTRv has an incomplete penetrance and can have an early onset, starting on the third to fourth decade, while a late onset will initiate on the sixth to eighth decade. [1,9,14,15]

It has a systemic impact and it is considered a systemic and progressive disease with a life expectancy without treatment of 10 years after the onset of symptoms. [16] The TTR V30M mutation is the most common mutation out of a group with more than 150 TTR mutations reported. It consists of a pathogenic variant in which a valine (Val) is replaced by methionine (Met) at the position 30 (Val30Met). [11,17]

TTR is a tetrameric protein, formed by four identical subunits, each subunit consisting of 127 amino acids residues in a β-sheet conformation. This protein is responsible for the transportation of retinol binding protein-vitamin A complex and thyroxine (T4). [9,18]

The pathogenesis behind TTR amyloidosis is complex and can be explained by various processes. In wild type ATTR (ATTRwt), there is a misfolding of the native wild-type TTR, which is characterized as an acquired amyloid disease associated with age and might be associated with local chemical-physical factors. This type mostly manifests as cardiomyopathy in older men and is associated with late onset.[9,18–21]

In both types of amyloidosis (ATTRwt and ATTRv), the mechanism for amyloid formation depends on the tetramer dissociation, as this is considered an initial and rate-limiting step. However, an alternative pathway was suggested with TTR dimers as an intermediate of tetramer dissociation process. In ATTRv patients, the presence of TTR mutation is also associated with less thermodynamic stability and kinetic instability, which makes them more prone to monomer

unfolding. [9,18,20]The proteolytic cleavage of TTR has also been described as a possible mechanism, with plasmin and/or trypsin as examples of responsible agents. This forms TTR fragments that will be more prone to amyloid formation. [9,18,20,21]

Amyloid fibrils demonstrate to have different compositions, with full-length only composition, type B fibrils, mostly in Val30Met ATTRv patients with early onset, and type A fibrils resulting from proteolytic cleavage, mainly contained C-terminal fragments of the precursor amyloidogenic protein in ATTRwt amyloidosis and in many late onset ATTRv patients. This can explain either the diversity of pathogenic process underling disease formation or the different clinical presentation. [21]

The range of possible clinical manifestations in ATTRv patients extends from neuropathic features, with peripheral sensorimotor neuropathy and autonomic involvement, to non-neuropathic features, including Central Nervous System (CNS), cardiac, gastrointestinal, genitourinary, renal and ocular involvement.[22] Frequently, the initial clinical feature in ATTRv patients involves the peripheral nervous system, which together with the cardiac system are the most affected sites. [21]

In early-onset patients, this autosomal dominant disease will manifest clinically as autonomic dysfunction, beginning with an impairment of temperature and pain sensibility in the patient's foot, and progressing to motor disability in a few years.[14,22]

Some focal manifestations can occur depending on amyloid deposition occurring randomly in the peripheral nervous system; one example is Carpal tunnel syndrome. [14]

In early onset ATTRv patients, various systems are affected including cardiovascular, gastrointestinal and genitourinary systems. In some cases, erectile dysfunction may precede neuropathy symptoms in affected men.[14,21]

In late onset ATTRv patients, there is a nerve length dependent progressive polyneuropathy and frequent cardiac involvement, with autonomic disfunction being less common. In these patients with the V30Met mutation, large and small fibers are involved from the beginning.[14,21]

Regarding CNS involvement, there are reports of leptomeningeal deposition, despite being a rare clinical feature. Concerning cardiac involvement, many features can appear, including: restrictive cardiomyopathy, arrhythmias, severe conduction disorders, and sudden death. [14]

TTR is mainly produced by the liver (90%). In addition, TTR is also synthesized by the brain's choroid plexus, the small intestine, the retinal pigment epithelium, and ciliary pigment epithelium cells.[1,4,23] Despite the main symptoms of ATTRv being neuropathic, there is a considerable ophthalmological burden in about 10% of cases, which increases greatly with the duration of the disease. [4]

Therefore, there are various ophthalmological manifestations associated with the deposit of mutant TTR, that include dry eye disease, abnormal conjunctival vessels, amyloid deposition on the anterior surface of the lens and on the pupil border, glaucoma, vitreous opacities, retinal microangiopathy, loss of corneal sensitivity, and neurotrophic corneal ulcers. In some cases, irreversible blindness can occur and glaucoma has been reported as the major cause.[4,9,24,25]Vitreous amyloidosis usually occurs late in the course of the disease and may manifest as progressive decreased visual acuity and floaters [17,26], that may have psychological implications, such as higher levels of anxiety, depression, and stress.[27]

Despite liver transplant, a major therapy in ATTRv patients that improves quality of life and survival, vitreous opacities formation is not interrupted since TTR production by the ciliary body pigmented epithelium and the retinal pigmented epithelium continues.[9,12] In ATTRv patients, other systemic therapeutic approaches have been approved. Two main groups can be mentioned: TTR stabilizers (tafamidis) and TTR gene inhibitors (antisense oligonucleotide – inortesen, and interfering RNA - patisiran). However, ocular penetration and efficacy are very limited, and the progression of ocular disease continues.[17,28,29]

The treatment of vitreous opacities is currently surgical. PPV has reported high safety and efficacy indexes in vitreous opacities.[17,26,30,31] Despite this, complications can occur, such as: postoperative cataract, retinal tears, retinal angiopathy, glaucoma, cystoid macular edema and vitreous hemorrhage.[31]

The aim of our study is to describe a large series of ATTRv patients with vitreous amyloidosis and assess the efficacy and safety of PPV for their treatment.

