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Title: Long term survival rates of patients undergoing vitrectomy for diabetic retinopathy in an Australian population - a population based audit.

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Importance: Five year survival rates in patients undergoing vitrectomy for diabetic retinopathy (DR) vary from 68-95%. No study has been conducted in an Australian population.

Background: We aimed to determine the survival rates of patients undergoing diabetic vitrectomy in an Australian population.

Design: Retrospective audit, tertiary centre hospitals and private practices

Participants: All individuals in South Australia and the Northern Territory who underwent their first vitrectomy for diabetic complications between 1st January 2007 to 31st December 2011

Methods: An audit of all eligible participants has been completed previously. Survival status as of 6th July 2018 and cause of death were obtained using SA/NT DataLink. Kaplan-Meier survival curves and multivariate cox-regressions were used to analyse survival rates and identify risk factors for mortality.

Main outcome measures: 5, 7 and 9 year survival rates

Results: The 5, 7 and 9 year survival rates were 84.4%, 77.9% and 74.7% respectively. The most common cause of death was cardiovascular disease. Associated with increased mortality independent of age were Indigenous ethnicity (HR 2.04, 95% CI 1.17-3.57, p=0.012), chronic renal failure (HR 1.76, 95% CI=1.07-2.89, p=0.026) and renal failure requiring dialysis (HR 2.32, 95% CI 1.25-4.32, p=0.008).

Conclusion and relevance: Long-term survival rates after diabetic vitrectomy in Australia are similar to rates reported in other populations. Indigenous ethnicity and chronic renal failure were the most significant factors associated with long term mortality. This information can guide allocation of future resources to improve the prognosis of these high risk groups.

Keywords: diabetic retinopathy, vitrectomy, long term mortality, Australia

Introduction

Diabetic retinopathy (DR) is the most common cause of blindness in the working population across developed countries, and therefore has a significant socioeconomic impact.[1] The proportion of blindness due to DR is as high as 15-17% in developed countries[1], and is predicted to increase exponentially as the global burden of diabetes increases.[2] From 1990 to 2010, the number of people with visual impairment due to DR increased by 65%.[1]

Proliferative DR (PDR) is an advanced stage of the disease which requires urgent management to prevent vision loss. While PDR can be initially treated with laser photocoagulation and/or anti-vascular endothelial growth factor injections, vitrectomy may be indicated when there is further progression of the disease with persisting vitreous haemorrhage or retinal detachment. Therefore, those that undergo vitrectomy for DR represent the worst end of the spectrum of the disease.

In Australia, the burden of diabetes and therefore DR is disproportionately high in Indigenous Australians. In remote central Australia, while the prevalence of DR and PDR in Indigenous Australians was similar to non-Indigenous Australians in those with diabetes, the prevalence of diabetes was more than five times higher in Indigenous Australians.[3] In the National Eye Health Survey, the prevalence of vision threatening DR (including PDR and clinically significant macular oedema) among those with self-reported diabetes was 9.4% compared with 4.5% for Indigenous and non-Indigenous Australians respectively.[4] Compared with non-Indigenous Australians, Indigenous Australians are five time more likely to go blind from DR.[5]

The presence of DR is a marker of advanced diabetic disease and is associated with reduced survival.[6] A recent meta-analysis reported a risk ratio of 2.33 when comparing all-cause mortality rates between diabetics with no DR and those with any DR.[7].Patients with end-stage DR requiring vitrectomy often have other severe diabetic complications and causes of significant morbidity such as visual disability, amputation, chronic renal disease and renal disease requiring dialysis.[8] Severity of retinopathy reflects the status of diabetes disease burden on the body and indicates the need for more urgent and comprehensive management. PDR also leads to significant visual impairment which is well-recognised to increase morbidity and mortality leading to social isolation, depression, increased risk of falls and loss of independence.[9-13]

Life expectancy is an important factor in determining when vitrectomy is performed. Over the last forty years, few studies have been performed to establish the long term survival rates of those with end stage DR requiring vitrectomy.

