

# Influence of Diabetic Retinopathy on the Relationship Between Body Mass Index and Mortality in Patients with Poorly Controlled Type 2 Diabetes

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**Purpose:** An “obesity paradox” has been observed in patients with type 2 diabetes. However, the optimal body mass index (BMI) for survival may be influenced by the stage of diabetes. We examined the relationship between BMI and mortality in patients with type 2 diabetes and the influence of diabetic retinopathy (DR).

**Patients and Methods:** This is a retrospective cohort composing patients with type 2 diabetes who were admitted due to poor glucose control. Presence of DR was confirmed by ophthalmologists. The primary outcome was all-cause mortality. The association between BMI and mortality was assessed using a Cox proportional hazards model with adjustment for age, sex, and traditional risk factors.

**Results:** A total of 2053 patients were enrolled. Over median follow-up of 6.7 years, there were 1060 deaths. Patients were classified into five categories based on admission BMI (kg/m<sup>2</sup>): <18.5, 18.5–23, 23–25, 25–27 (reference), 25–30 and >30. Mortality risk was significantly higher in the <18.5 kg/m<sup>2</sup>, 18.5–23 kg/m<sup>2</sup>, and 23–25 kg/m<sup>2</sup> categories than in the reference category (P <0.001). The similar obesity paradox was observed in the subgroup of patients without DR. However, in patients with DR, only patients with BMI <18.5 kg/m<sup>2</sup> had significantly increased mortality than those in the reference category. The presence of DR significantly modified the shape of the association between BMI and mortality (P = 0.019).

**Conclusion:** The obesity paradox exists in patients with poorly controlled type 2 diabetes. The presence of DR appears to significantly influence the shape of the association between BMI and mortality.

**Keywords:** cohort, inpatient, obesity, paradox, overweight, retrospective

## Introduction

Obesity is a well-established risk factor for cardiovascular disease.<sup>1</sup> In patients with type 2 diabetes, obesity not only escalates cardiovascular risk, but also worsen glucose control.<sup>2</sup> Therefore, maintaining normal weight has traditionally been an important component of diabetes management. However, recent large-scale epidemiologic studies have shown that overweight is associated with survival benefit as compared with normal weight in patients with type 2 diabetes. This phenomenon is referred to as the “obesity paradox”,<sup>3–8</sup> and it raises doubts regarding the optimal weight status for patients with type 2 diabetes.

Although the majority of research supports the existence of the obesity paradox, a growing body of literature suggests that this observation might be biased by reverse

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causality or unknown confounders.<sup>9–11</sup> Differences in the sample populations may be responsible for the inconsistent results.<sup>12</sup> Specifically, Lee et al<sup>13</sup> reported that the optimal body mass index (BMI) for survival depends on the patient's glucose regulation status. Xing et al<sup>14</sup> reported no obesity paradox in patients with long-standing type 2 diabetes. As type 2 diabetes is a heterogeneous disease comprising a wide spectrum of phenotypes, we hypothesized that the shape of the association between BMI and mortality might differ among various diabetic phenotypes. Although previous studies have been reported in patients with incident diabetes, little is known about the relationship between BMI and mortality in patients with poorly controlled diabetes.<sup>3,7</sup>

A recent analysis of Swedish National Diabetes Register data suggested that control status of five risk-factor variables, including glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol, albuminuria, smoking, and blood pressure, influences long-term mortality in patients with type 2 diabetes.<sup>15</sup> Comorbid conditions such as cardiovascular disease,<sup>5</sup> heart failure,<sup>16,17</sup> and chronic kidney disease<sup>18</sup> also influence the relationship between BMI and mortality. However, the effect of diabetic retinopathy (DR) on the relationship between BMI and long-term mortality has not been explored in patients with type 2 diabetes. Therefore, we examined the relationship between BMI and all-cause mortality in patients with poorly controlled type 2 diabetes, and determined whether the presence of DR affects this relationship.

## Materials and Methods

### Setting and Participants

This retrospective cohort study was conducted at Taichung Veterans General Hospital. Clinical data were obtained by reviewing the medical records of patients with type 2 diabetes who were hospitalized between August 1996 and August 2007. The inclusion criteria were (1) adults with type 2 diabetes who were admitted to the Endocrinology and Metabolism section due to a primary diagnosis of poor glucose control based on the endocrinologists' evaluations; and (2) fundal examination performed by an ophthalmologist during hospital stay. The exclusion criteria were (1) no available BMI data measured in standing position on admission; (2) end-stage renal disease; (3) pregnancy; or (4) death in hospital or within 24 hrs of discharge. The research protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital. The need for informed consent was waived in the

view of the retrospective nature of the study. This study was conducted in accordance with the Declaration of Helsinki, and all data were maintained with confidentiality.