METHODS

Study design

It consists of a retrospective medical record review in CHUdSA, a tertiary ophthalmology center and the national reference center for hereditary amyloidosis. It was approved by the Ethical Committee with the number 2022.213 (171- DEFI/174-CE).

Study population

Patients with ATTRv due to the V30M mutation who underwent vitrectomy for vitreous amyloidosis between January 1st, 2010 and December 31st, 2020 (with both genetic and histopathological confirmation via a salivary gland biopsy). Only cases with a minimum follow-up of 3 months after the last surgery were considered. The total number of vitrectomies included in the study was 415.

Indications for surgery

Patients were eligible for surgery when significant vitreous opacities were present, resulting in incapacitating myodesopsia and/or a 2 lines decrease in BCVA.

Surgical procedure

The preferred type of anesthesia for this procedure was peribulbar with sensory and motor block. If patients were not expected to collaborate, general anesthesia was a valid alternative. A 3 port 23-gauge vitrectomy system (Constellation®, Alcon) was used. Induction of posterior vitreous detachment and core vitrectomy were performed to clear the visual axis. Extreme peripheral vitreous was left as some authors believe that it will work as a buffer for amyloid deposition before it reaches the trabecular meshwork and causes glaucoma.[32] Before closure, we checked for regmatogenous lesions, presence of amyloid retinopathy, and applied photocoagulation or cryotherapy, when necessary. To finalize the procedure, we sutured the sclerotomies with absorbable 8-00 sutures and injected subconjunctival cefazoline and dexamethasone.

Data and statistical analysis

Preoperative data included age at beginning of systemic symptoms (ABS) of ATTRv, age at surgery for vitreous amyloidosis, gender, previous liver transplant, history of treatment with tafamidis, as well as retinal angiopathy and glaucoma previous to surgery. We also recorded the date of surgery, intraoperative posterior vitreous detachment (if already detached, if detachment

was induced easily, or if the use of triamcinolone was necessary), and intraoperative complications. During the follow-up period, we analyzed the development of glaucoma, retinal angiopathy and retinal detachment. One eye per patient was included in the initial analysis. Finally, we studied the fellow eyes separately.

Descriptive statistics are shown as relative percentages of the total, for categorical variables, and mean and standard deviation (SD) for numerical variables. To compare proportions between several independent groups, the chi-square test was used, while to compare means between groups t-test for two independent samples or t-test two paired samples were used, if the assumptions were not met the respective non-parametric version was used. Survival curves were represented using the Kaplan-Meier method and Cox-regression model was used to estimate the Hazard Ratio and the respective confidence intervals.

Analysis was performed using the software R.4.2.1.

Statistical significance was set as a p-value inferior to 0.05.

RESULTS

PREOPERATIVE DATA

The study included 267 patients, of which 54.9% were women. The age at surgery was 52.4 (7.6) years. The ABS value was 35.6 (9.7) years. The median *follow-up* period until the last visit was 4.70 [4.16-5.42] years.

A strong positive linear association between ABS and surgery time (or age at surgery) is shown in Figure 1.

Regarding systemic treatments for ATTRv, 88% of patients had undergone liver transplant before surgery, and 7% were under treatment with tafamidis.

At the age at surgery, 3% of patients had been previously diagnosed with retinal angiopathy associated with ATTRv. In addition, at the age at surgery, 39% of patients had glaucoma.

Differences according to gender are analyzed in Table III.

There was no significant association between glaucoma and ABS (p=0.92).

SURGICAL DATA / INTRAOPERATIVE COMPLICATIONS

Intraoperative difficulty in posterior vitreous detachment was associated with age at surgery (Table IV) and ABS (p<0.001). Whereas there was no association in intraoperative difficulty in posterior vitreous detachment associated with gender, as shown in Table III. Retinal tears were detected in 6.4% of patients. (Table III)

Association between glaucoma/liver transplant/tafamidis and age at surgery:

Patients with glaucoma at baseline had surgery at an older age when compared to those without glaucoma (mean=54 (SD=7.2) vs. 52 (SD=7.7) years of age, p=0.01).

Regarding liver transplant, patients with previous liver transplant had surgery at a younger age compared to patients without previous liver transplant (mean=52 (SD=6.5) vs 59 (SD=11.3) years of age, p=0.001).

However, there was no significant mean difference between those who had tafamidis and those who did not (mean = 58 (SD = 13.6) vs. 52 (SD = 6.8) years of age, p = 0.06).

There was a significant linear association between the age at surgery and ABS (B=0.81, p<0.001, CI95%: 0.58-0.69).

There were two cases (0.8%) of peroperative retinal detachment.

POSTOPERATIVE OPHTHALMOLOGICAL DATA

Systemic ATTR-related death occurred in 73 (27,4%) of cases during the *follow-up* after surgery. The median time since surgery until death was 9.32 years, as shown in Figure 2. Regarding the mean time of survival, we analyzed the result compared to gender, ABS, age at surgery on the first eye and history of liver transplant. We concluded there was no significant association between gender (p=0.90) or liver transplant (p=0.15). In contrast, there was a significant association with ABS (p=0.04), where patients who were under 50 years old when their symptoms first appeared had a higher median time of survival. Additionally, patients who were 50 years old or older at the time at surgery had a shorter mean time of survival (p=0.005).

After adjustment, there was no significant difference in survival after surgery between male and female [HR:1.02 (95% CI:0.64-1.64)]; or when first symptoms appear at the age of 50 or older [HR:1.72 (95% CI:0.77-3.87)]; as well as when liver transplant is performed [HR:0.91 (95% CI:0.40-2.07)] (table V). Surgeries performed after 2014 were not associated with a longer survival time compared to surgeries performed before this date [HR:0.68 (95%CI: 0.39-1.19)] (table V).