Reported survival rates at five years vary widely from 68-96% worldwide[14-19] and no studies of this type have been performed in an Australian cohort.

A retrospective population based audit of all vitrectomies performed by public and private vitreoretinal surgeons in South Australia and the Northern Territory during a five year period (between 1st January 2007 and 31st December 2011) has been previously performed.[8] The purpose of this follow-up study was to establish the long term survival rates of these patients, to identify risk factors associated with increased mortality, and to compare survival rates and risk factors between Indigenous and non-Indigenous Australians.

Methods

This project has been approved by the South Australia Clinical Human Research Ethics Committee (HREC), the Southern Adelaide HREC, the Aboriginal HREC and the Central Australia HREC. It adheres to the tenets of the Declaration of Helsinki.

Patient demographics, diabetes history and diabetic complications prior to vitrectomy surgery were available from our previous audit. Further details regarding data collection have been published elsewhere.[8] In brief, files of all patients identified as having had a vitreoretinal surgery during the audit period were manually examined. Data were collected retrospectively and included sex, age at time of primary vitrectomy, ethnicity (as per hospital record), type of diabetes, duration of diabetes, insulin use, pre-operative haemoglobin A1c (HbA1c, most recent value available prior to date of surgery), baseline best corrected visual acuity, chronic renal failure, renal failure requiring dialysis, and amputation. Legal blindness was defined as worse than best corrected visual acuity Snellen 6/60 (35 ETDRS letters equivalent) in the better eye.[20] Chronic renal failure was defined as glomerular filtration rate less than 60mL/min for more than 3 months.

Only patients who underwent their first vitrectomy for the following indications were included in this study: (i) media opacities (including recurrent or non-resorbing vitreous haemorrhage) and (ii) vitreoretinal traction, with or without haemorrhage (including tractional retinal detachment). Diabetic patients undergoing vitrectomy for all non-diabetes related indications were not included in the study Perceived life expectancy was not an inclusion criterion for this study. Patients who were indicated for diabetic vitrectomy but could not due to poor fitness for surgery were also not included in this study.

Date of death and cause of death was obtained from the South Australian and Northern Territory Deaths Registry, using survival status on the 6th July 2018 as the primary end point. Data linkage was performed through SA NT DataLink services, using the separation principle to ensure patient confidentiality.

Statistical analyses were performed on Statistical Package for Social Sciences (SPSS) version 25.0 for Mac OS X (IBM SPSS Statistics 25.0, SPSS Inc., Armonk, NY, USA). Kaplan Meier survival curves were generated to determine survival rates from 1 to 9 years after primary vitrectomy. Mann–Whitney U and chi-square tests were used to compare demographic variables among different groups. Risk factors were explored using univariate and multivariate regression analyses (Cox proportional hazard model). P-values <0.05 were considered statistically significant. Less significant variables were removed from the model in a stepwise manner until the strongest multivariate model remained.

Results

In South Australia and the Northern Territory, between 1st January 2007 and 31st December 2011, 307 primary vitrectomies were performed for diabetic retinopathy complications (media opacity or vitreoretinal traction). Demographic details and baseline clinical variables are shown in table 1. The number of participants with available and missing data for each variable studied is presented in supplementary table 1. The mean age at the time of vitrectomy was 57 years (range 22-90). A higher percentage of participants were male (59.2%), had type 2 diabetes (77.7%) and comorbidities such as chronic renal failure (55.9%). A significant proportion of the cohort was Indigenous Australian (n = 65, 21.2%). Compared with non-Indigenous Australian participants, Indigenous Australians were younger at the age of primary vitrectomy (51 versus 63 years old, p<0.001), had a shorter duration of diabetes (14 versus 18 years, p<0.001), yet a higher proportion had chronic renal failure (79.6% versus 51.8%, p<0.001), renal failure on dialysis (32.2% versus 6.7%, p<0.001) and amputation (36.6% versus 12.6%, p =0.004).

