Association of Age-Related Macular Degeneration With Mortality: A Propensity Score-Matched Analysis

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Introduction

Age-related macular degeneration (AMD) is one of the leading causes of visual impairment and blindness worldwide. The number of people with AMD globally is projected to increase to 288 million in 2040. As the population ages, the prevalence of AMD is likely to increase further, leading to significant economic and societal costs.

Accumulating evidence has suggested that AMD is an independent risk factor for all-cause mortality.[1] However, the results for its association with cause-specific mortality remain inconsistent. Some studies have reported that AMD was associated with an increased risk of CVD mortality,[1] while others did not find any significant association between AMD and CVD mortality.[2]

Our previous study[3] published in 2018 found that only late AMD increased the risk of 5-year all-cause and non-CVD non-cancer mortality, while no significant association was found between AMD and CVD mortality using data from the National Health and Nutrition Examination Survey (NHANES). The availability of 10-year mortality data empowers us with longer follow-up and more statistical power to investigate the long-term mortality among patients with AMD. Therefore, we aim to investigate the association of AMD with 10-year all-cause and cause-specific mortality.

Methods

Data from the 2005-2008 cycles of the National Health and Nutrition Examination Survey were used to assess the risk of mortality in relation to AMD in a propensity score-matched cohort.

AMD status was assessed by retinal images with the standardized grading scheme. Mortality data until 31st December 2015 were derived from mortality archives. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for survival.

Results

A total of 4691 participants were included in the analysis. After a median follow-up of 8.42 (IQR: 7.58-9.67) years, 698 participants died. Participants with any AMD had an increased risk of all-cause mortality (HR, 2.02; 95% CI, 1.37-2.98). Similar results were observed for early (HR, 1.93; 95% CI, 1.31-2.85) and late AMD (HR, 4.29; 95% CI, 2.10-8.79). With respect to cause-specific mortality, any (HR, 2.17; 95% CI, 1.39-3.39), early (HR, 2.18; 95% CI, 1.36-3.51), and late AMD (HR, 3.95; 95% CI, 1.65-9.46) were associated with significantly higher mortality due to causes other than cardiovascular disease (CVD) or cancer. We also found that late AMD independently predicted a higher risk of CVD mortality (HR, 2.48; 95% CI, 1.32-4.65). (Table 1)

Table 1. Risk for All-Cause Mortality and Specific-Cause Mortality in Participants With AMD Compared With Non-AMD After Propensity Score Matching

AMD status	All-Cause Mortality		CVD Mortality		Cancer Mortality		Non-CVD/Non-cancer Mortality	
	Events/Number	HR (95% CI)[a]	Events/Number	HR (95% CI)[a]	Events/Number	HR (95% CI)[a]	Events/Number	HR (95% CI)[a]
No AMD	571/4331	Reference	110/4331	Reference	142/4331	Reference	319/4331	Reference
Any AMD	127/360	**2.02 (1.37-2.98)**	19/360	1.42 (0.69-2.92)	22/360	1.42 (0.72-2.82)	86/360	**2.17 (1.39-3.39)**
Early AMD	104/318	**1.93 (1.31-2.85)**	15/318	1.27 (0.58-2.82)	20/318	1.45 (0.73-2.89)	69/318	**2.18 (1.36-3.51)**
Late AMD	23/42	**4.29 (2.10-8.79)**	4/42	**2.48 (1.32-4.65)**	2/42	0.44 (0.06-3.27)[b]	17/42	**3.95 (1.65-9.46)**

Abbreviations: AMD, age-related macular degeneration; CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age, gender, race, education, marital status, family income, smoking status, alcohol consumption, diabetes mellitus, hypertension, high cholesterol, BMI, high CRP, depressive symptom, coexisting ocular diseases, walking disability, self-rated health, history of cardiovascular diseases, and cancer.

[b] Adjusted for age and gender. Boldface indicates statistical significance.

Discussion

Consistent evidence on the association between late AMD and increased risks of all-cause mortality has been reported.[4] Whereas conflicting results were found on the associations of early or any AMD with all-cause mortality.[2] These conflicting results might be due to the heterogeneity in the study population, detection of AMD, statistical methods, and confounding factors adjusted for. The present analysis indicated that any form of AMD was associated with increased risks of mortality, suggesting the presence of AMD might be a biomarker for aging and frailty. Even though the exact mechanism for the significant association between AMD and mortality remains unclear, growing evidence has indicated some common pathways shared between the ageing process and the pathogenesis of AMD, such as increased oxidative stress and chronic inflammation.

The present study found that participants with late AMD had significantly higher CVD mortality. Growing evidence has demonstrated a close relationship between late AMD and increased CVD mortality.[1,2,5] The association between late AMD and CVD mortality might be explained by their common pathogenesis pathways (e.g., local inflammation and oxidative stress) and risk factors (e.g., age and smoking). The 'hallmark' of AMD, drusen, closely resembled atherosclerotic plaques in composition. In addition, the use of anti-VEGF to treat neovascular AMD might also increase CVD risks leading to higher CVD mortality.

Consistent with previous studies, we also found a strong association between AMD and non-CVD non-cancer mortality. Several hypotheses may explain this. Firstly, participants with AMD may be more generally frail. Secondly, increasing evidence suggested that AMD was significantly associated with neurodegenerative diseases (e.g., Alzheimer's disease). Last but not least, participants with AMD might be more likely to suffer from functional disabilities and social deprivation due to impaired vision.

The present study has the advantage of a large-scale nationally representative sample, long-term follow-up and the use of propensity score matching method to eliminate confounding effects. Limitations include the relatively small number of participants with late AMD preventing us from conducting further subgroup analyses, and the AMD status being assessed at a single time point.

Conclusions

The current study showed that any, early, and late AMD were associated with increased risks of all-cause mortality and mortality due to causes other than CVD or cancer. In addition, we found that late AMD was associated with increased risks of CVD mortality.

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