Visual results

BCVA improved after vitrectomy (0.38 vs 0.89, p<0.001). There was a significant BCVA gain in patients with or without previous glaucoma (0.41 vs 0.58, p<0.001) (Table VI).

We can also observe that before 2015 the median preoperative BCVA was significantly lower than after 2015 (0.32 vs 0.41, p<0.001). However, there was no significant difference in postoperative BCVA (p=0.52), regardless of the year the surgery was performed (Table VI).

Excluding patients who already had glaucoma and retinal angiopathy prior to surgery, the percentage of patients with postoperative glaucoma was 68.5% and postoperative retinal angiopathy was 21.7%.

FELLOW EYE

During *follow-up*, 149 patients (57%) needed surgery in the fellow eye. Patients who received a liver transplant required surgery in the other eye more often than non-transplant patients (59.6% vs. 38.7%, p =0.03). There was no association between the need for surgery in the fellow eye and ABS (p =0.35), age at surgery (p=0.06) or gender (p=0.90) (Table VII).

The median time between surgery in the first eye and surgery in the fellow eye was 2.6 years.

The overall preoperative BCVA in the fellow eye was 0.52, while overall postoperative BCVA was 0.89.

There was no significant difference between gender and BCVA in both pre and postoperative moments (p=0.18 / p=0.89) (Table VIII). In addition, there was a significant difference between the presence or not of glaucoma and BCVA in both pre and postoperative moments (p=0.002 and p<0.001), with a lower BCVA gain when glaucoma was present.

The association between the BCVA gain and the age at surgery was not significant (p =0.50).

Intraoperative difficulty in posterior vitreous detachment was not significantly associated with gender (p=0.67) or ABS (p=0.10). It was also shown that there was a significant association between intraoperative difficulty in posterior vitreous detachment and age at surgery (p = 0.02) (Table IX).

Comparing the median time between the first and second vitrectomy, we found no association when analyzing gender (p=0.59), ABS (p=0.37), age of first vitrectomy (p=0.2), previous liver transplant (p=0.12) and the presence of a retinal tear (p=0.091).

DISCUSSION

To our best knowledge, this study is the largest series of vitrectomized patients with vitreous amyloidosis. We report the demographic and clinical features of these patients, as well as the efficacy and safety of PPV for the treatment of vitreous amyloidosis.

Two previous small series have addressed this issue, however, the follow-up time after vitrectomy in these studies was shorter (mean 40 and 44.7 months) compared to our study (mean 56.4 months). [17,33] Besides that, there is a reduced characterization of the sample in one of the papers, with no reference to the date of onset of systemic symptoms, the date of appearance of glaucoma and retinal angiopathy prior to vitrectomy, and date of liver transplant or other systemic treatments (such as use of tafamidis). In this same study, the surgical procedure was not standardized, using 20, 23 and 25 gauge PPV and it was considered either complete or incomplete PPV. Also, different TTR mutations were presented (Val30Met, Lys55Thr, Arg124Cys). [17]

In the other study, not all patients had the same variant (one patient who had the Ile84Asn variant instead of the Val30Met variant). No reference is made in the study to the BCVA value that was considered for PPV and the 25- gauge vitrectomy was performed using either CONSTELLATION Vision System or ACCURUS Surgical System. [33]

The vitreous body is a transparent, acellular gel, that lies between the lens and the retina, adhering to the inner limiting lamina of the retina. It fills the posterior ocular cavity and is mainly composed of water (98%). However, it also has in its constitution a set of mixed collagen fibrils (types II, V/XI and IX) and a hyaluronan network.[34–37] TTR amyloid aggregation in the vitreous is associated with his constitution, given the high affinity for collagen in the main basement membrane, which has biochemical and structural similarity to type II collagen, a component of the vitreous body. With a bilateral and asymmetrical component usually present, vitreous amyloidosis may manifest as *pseudopodia lentis* (specific white opacities on the posterior lens capsule), perivascular amyloid deposits in the retina, and a “glass wool” appearance of the vitreous. [38]

The manifestation of vitreous opacities occurs earlier and more often when associated with Arg34Gly, Tyr114Cys, Thr49Ala and Glu54Lys mutations compared to Val30Met patients.[4]

Mutated TTR deposition in the form of amyloid in the vitreous with the opaque (white) nature of this material leads to endocular light scattering posteriorly to the main nodal point of the eye, resulting in bothersome myodesopsia and a progressive decrease in visual acuity.[1,26,37]

The amount of type IX collagen reduces with age and gives way to an increase in type II collagen fibers aggregation, thus inducing synchisis and syneresis.[39] These opacities create visual phenomena in the vitreous and will give rise to symptomatic floaters. Age-related posterior vitreous

detachment is the main cause of vitreous floaters with myopic vitreopathy being the second cause.[37,40] In some cases, there may be a decrease in visual acuity and a negative impact on quality of life, which is called vision degrading myodesopsia when it has a bothersome effect. A possible explanation is the scattering of incident light that can be associated with a decrease in contrast sensitivity function.[37]

As mentioned before, the amyloid production persists after liver transplant and leads to an increase in the incidence of vitreous opacities.[23,26] Due to the increased survival of these patients, there is still a long-term increased risk of ocular manifestations, mainly vitreous opacities and glaucoma in ATTRv patients after liver transplant according to Hara R et. al. [41] This was observed in our study where there was a larger need for surgery in the fellow eye in patients with liver transplant. In the current study, PPV emerged as a method to treat the loss of visual acuity and improve visual acuity.