Table 1 Demographic details and baseline clinical variables for the total cohort and the indigenous and non-indigenous group separately. P values comparing variables between the indigenous and non-indigenous groups are presented.

Variable	Total	Indigenous	Non-indigenous	P
Male (n, %)*	181 (59.2)	29 (44.6)	152 (65.8)	**0.002**
Age at time of primary vitrectomy, years (mean, range)	57 (22-90)	51 (32-74)	63 (25-90)	**<0.001**
Type 2 diabetes (n, %)*	238 (77.7)	61 (93.8)	177 (76.6)	**0.001**

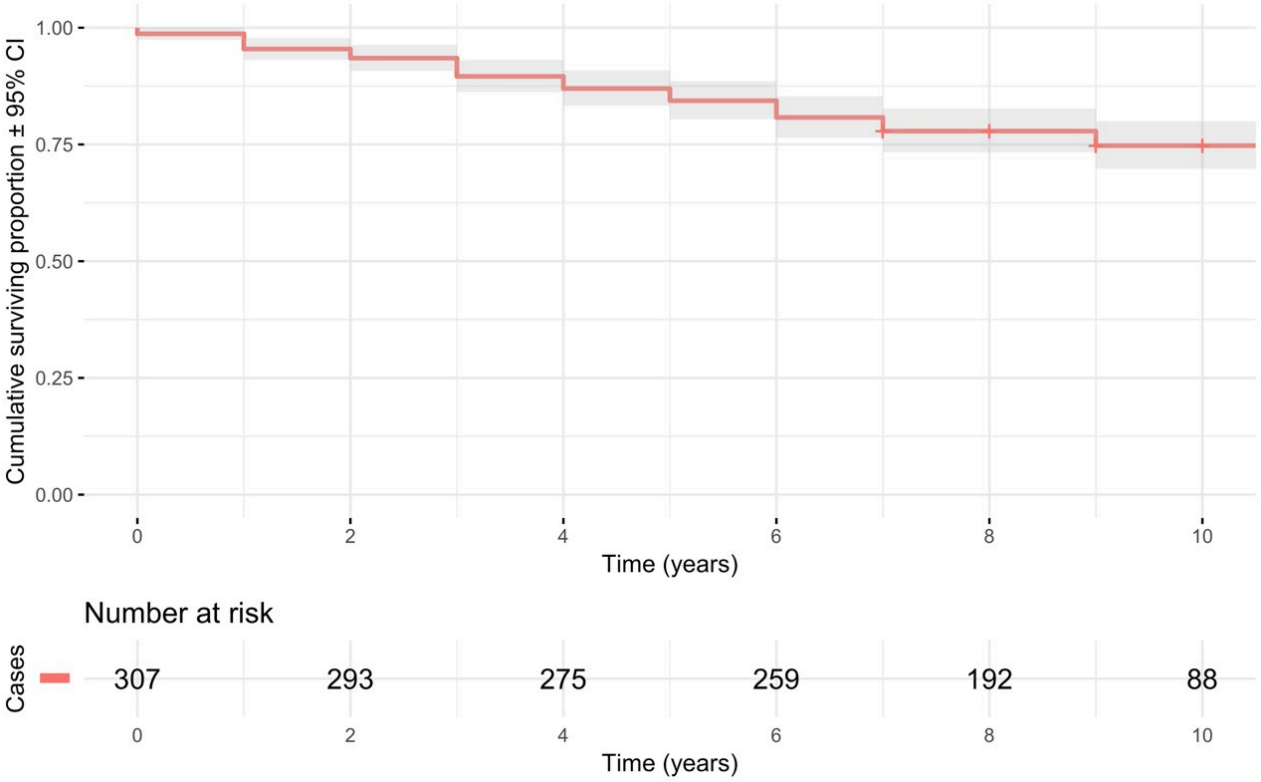
Diabetes duration, years (mean, range)	19 (0-53)	14 (2-29)	18 (0-45)	**<0.001**
Insulin use in type 2 diabetes (n, %)*	127 (52.2)	27 (44.3)	100 (56.5)	0.10
Pre-operative HbA1c, %(mean, range)	8.4 (5-17)	15 (32.6)	49 (21.1)	0.750
Legally blind at baseline (n, %)*	64 (22.8)	15 (24.2)	49 (23.6)	0.918
Chronic renal failure (n, %)*	157 (55.9)	47 (79.6)	110 (51.8)	**<0.001**
Renal failure requiring dialysis (n, %)*	35 (11.8)	20 (32.2)	15 (6.7)	**<0.001**
Amputation (n, %)*	41 (15.3)	15 (36.6)	26 (12.6)	**0.004**