### Measurements

Based on the standard procedures for hospitalization, standing height and weight were measured on admission, and the BMI was calculated using the following formula: weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Blood samples were collected for biochemistry assessment after overnight fasting during the hospitalization period. DR included non-proliferative DR (NPDR) and proliferative DR (PDR). DR was screened using fundoscopic examinations by ophthalmologists via formal consultations. In cases with abnormal fundoscopic findings, retinal angiography (CF-60UVi Fundus camera, Canon, Tokyo, Japan) was subsequently performed to confirm the retinopathy diagnosis. The history of coronary artery disease (CAD) was obtained from the electronic medical records. Self-reported current smoking status was obtained from the medical records.

HbA1c level was determined using National Glycohemoglobin Standardization Program (NGSP) certified cation-exchange high-performance liquid chromatography (G8, TOSOH, Tokyo, Japan). LDL cholesterol level was determined using enzymatic methods (Advia 1800, Siemens, NY, USA). Serum creatinine level was determined using the Jaffé method (Advia 1800, Siemens, NY, USA). The estimated glomerular filtration rate (eGFR) was calculated by  $186 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age (year)}^{-0.203}$  ( $\times 0.742$  if female)  $\text{mL}/\text{min}/1.73 \text{ m}^2$  based on the modification of diet in renal disease (MDRD) equation.<sup>19</sup>

According to World Health Organization (WHO) recommendations,<sup>20</sup> underweight, overweight, and obesity are defined as BMI ( $\text{kg}/\text{m}^2$ ) of  $<18.5$ ,  $\geq 25$ , and  $\geq 30$ , respectively. Furthermore, the BMI cutoff point for obesity or high risk should depend on the assessed population.<sup>20</sup> To facilitate the exploration of mortality and BMI, we added BMI of  $27 \text{ kg}/\text{m}^2$ , defined as obesity in Taiwan, as the cutoff for high risk.<sup>21</sup> In our study, therefore, BMI was categorized into  $<18.5 \text{ kg}/\text{m}^2$ ,  $18\text{--}23 \text{ kg}/\text{m}^2$ ,  $23\text{--}25 \text{ kg}/\text{m}^2$ ,  $25\text{--}27 \text{ kg}/\text{m}^2$ ,  $27\text{--}30 \text{ kg}/\text{m}^2$ , and  $>30 \text{ kg}/\text{m}^2$  groups for analysis. The primary endpoint was all-cause mortality after discharge. We applied the mortality data up to December 2011 from the Collaboration Center of Health Information Application, Department of Health, Executive Yuan, Taiwan.

## Statistical Analysis

Continuous data were summarized as the means  $\pm$  standard deviations (SD); categorical data as numbers (with percentages). One-way analysis of variance (ANOVA) was used to determine the significance of the differences among groups. Kruskal–Wallis test was used for analysis of diabetic duration and follow-up duration due to the skewed distributions of these measures. Chi-square test was used to compare categorical variables across groups. Cox proportional hazards regression analysis was used to determine the hazard ratios for mortality. Proportionality was checked using Schoenfeld residuals, and models were stratified on variables which were found to violate proportionality. To assess the influence of DR on the relationship between BMI and mortality, we introduced an interaction term (BMI  $\times$  DR) in the Cox model, using BMI treated as a continuous variable. We also checked the interaction effect using BMI as a category variable. We compared the Cox models with and without the interaction term (BMI category  $\times$  DR) and used ANOVA to test the significance. Statistical significance was at  $P < 0.05$ . Statistical analysis was performed using R 3.4 software.

## Results

A total of 2053 patients were included in this analysis. There were 163 patients with BMI  $<18.5$  kg/m<sup>2</sup>, 730 with

BMI 18–23 kg/m<sup>2</sup>, 417 with BMI 23–25 kg/m<sup>2</sup>, 289 with BMI 25–27 kg/m<sup>2</sup>, 276 with BMI 27–30 kg/m<sup>2</sup>, and 178 with BMI  $>30$  kg/m<sup>2</sup>. Duration of diabetes, serum LDL cholesterol, and smoking status were comparable between groups. However, mean age, mean systolic pressure, mean diastolic pressure, and CAD prevalence were significantly lower; and HbA1c was significantly higher in the BMI  $<18.5$  kg/m<sup>2</sup> category than in the other BMI categories ( $P < 0.001$  for all). There was a significant inverse trend between mean eGFR and BMI (Table 1).