Beirão *et al*. reported that the recurrence of vitreous amyloidosis occurred mainly in non-extensive vitrectomies (vitreous removal but leaving some peripheral vitreous body) and Miele et al. concluded that PPV may be associated with an increased risk of open-angle glaucoma and ocular hypertension[26,32].

There was a significant improvement in BCVA gain in our study, which matches the results of other studies.[17,26,33]

Postoperative visual acuity was higher in patients without glaucoma prior to vitrectomy which can be interpreted as glaucoma being a factor of poorer prognosis for vitrectomy outcome and the prior loss of potential gain in vision. Despite this, most patients didn't have glaucoma before vitrectomy, as seen in the results.

Before 2015, vitrectomies were performed with a lower preoperative BCVA compared to vitrectomies performed after 2015. Most likely the threshold to operate these patients was lowered, therefore the surgery would be performed earlier and with greater confidence on the part of doctors and patients.

Ocular manifestations in ATTRv patients can develop over time, with secondary glaucoma, the leading cause of irreversible blindness, receiving special attention.[1,42] The mechanism of secondary glaucoma in ATTRv patients may involve obstruction of the aqueous outflow route with amyloid deposition and elevation in intraocular pressure produced by perivascular amyloid deposition in conjunctival and episcleral tissue, which leads to elevation in episcleral venous pressure.[42,43] The deposition of amyloid fibrils also occurs in the intertrabecular space of the corneoscleral and uveoscleral meshwork and juxtacanalicular tissue. [44] It was also reported that pupillary amyloid deposition and vitreous opacities seem to be associated with the appearance of glaucoma and can be used to predict its onset. [42,43] Autonomic nervous system dysfunction occurs

early in ATTR patients and it was also considered in the development of glaucoma by inducing a chronic ischemia in the optic nerve through dysfunction of autonomic control of the cardiovascular response.[15,45] In general, glaucoma secondary to amyloidosis may be associated with either mechanical or neuropathic actions of the structures necessary for proper functioning of the trabecular meshwork, given the degeneration of endothelial cells and nerve fibers arising from amyloid deposition. Thus, an increased resistance to aqueous humor outflow through the trabecular meshwork occurs, which explains the onset of glaucoma. [44]

Despite PPV improving visual acuity, there is an increase in postoperative glaucoma.[15] Vitrectomy can increase oxidative stress in the trabecular meshwork and it is easier for amyloid to aggregate and to deposit in trabecular meshwork and in Schlemm's channel, which will be responsible for the development of glaucoma.[17] Since the vitreous works like a buffer for amyloid deposition, an incomplete vitrectomy could be the solution to delay progression of postoperative glaucoma in ATTRv patients. [1]

The use of 20-gauge PPV is more associated with failure filtering bleb, which was reported by Thompson et al. since the procedure can induce scarring at the conjunctival and scleral level.[33,46] Using 23/25-gauge PPV, this complication can be reduced due to less induced postoperative inflammation and surgical damage, and it has been demonstrated to be an optimal therapy in ATTRv patients with vitreous opacities.[47] In addition, it will have a smaller impact if future filtration surgeries are needed.[33] It was also discovered that the ocular amyloid deposition can be reduced by retinal laser photocoagulation, as mentioned by Kawaji T et al.[48]

In conclusion, these previous studies reported that the ideal therapy in ATTRv patients with vitreous opacities is an incomplete small-gauge vitrectomy with subsequent follow-up of intraocular pressure and glaucoma management, along with retinal laser photocoagulation as a beneficial adjuvant treatment in patients with retinal angiopathy. In our study, using a 3 port 23-gauge vitrectomy system (Constellation®, Alcon), we had 68.5% of postoperative glaucoma, which shows a considerable percentage of postoperative glaucoma, despite the fact that we have taken into account the performance of an incomplete vitrectomy. This result could perhaps have been minimized by performing a 25-gauge vitrectomy, as mentioned previously.[47]

Regarding our study, it remains unclear if the presence of glaucoma prior to surgery has an impact on the age at which PPV is performed, since patients who had glaucoma prior to surgery were generally older.

Considering systemic treatments, there was a significant association with gender in our study, with a higher percentage of females than males (12%/4.2%) using tafamidis. This may be related to the better treatment response in female patients.[49] A possible hypothesis is that there is an association between gender and the disease mechanism, which is considered in some

studies.[49,50] Additionally, when comparing gender with systemic disease in ATTRv patients, transthyretin amyloid cardiomyopathy was observed mainly in older men, which may also be explained by biological mechanisms that allow easier amyloid myocardial deposition in men.[51] More studies should be conducted to compare the impact of gender on this disease.

Interestingly, we found an earlier need for surgery in men compared to women. A possible hypothesis may be the general faster progression of the ocular disease in men. The same association has been described in a previous study.[50] The disease is more aggressive in men, which is also demonstrated by earlier onset, as mentioned in our study and previously demonstrated.[52] In addition, it has been previously determined that the gender of the transmitting parent has an effect on the age of symptom onset in offspring, being lower when maternal transmission occurs, which demonstrates the variety of factors that can influence the age of onset besides patient gender. Lemos et al. also found a greater anticipation when mother-to-son transmission occurred, although it also occurred in other associations, and that the offspring of patients with a late age of onset (93% in the 50-59 age group, 94% in the 60-69 age group, and 53% in the ≥70 age group) had an early age of onset of disease.[52] Considering these findings, it is relevant to study anticipation in ATTRv families, so that genetic counseling can be addressed.