**Percentages are calculated from the number of individuals with available data. Please refer to supplementary table 1 for the numbers in each category.*

At the primary end point, 73 out of 307 patients had a death record from the South Australian and Northern Territory Deaths Registry. The most common cause of death was cardiovascular disease (n=30), followed by sepsis (n=14), renal failure (n=11), cerebrovascular disease (n=8), cancer (n=5) and other causes (n=5).

Figure 1 shows the Kaplan-Meier plot estimating survival rates from 1 to 9 years after the primary vitrectomy. Survival rates for 5, 7 and 9 years were 84.4%, 77.9% and 74.7% respectively.

Figure 1: Kaplan-Meier plot estimating survival rates from 1 to 9 years after the primary vitrectomy



After univariate cox proportional hazard model analyses, the most significant factor associated with increased mortality was older age at the time of primary vitrectomy, (HR 1.03, 95% CI 1.02-1.05, p<0.001) and type 2 diabetes (HR 2.18, 95% CI 1.04-4.56, p=0.037) (Table 3).

Independent of age, Indigenous Australian ethnicity and chronic renal failure were significantly associated with increased mortality (HR 2.04, 95% CI 1.17-3.57, p=0.012 and HR 1.76, 95% CI=1.07-2.89, p=0.026 respectively) (Table 3).

Table: 3 Cox proportional hazard model analyses of available baseline clinical variables and their associations with mortality

Variable	Univariate analysis		Adjusting for age at time of primary vitrectomy	
	HR, 95% CI	P value	HR, 95% CI	P value
Male	0.82 (0.52-1.30)	0.393	0.81 0.51-1.28	0.362
Age at time of primary vitrectomy	1.03 (1.02-1.05)	**<0.001**	NA	NA
Indigenous Australian ethnicity	1.42 (0.85-2.38)	0.186	2.04 (1.17-3.57)	**0.012**
Type 2 diabetes	2.18 (1.04-4.56)	**0.037**	1.34 0.61-2.95	0.462
Diabetes duration	1.02 (0.99-1.04)	0.263	1.00 0.98-1.03	0.618
Insulin use in type 2 diabetes	1.18 (0.72-1.92)	0.509	1.19 0.73-1.94	0.490

Pre-operative HbA1c <7%	0.73 (0.41-1.29)	0.276	0.82 (0.46-1.45)	0.490
Legally blind at baseline	1.34 0.78-2.30	0.289	1.51 (0.88-2.62)	0.137
Chronic renal failure	1.54 0.95-2.53	0.083	1.76 (1.07-2.89)	**0.026**
Renal failure requiring dialysis	1.78 0.98-3.25	0.06	2.32 (1.25-4.32)	**0.008**
Amputation	0.86 0.46-1.60	0.626	1.17 0.63-2.18	0.624
Tripathy	1.45 0.71-2.94	0.304	1.47 0.72-2.98	0.290

Patients with chronic renal failure requiring dialysis had an even higher risk of death (HR 2.32, 95% CI 1.25-4.32, p=0.008). Type 2 diabetes, duration of diabetes, insulin use in type 2 diabetes, pre-operative HbA1c and amputation were not associated with mortality even after adjustment for age.