Over median of 6.7 years (interquartile range, 3.9–9.6 years) of follow-up, 1060 patients died. Mortality risk was significantly higher in the BMI  $<18.5$  kg/m<sup>2</sup>, 18.5–23 kg/m<sup>2</sup>, and 23–25 kg/m<sup>2</sup> categories than in the reference category of BMI 25–27 kg/m<sup>2</sup>; however, mortality risks in the 27–30 kg/m<sup>2</sup> and  $>30$  kg/m<sup>2</sup> categories were comparable to that in the reference category (Figure 1).

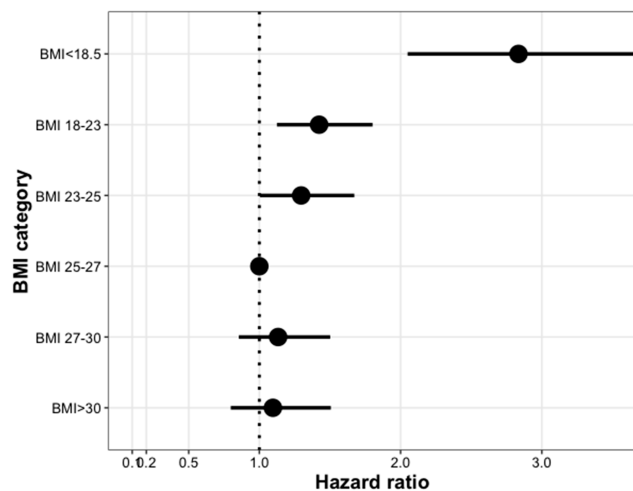
There were 885 patients with DR and 1168 patients without DR. We stratified the study cohort according to presence or absence of DR. The incidence of all-cause mortality was 9.3/100 person–year in patients with DR and 6.5/100 person–year in those without DR. The risk of all-cause mortality was significantly higher in the patients with DR than those without DR (Log-rank test  $P < 0.001$ , using Kaplan–Meier analysis; Figure 2). Table 2

**Table 1** Characteristics of Enrolled Patients Stratified by Body Mass Index (BMI)

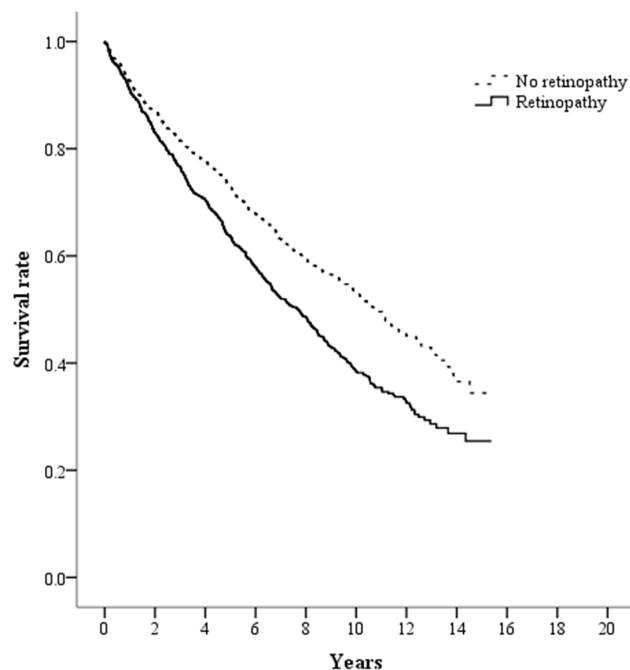
	BMI $<18.5$ (n = 163)	BMI 18.5–23 (n = 730)	BMI 23–25 (n = 417)	BMI 25–27 (n = 289)	BMI 27–30 (n = 276)	BMI $>30$ (n = 178)	P
Age (years)	56 $\pm$ 19	61 $\pm$ 16	63 $\pm$ 14	63 $\pm$ 14	64 $\pm$ 14	62 $\pm$ 14	$<0.001$
Male, n (%)	93 (57.1%)	414 (56.7%)	256 (61.4%)	153 (52.9%)	156 (56.5%)	79 (44.4%)	0.007
BMI (kg/m <sup>2</sup> )	17.1 $\pm$ 1.2	21.1 $\pm$ 1.2	24.0 $\pm$ 0.6	26.0 $\pm$ 0.6	28.2 $\pm$ 0.9	32.7 $\pm$ 2.5	$<0.001$
Current smoking, n (%)	51 (31.3%)	203 (27.8%)	116 (27.8%)	69 (23.9%)	78 (28.3%)	42 (23.6%)	0.476
DM duration (years)*	7 (2–13)	10 (3–15)	10 (4–16)	10 (3–15)	10 (3–17)	9 (3–12)	0.236
SBP (mmHg)	121 $\pm$ 16	130 $\pm$ 17	133 $\pm$ 17	133 $\pm$ 16	135 $\pm$ 17	135 $\pm$ 17	$<0.001$
DBP (mmHg)	71 $\pm$ 11	74 $\pm$ 11	75 $\pm$ 11	76 $\pm$ 10	77 $\pm$ 11	77 $\pm$ 11	$<0.001$
HbA1c (%)	11.5 $\pm$ 3.1	10.7 $\pm$ 3.1	10.4 $\pm$ 2.9	10.4 $\pm$ 2.9	10.2 $\pm$ 2.8	10.1 $\pm$ 2.7	$<0.001$
LDL-C (mg/dL)	114 $\pm$ 63	109 $\pm$ 42	114 $\pm$ 51	118 $\pm$ 40	115 $\pm$ 42	111 $\pm$ 42	0.233
eGFR (mL/min/1.73 m <sup>2</sup> )	80 $\pm$ 38	66 $\pm$ 32	61 $\pm$ 30	63 $\pm$ 34	60 $\pm$ 32	59 $\pm$ 32	$<0.001$
DR, n (%)							0.027
NPDR	40 (24.5%)	223 (30.5%)	128 (30.7%)	87 (30.1%)	61 (22.1%)	55 (30.9%)	
PDR	15 (9.2%)	108 (14.8%)	59 (14.1%)	43 (14.9%)	35 (12.7%)	31 (17.4%)	
CAD, n (%)	8 (4.9%)	55 (7.5%)	54 (12.9%)	32 (11.1%)	42 (15.2%)	22 (12.4%)	$<0.001$
Incidence of mortality (100 person-year) #	11.0	7.8	7.9	6.1	7.6	6.9	$<0.001$