Patients with late-onset and vitrectomy for vitreous amyloidosis have a lower life expectancy after the age of 50. This may be due to older patients (shorter life expectancy) and the greater cerebral involvement of the disease, as there is some parallelism between the more severe eye disease and the greater involvement of cerebral amyloid angiopathy. This late manifestation of ATTR is one of the main causes of death in these patients.[53,54]

According to Maia et al., the CNS involvement observed in ATTRv V30M patients submitted to liver transplant has an association with the higher disease duration, which is closely related to the increased average life expectancy in these cases. In addition, they determinate that focal neurological episodes only appear on average 14.6 years after peripheral disease onset, which could not be observed without a liver transplant since in these cases the patients dies earlier. With more than 8 years of disease duration, TTR deposition occurred in meningocortical brain vessels and superficial parenchyma. At least another relevant report by Maia et. al was higher risk of focal neurological episodes in male ATTRv-V30M patients, highlighting the worse prognosis in male patients.[55] We can correlate this to our study, considering a higher percentage of liver transplant in men with ATTRv amyloidosis, which will allow a higher life expectancy and the possibility of new phenotypes such as CNS involvement, even though this wasn't a subject of interest in our study.

As previously mentioned, in addition to ocular involvement after liver transplant, given intraocular production of amyloid that is not suppressed by current therapies used in systemic

amyloidosis, a new clinical expression has emerged associated with the 10% extrahepatic production of TTR, which is CNS involvement.[29]

As a result of these novel clinical expressions, it is now necessary to develop therapies that can pass through the blood-brain and blood-ocular barriers and are selective for mutant TTR, as wild type-TTR serves critical functions and has a neuroprotective effect. A further difficulty lies in the difficulty of replacing TTR in this location. [29]

Tafamidis is the only medical approved treatment for ATTRv patients that can pass, in small amount, the blood-brain barrier and reach the cerebrospinal fluid (1.5%). The other approved therapies cannot pass the blood-brain barrier, as is the case of inortesen and patisiran.[29]

The CNS clinical expression can vary, including subarachnoid and intra parenchymal hemorrhage, dementia and stroke like episodes. [29,55] These serious manifestations alert us to the need for further studies to create therapies that can cross the blood-brain barrier and are efficient in preventing the creation of these new harmful phenotypes.

On our study, we determined that the time between surgeries on each eye was 3 years. Despite ATTRv amyloidosis being a monogenic disease and genetically being the same in both eyes, there might be an interaction of TTR with other factors to explain the asymmetric natural history between eyes, making this an interesting result for further investigation.

Another finding in our investigation was that patients with systemic symptoms at a younger age had a more difficult intraoperative posterior vitreous detachment, with more cases requiring triamcinolone. This can be explained by the age of the patients and the consequent easier posterior vitreous detachment in older patients. It is also feasible that the amyloid deposit at the posterior hyaloid membrane tightens its attachment to the retina. [56]

To summarize, PPV is effective and safe in the treatment of vitreous amyloidosis however, there is a need for long term *follow-up* to detect other possible manifestations after surgery, such as the onset/worsening of amyloidotic glaucoma and retinal angiopathy.

LIMITATIONS OF THE STUDY

The first limitation to mention is its retrospective design. ATTRv patients are a diverse group, with varying onset of systemic symptoms, a distinct disease progression, and an uneven *follow-up* period. In addition, PPV was performed at different times and it is difficult to differentiate complications resulting from surgery from those resulting from the disease. Also, we lack a control group of non-vitrectomized patients.

CONCLUSIONS

With the increase in the average life expectancy of ATTRv patients due to the therapies implemented, particularly liver transplant and systemic therapies such as tafamidis, and patisiran, the ophthalmological implications in patients with ATTRv amyloidosis have become a growing problem.

Given the high incidence of ATTRv amyloidosis in Portugal, several studies have been carried out in this area in order to be able to cover the new phenotypes that have appeared in these patients. Apart from ocular manifestations, with particular emphasis on the appearance of vitreous opacities that limit visual acuity and quality of life in these patients, manifestations in the CNS have also appeared due to the maintenance of intracerebral TTR production after liver transplant. This highlights the importance of investigating the mechanism behind ATTRv amyloidosis and the creation of new therapies in order to eliminate the production and remaining mutant TTR with minimal side effects.

As mentioned in this study, PPV has emerged as an asset in the treatment of ATTRv patients with vitreous amyloidosis. However, there are possible postoperative complications such as amyloidotic glaucoma and retinal angiopathy that have been reported in several previous studies and observed in this study as well. Therefore, doubts have emerged about this therapeutic option in patients with vitreous amyloidosis.

A common conclusion to almost all studies is that PPV is the only effective and safe therapeutic option in patients with vitreous amyloidosis, showing a significant improvement in visual acuity, despite the need for perioperative control and strict long term postoperative monitoring of these patients in order to control possible postoperative complications and progression of ocular disease.

Another aspect highlighted in these previous studies and applied in this study was possible intraoperative modifications that when carried out minimized the risk of post-vitrectomy glaucoma, as in the case of an incomplete PPV. The effectiveness of laser photocoagulation of the retina was also discovered to be beneficial in reducing the production of ocular amyloid.

Additionally, an interesting finding of this study was the need for vitrectomy at an earlier age in males, which highlights the interference of gender on the severity of clinical manifestations in ATTRv amyloidosis. This phenomenon, as mentioned in other studies concerning the faster progression of the disease in male patients, emphasizes the importance of understanding other factors involved in the pathogenesis that influence the natural course of the disease.

In order to better understand vitreous amyloidosis and how to treat it in a more efficient and safe way, it will be relevant in the future to carry out further studies to understand the multifactorial complexity that may influence the course of the disease and its clinical aggressiveness.