Five variables were included in the multivariate model based on level of significance from the univariate analyses: age at time of primary vitrectomy, Indigenous Australian ethnicity, type 2 diabetes, chronic renal failure and renal failure requiring dialysis. The strongest model had two variables: age at time of primary vitrectomy and renal failure requiring dialysis with an overall chi-square value of 17.6, p<0.001 (Table 4).

Table 4: Best fitting multivariate cox proportional hazard model for baseline variables and their association with mortality

Variables in model	HR, 95% CI	P value
Age at time of primary vitrectomy	2.32 (1.25-4.32)	**0.008**
Renal failure requiring dialysis	1.04 (1.02-1.05)	**<0.001**
Overall model chi-square = 17.6, p<**0.001**		

Sub-analysis by ethnicity

As the Indigenous Australian cohort in this study are significantly younger and have a shorter duration of diabetes than non-Indigenous Australians (Table 2), sub-analyses between the two ethnicities were done for comparison. Five, seven and nine year survival rates after primary vitrectomy for Indigenous Australians (n=65) were 83.1%, 73.8% and 66.2% respectively. Five, seven and nine year survival rates for non-Indigenous Australians (n= 242) were 85.3%, 79.3% and 77.3% respectively. This was not statistically significant (Kaplan-Meier curves, log rank test, chi-square 1.82, p=0.177) without adjustment for age in a multivariate cox regression model (as described in table 3).

No baseline variables were found to be significantly associated with mortality in the Indigenous Australian group after univariate and multivariate analysis, and this could be because of inadequate power (n=65).

However, in the non-Indigenous Australian group (n=242), older age at time of primary vitrectomy (HR 1.05, 95% CI 1.02-1.07, p<0.001) and diabetes duration (HR 1.04, 95% CI 1.01-1.07, p=0.022) were associated with increased mortality (Table 5).

Table 5: Cox proportional hazard model analyses of available baseline clinical variables and their associations with mortality: non-indigenous Australians

Variable	Univariate		Adjusting for age at time of primary vitrectomy	
Non-indigenous (n = 242)	HR, 95% CI	P value	HR, 95% CI	P value
Male	0.71 (0.41-1.24)	0.231	0.78 (0.44-1.38)	0.396
Age at time of primary vitrectomy	1.05 (1.02-1.07)	**<0.001**	NA	NA
Type 2 diabetes	2.04 (0.92-4.53)	0.080	0.88 (0.36-2.14)	0.778
Diabetes duration	1.04 (1.01-1.07)	**0.022**	1.03 (0.99-1.06)	0.103
Insulin use in type 2 diabetes	1.58 (0.85-2.95)	0.149	1.65 (0.88-3.07)	0.117
Pre-operative HbA1c <7%	0.94 (0.47-1.89)	0.860	0.90 0.45-1.82	0.771
Legally blind at baseline	1.64 (0.87-3.10)	0.126	1.92 1.02-3.65	**0.045**
Chronic renal failure	1.59 (0.90-2.82)	0.110	1.81 1.02-3.21	**0.044**
Renal failure requiring dialysis	1.63 (0.65-4.10)	0.301	2.01 (0.79-5.10)	0.142
Amputation	0.89 (0.38-2.10)	0.799	0.83 (0.35-1.95)	0.669

After adjusting for age, the only significant variables associated with mortality were found to be legal blindness at baseline (HR 1.92 95% CI 1.02-3.65, p=0.045) and chronic renal failure (HR 1.81 95% CI 1.02-3.21, p=0.044) (Table 5). However the strongest multivariate cox proportional model included the variables, age at time of primary vitrectomy, type of diabetes and duration of diabetes, with an overall chi-square value of 19.96, p<0.001 (Table 6).