In conclusion, the treatment of vitreous amyloidosis in patients with ATTRv remains a highly debated topic due to the emergence of postoperative complications with the use of PPV. However, the therapy's demonstrated efficacy outweighs its potential risks, making it an advantageous weapon for improving the quality of life in these patients. Further studies should be carried out in order to create a universal model for the treatment of vitreous amyloidosis with particular emphasis on strict long-term monitoring and the creation of preventive measures to avoid the appearance of ocular complications after vitrectomy. There is an enormous hope in the emergence of new eye-target therapies.

APPENDIX

Table I. Amyloid Classification, amyloid fibril proteins and their precursors and target organs. This table was based on Buxbaum JN, Dispenzieri A, Eisenberg DS, Fändrich M, Merlini G, Saraiva MJM, et al. Amyloid nomenclature 2022: update, novel proteins, and recommendations by the International Society of Amyloidosis (ISA) Nomenclature Committee. Amyloid. 2022 Nov 24;1–7.

Amyloid Classification	Fibril protein	Precursor Protein	Target Organs
Localized	**AαSyn**	α-Synuclein	CNS
	ATau	Tau	CNS
	ATMEM106B	Transmembrane 106B (TMEM106B)	Frontotemporal lobar degeneration diseases
	AIAPP	Islet amyloid polypeptide	Islet of Langerhans, insulinomas
	AANP	Atrial natriuretic peptide	Cardiac atria
	APro	Prolactin	Pituitary prolactinomas, ageing pituitary
	ASom	(Pro)somatostatin	Somatostatinomas
	AGluc	Glucagon	Glucagonomas
	APTH	Parathyroid hormone	Parathyroid tumors, ageing parathyroid glands
	AIns	Insulin	Iatrogenic, local injection
	AEnf	Enfurvitide	Iatrogenic, local injection
	ASPC	Lung surfactant protein	Lung
	ACor	Corneodesmosin	Cornified epithelia, hair follicles
	AMed	Lactadherin (MFG-E8)	Ageing aorta, media, elastic arteries
	AKer	Kerato-epithelin	Cornea, hereditary
	ALac	Lactoferrin	Cornea
	AOAAP	Odontogenic ameloblast-associated protein	Odontogenic tumors
	ASem1	Semenogelin 1	Vesicula seminalis
	ACatK	Cathepsin K	Tumor associated
	AEFEMP1	EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1)	Veins, Ageing associated
	Aβ	**Aβ protein precursor, wild type** Aβ protein precursor, variant	CNS
	ADan	ADanPP, variants	CNS
	AGLP1	Glucagon-like peptide 1 analog	Iatrogenic, local injection
	AIL1RAP	Interleukin- 1 receptor antagonista protein	Iatrogenic, local injection
	AApoAIV	Apolipoprotein A IV, wild type	Kidney medulla and systemic

Systemic	**ALECT2**	Leukocyte chemotactic factor-2	Kidney, primarily
	ATTR	**Transthyretin, wild type**	Heart mainly in males, lung, ligaments, tenosynovium
		Transthyretin, variants	PNS, ANS, heart, eye, leptomeninges
	Aβ2M	**β2-microglobulin, wild type**	Musculoskeletal system
		β2-microglobulin, variants	ANS, tongue, heart
	AA	(Apo) serum amyloid A	All organs except CNS
	AApoAI	Apolipoprotein A I, variants	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
	AApoAII	Apolipoprotein A II, variants	Kidney
	AApoCII	Apolipoprotein C II, variants	Kidney
	AApoCIII	Apolipoprotein C III, variants	Kidney
	AGel	Gelsolin, variants	Kidney
	AFib	Fibrinogen α, variants	Kidney, primarily
	ACys	Cystatin C, variants	PNS, skin
	ABri	ABriPP, variants	CNS
	APrP	Prion protein, variant	PNS
	ALys	Lysozyme, variants	Kidney
Localized and Systemic	**AH**	Immunoglobulin heavy chain	All organs except CNS
	ACal	(Pro)calcitonin	C-cell thyroid tumor
			Kidney
	AL	Immunoglobulin light chain	All organs, usually except CNS
	APrP	**Prion protein, wild type (L)**	CJD, fatal insomnia
		Prion protein variants (L)	CJD, GSS syndrome, fatal insomnia
		Prion protein variant (S)	PNS

Abbreviations: **Bold:** Acquired; Underlined: Hereditary; **Bold and Underlined:** Acquired and Hereditary; CNS: Central Nervous System; PNS: Peripheral Nervous System; ANS: Autonomic Nervous System; CJD: Creutzfeldt – Jakob disease; GSS: Gerstmann-Sträussler-Scheinker syndrome

Table II. Ocular manifestations according type of amyloid classification. This table was based on the scheme from Beirão J. Oculopatia na polineuropatia amiloidótica familiar tipo Português. 2014.

		AMYLOID CLASSIFICATION				
		Primary Amyloidosis		Secondary Amyloidosis		Hereditary Amyloidosis
		Localized	Systemic	Localized	Systemic	
OCULAR STRUCTURE	Eyelids, Orbit and Appendices	X	X	X	X	
	Conjunctiva	X	X	X		
	Cornea	X	X			
	Anterior Chamber, Iris		X			X
	Retina, Vitreous					X

Table III. Baseline patient demographics and clinical data by gender

Variable	Overall	Female	Male	p-value
Age at beginning of systemic symptoms (n) (%)				0.07
Age <50 years	241(90.6)	128(87.7)	113(94.2)	
Age≥50 years	25(9.4)	18(12.3)	7(5.8)	
Transplant(n) (%)				0.09
No	32(12.0)	22(15.1)	10(8.3)	
Yes	234 (88.0)	124 (84.9)	110 (91.7)	
Tafamidis(n) (%)				0.002
No	247(92.9)	129(88.4)	118(98.3)	
Yes	19(7.1)	17(11.6)	2(1.7)	
Retinal Angiopathy (n) (%)				0.46
No	258(97.4)	140(96.6)	118(98.3)	
Yes	7(2.6)	5(3.4)	2(1.7)	
Glaucoma (n) (%)				0.60
No	162(60.9)	91(62.3)	71(59.2)	
Yes	104(39.1)	55(37.7)	49(40.8)	
Time of Follow-up, M (SD)	4.09(2.94)	4.16(2.80)	4.00(3.11)	0.68
Surgical data				
Age at surgery,M(SD)	52.4(7.6)	53.6(7.5)	51.0(7.5)	0.006
Retinal tear				0.74
No	249 (93.6)	136 (93.2)	113 (94.2)	
Yes	17 (6.4)	10(6.8)	7(5.8)	
Posterior Vitreous Detachment				0.54
Already detached	42(15.9)	20(13.9)	22(18.3)	
Normal detachment	213(80.7)	118(81.9)	95(79.2)	
Triamcinolone	9(3.4)	6(4.2)	3(2.5)	
Per operative retinal detachment(n) (%)				1.00

No	264(99.2)	145(99.3)	119(99.2)
Yes	2(0.8)	1(0.7)	1(0.8)

Abbreviations: M: mean; SD: standard deviation; n:number; PVD: Posterior Vitreous Detachment

Table IV. Association between difficulty in Posterior Vitreous Detachment and age at surgery

Surgery age	<50years	≥50years	p-value
Difficulty in PVD n(%)			<0.001
Already detached	8(7.0)	34(22.8)	
Normal detachment	100(87.0)	113(75.8)	
Triamcinolone	7(6.1)	2(1.3)	

Abbreviations: <50: age less than 50 years; ≥50: age more or equal to 50 years; PVD: Posterior Vitreous Detachment

Table V. Cox-Regression to measure the effect of the exposures on time of death

Variable	Beta (SE)	HR (95%CI)	p-value
Gender			
Female	Ref		
Male	0.00 (0.24)	1.00 (0.62, 1.62)	0.99
ABS			
<50 years	Ref		
≥50 years	0.64 (0.41)	1.90 (0.85, 4.27)	0.12
Transplant			
No	Ref		
Yes	0.05 (0.44)	1.05 (0.45, 2.47)	0.91
Date of surgery			
<=2014	Ref		
>2014	-0.35 (0.29)	0.70 (0.40, 1.23)	0.22

Abbreviations: ABS: age at beginning of systemic symptoms; HR: hazard ratio; SE: standard error

Table VI. Association between Visual Acuity pre and post-surgery with gender, glaucoma and age at surgery

Variable	BCVA Pre-surgery Mean (SD)	BCVA Post-surgery Mean (SD)	Difference	p-value
Overall	0.38(0.14)	0.89(0.18)	0.51(0.17)	<0.001
Gender				
Female	0.37(0.14)	0.89(0.17)	0.53 (0.17)	
Male	0.39(0.14)	0.88(0.20)	0.49 (0.17)	
p	0.13	0.63	0.08	
Glaucoma				
No	0.38(0.14)	0.96(0.11)	0.58 (0.15)	
Yes	0.37(0.14)	0.78(0.21)	0.41(0.15)	
p	0.59	<0.001	<0.001	
Date of Surgery				
<2015	0.32(0.12)	0.88(0.19)	0.56 (0.19)	
≥ 2015	0.41(0.13)	0.89(0.17)	0.48 (0.15)	
p	<0.001	0.52	<0.001	

Abbreviations: BCVA: best corrected visual acuity; M: median; SD: standard deviation

Table VII. Comparation between unilateral vs bilateral surgery by demographic and clinical data

Variable	Unilateral	Bilateral	p-value
Gender(n) (%)			0.90
Female	60(42.6)	81(57.4)	
Male	52(43.3)	68(56.7)	
ABS(n) (%)			0.35
<50years	100(42.0)	138(58.0)	
≥50years	12(52.2)	11(47.8)	
Age at surgery (M)(SD)	53.3(8.1)	51.5(6.8)	0.06
Liver Transplant (n) (%)			0.03
no	19(61.3)	12(38.7)	
yes	93(40.4)	137(59.6)	

Abbreviations: n: number; M: median; SD: standard deviation; ABS: Age at Beginning of Systemic Symptoms

Table VIII. Association between pre and postoperative visual acuity with gender, glaucoma and age at surgery in the fellow eye

Variable	BCVA(M)(SD) Pre surgery	BCVA(M)(SD) Post surgery	difference	p-value
Overall	0.52(0.14)	0.89(0.16)		<0.001
Female	0.51(0.14)	0.89(0.16)	0.38 (0.12)	
Male	0.54(0.13)	0.89(0.16)	0.34 (0.12)	
p	0.18	0.89	0.09	
Glaucoma				
No	0.55(0.11)	0.96(0.08)	0.41 (0.11)	
Yes	0.48(0.15)	0.77(0.19)	0.29 (0.10)	
p	0.002	<0.001	<0.001	
Date of Surgery				
<2015	0.50(0.15)	0.87(0.16)	0.37 (0.13)	
≥ 2015	0.54(0.13)	0.89(0.16)	0.36 (0.11)	
p	0.12	0.39	0.50	