Table 6: Best fitting multivariate cox proportional hazard model and their associations with mortality: non-indigenous Australians

Variables in model	HR, 95% CI	P value
Age at time of primary vitrectomy	2.32 (1.25-4.32)	**0.008**
Type 2 diabetes	3.99 (1.07-14.88)	**0.039**

Duration of diabetes	1.05 (1.01-1.08)	**0.035**
Overall model chi-square = 19.96, p<0.001		

Discussion

[67]This is the first study to explore mortality rates after diabetic vitrectomy in an Australian population. We found the 5, 7 and 9 year survival rates after primary vitrectomy performed for diabetic complications in South Australia and the Northern Territory were 84.4%, 77.9% and 74.7%, respectively.

This is similar to rates found in other studies, but it is difficult to make direct comparisons because of different study populations, sampling methods, time-frames and follow up periods. The most recent published study analysed 182 diabetic eyes at a single hospital in New Zealand that underwent vitrectomy for vitreous haemorrhage and/or tractional retinal detachment, and found a 5 year survival rate of 70.1%.[19] They also found renal failure on dialysis, creatinine levels (indicative of renal function), age and non-European ethnicity to be significantly associated with increased mortality. The New Zealand study included 49.5% patients of Maori descent, while our sample comprised of 21.2% Indigenous patients. Indigenous populations worldwide have lower life expectancy[21] and this may explain the lower survival rate found in the New Zealand study when compared with our study. Despite earlier indications for diabetic vitrectomy[22] and improved diabetes management,[23] mortality rates have remained similar over the decades. Older studies conducted between 1970's to early 2000's report 5 year survival rates that range widely from 68-96% in countries such as Japan, Germany, Finland and the United Kingdom.[14-19]

The Australian population that we have studied is unique in that a large proportion (21.2%) is of Indigenous Australian ethnicity. This is significantly higher than the estimated proportion of indigenous Australians with diabetes in SA and NT (1.44 (1.09 – 1.89; p = 0.01).[24, 25] Indigenous Australians are on average 10 years younger than non-Indigenous Australians when diagnosed with type 2 diabetes and at the onset of primary diabetic vitrectomy.[8] They are more likely to have type 2 diabetes, have a shorter duration of diabetes, a higher risk of developing severe complications, and this is not necessarily associated with poorer glycaemic control.[8] The reasons for earlier onset of diabetes are not well understood but could be attributed to more prevalent gestational diabetes and intrauterine risks, genetic predisposition, obesity, physical inactivity, nutrition and associated socioeconomic factors.[26] Earlier onset of type 2 diabetes is an independent risk factor for increased prevalence and severity of DR.[27]

These differences may skew our analyses. From our unadjusted results, there appears to be no difference in survival between Indigenous and non-Indigenous Australians requiring diabetic vitrectomy. However after adjustment for age,

the risk of death after vitrectomy over the next 5 to 9 years is twice as high for Indigenous Australians (HR 2.04, 95% CI 1.17-3.57, p=0.012). A similar pattern was also reported for the gap in survival between Indigenous and non-Indigenous Australians commencing renal replacement therapy before and after adjustment of age and other comorbidities.[28]

The differences in baseline characteristics between the Indigenous and non-Indigenous cohorts make interpretation of other mortality risk factors difficult. While our study did not have enough power to separately analyse the Indigenous Australian cohort, by comparing the overall cohort (including Indigenous Australians) with the non-Indigenous cohort, a few conclusions can be extrapolated.

Chronic renal failure and renal failure requiring dialysis were the most significant variables predicting mortality in the overall cohort, but lost significance in the non-Indigenous Australian cohort. This suggests that renal failure is a more important risk factor of mortality in Indigenous Australians. In the Central Australian Ocular Health Study, the presence of DR among diabetic Indigenous Australians, increased the risk of death from renal disease by almost 3 fold.[29] End stage renal disease is more than six fold more prevalent in Indigenous Australians compared with non-Indigenous Australians,[30] and in our study population, renal failure requiring dialysis was the most significantly different baseline variable when comparing Indigenous and non-Indigenous Australians (23.1% versus 10.7%, p<). In other studies, renal failure is the most common significant predictor of mortality following diabetic vitrectomy.[14, 16, 18, 19] Helbig et al reported a hazard ratio of 1.42 (p=0.044) for a creatinine level >150mmol[14] and Kim et al reported a hazard ratio of 4.2 (p<0.001) for renal failure requiring dialysis.[19] The link between renal failure and mortality is unsurprising because chronic renal failure is known to be associated with a high risk of cardiovascular related death[31] and this is the most common cause of death following diabetic vitrectomy.