Abbreviations: M: median; SD: standard deviation; BCVA: best corrected visual acuity

Table IX. Association between difficulty in Posterior Vitreous Detachment with age at surgery, ABS and gender, in the fellow eye

Variable	Difficulty in PVD Already detached n(%)	Difficulty in PVD Normal detachment n(%)	Difficulty in PVD Triamcinolone n(%)	p-value
Age at surgery				0.02
<50 years	4(6.2)	60(92.3)	1(1.5)	
≥ 50 years	17(21.0)	63(77.8)	1(1.2)	
ABS				0.10
<50 years	17(12.6)	116(85.9)	2(1.5)	
≥ 50 years	4(36.4)	7(63.6)	0(0.0)	
Gender				0.67
Female	12(14.8)	67(82.7)	2(2.5)	
Male	9(13.8)	56(86.2)	0(0.0)	

Abbreviations: PVD: Posterior Vitreous Detachment; ABS: Age at Beginning of Systemic Symptoms

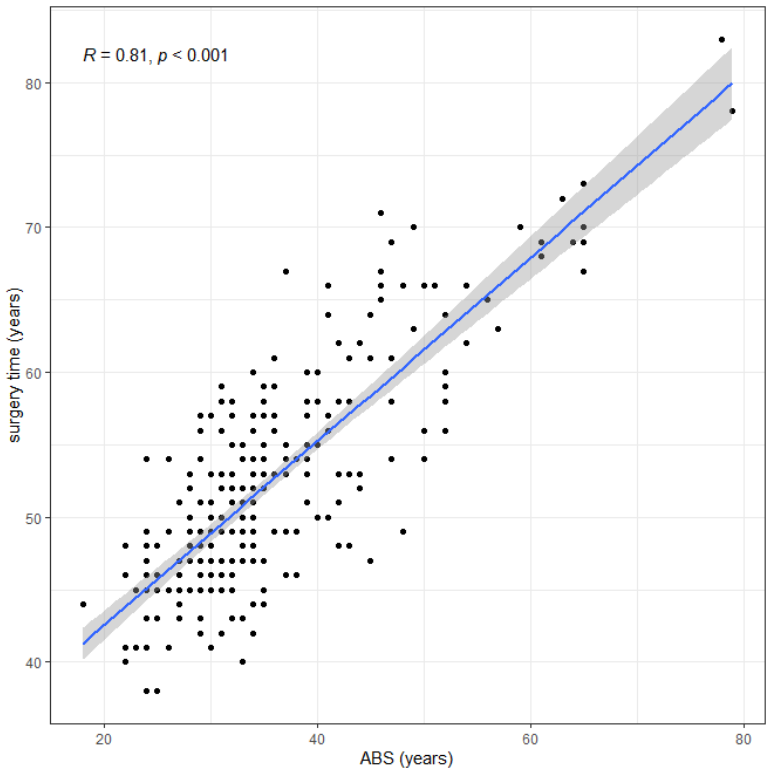

Figure 1. Association between age at beginning of systemic symptoms (ABS) and age at surgery
Abbreviations: ABS: Age at Beginning of Systemic Symptoms

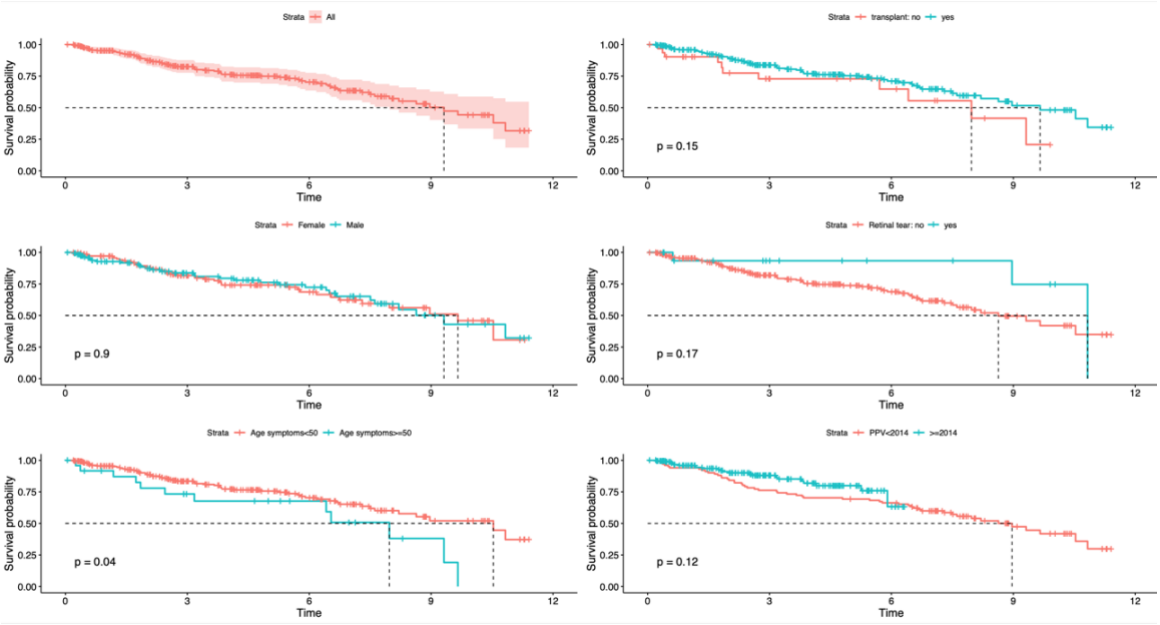

Figure 2. Survival curve from surgery to death
Abbreviations: PPV: Pars Plana Vitrectomy

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