Our data suggest that type 2 diabetes, longer duration of diabetes and legal blindness at baseline also contribute to mortality risk, although to a lesser degree and these associations only reached statistical significance in non-Indigenous Australians. Type of diabetes and duration of diabetes were not strongly associated with mortality in the overall cohort, however once Indigenous Australians were removed from the analyses, these variables were selected for the multivariate model. In other studies, type and duration of diabetes were also important predictors of mortality but were not the most significant.[11] Type 2 diabetes and longer duration of diabetes are associated with increasing age, and therefore increased mortality. Longer duration of diabetes increases risk of microvascular and macrovascular complication of diabetes such as chronic renal disease and cardiovascular disease. Interestingly, legal blindness at time of vitrectomy became significant in the non-Indigenous population of our study, but lost significance after multivariate

analyses. Poor vision is associated with social, functional and medical decline,[11] and poor visual acuity has been previously independently linked to mortality.[32]

The overall strengths of this study include the study design which allowed us to accurately capture the whole target population. Accurate data that includes rural and remote communities in South Australia and the Northern Territory are often difficult to obtain, and therefore a challenge when conducting population based studies. Vitrectomies in South Australia and the Northern Territory are only performed in two tertiary centre hospitals and a small number of private hospitals and all of these were audited between 2007 and 2011. The study had a long follow up time, of up to 9 years and it is the first study to be conducted in an Australian population.

There are some limitations to this study. It is possible that not all deaths were captured as participants may have moved interstate. Only deaths recorded in South Australia and the Northern Territory were captured through our methodology. Death data are also more likely to be underestimated in Indigenous Australians due to under-identification.[33] Patients who were unable to have a vitrectomy (due to poor fitness for surgery, declined surgery or socioeconomically disadvantaged) would not be included in this study and this could further underestimate mortality rates. Pars plana vitrectomy was performed by a small number of surgeons in South Australia, and we have made the assumption that there were no major differences in surgical methods during the five year period of the audit. We were also not able to accurately explore all prognostic variables. The HbA1c measurement available to us was a single measurement prior to surgery, and this may not accurately reflect that patient's overall glycaemic control over time. Data on prior heart disease or neuropathy, which have been shown to be associated with mortality in other similar studies,[16, 18] were also not available. While a significant proportion of the cohort was indigenous Australian, separate analyses of this group did not have enough power to fully explore risk factors associated with mortality and make comparisons to the non-indigenous Australian group.

Long term mortality rates after primary diabetic vitrectomy in South Australia and the Northern Territory are similar to other populations around the world.[14-19] A substantial proportion of those undergoing diabetic vitrectomy in Australia are Indigenous Australians. The risk of death over the next 5 to 9 years is twice as high for Indigenous Australians compared with non-Indigenous Australians after age adjustment. It is important to recognise chronic renal failure as a significant comorbidity contributing to mortality, particularly in Indigenous Australians. Our data suggest that ophthalmologists managing Indigenous patients with severe diabetic retinopathy should refer patients for investigation and management of potentially co-existing renal failure. In non-Indigenous Australians, type 2 diabetes, longer duration of diabetes and being legally blind at baseline are additional risk factors for increased mortality. Patients with these risk

factors should be referred to a physician for better management of their diabetes and cardiovascular health. This information can guide allocation of future resources to improve the prognosis of these high risk groups, and assist in closing the gap in mortality between Indigenous and non-Indigenous Australians.

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