**Notes:** \*Data are reported as median (interquartile range), P value for Kruskal–Wallis test. #Denotes P value for Log-rank test.

**Abbreviations:** BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure.



**Figure 1** Hazard ratios for all-cause mortality according to predefined body mass index (BMI) categories in all participants.



**Figure 2** Survival rates shown by Kaplan-Meier curves according to the presence or absence of retinopathy (Log-rank test  $P < 0.001$ ).

shows the hazard ratio for mortality in each BMI category as compared to the reference category in the Cox regression model, and we selected the covariates which were significantly associated with BMI shown in Table 1. As current smoking is an important correctable factor for mortality in type 2 diabetes,<sup>9,15</sup> we also included current smoking as a covariate in the Cox regression model. Among the patients without DR, the relationship between BMI and all-cause mortality was similar to that seen in the entire cohort: i.e. significantly higher risk of mortality in

the BMI categories  $<18.5 \text{ kg/m}^2$ ,  $18.5\text{--}23 \text{ kg/m}^2$ , and  $23\text{--}25 \text{ kg/m}^2$  than in the reference category, and comparable risk of mortality among the  $27\text{--}30 \text{ kg/m}^2$ ,  $>30 \text{ kg/m}^2$ , and the reference categories. Among the patients with DR, however, only those with BMI  $<18.5 \text{ kg/m}^2$  had significantly higher risk of mortality than the reference group (Table 2). The shape of the relationship between BMI and mortality risk was obviously different between the patients with and without DR (Figure 3). There was significant interaction between continuous BMI data and DR ( $P = 0.019$ ), as well as between categorized BMI data and DR ( $P = 0.036$ ).

## Discussion

Among the patients hospitalized because of poorly controlled diabetes, those with BMI of  $<18.5 \text{ kg/m}^2$ ,  $18.5\text{--}23 \text{ kg/m}^2$ , and  $23\text{--}25 \text{ kg/m}^2$  had a higher mortality risk than those with BMI of  $25\text{--}27 \text{ kg/m}^2$ . Therefore, an existence of the obesity paradox was shown in this cohort. The lowest mortality was observed in patients with BMI of  $25\text{--}27 \text{ kg/m}^2$ , which harbored in the overweight range in Asians according to the criteria of WHO<sup>20</sup> or in Taiwan.<sup>21</sup> Interestingly, there was a significant interaction between DR and BMI. In patients with DR, only those with BMI  $<18.5 \text{ kg/m}^2$  had significantly higher risk of mortality than the reference group (BMI of  $25\text{--}27 \text{ kg/m}^2$ ). Thus, the presence of DR changed the shape of the association between BMI and all-cause mortality in patients with type 2 diabetes.

Several studies have shown a U-shaped association between BMI and mortality. The optimal BMI for survival appears to depend on the characteristics of the populations. Among the patients with newly diagnosed diabetes, the lowest mortality rate in the obesity group (BMI of  $30\text{--}35 \text{ kg/m}^2$ ) was reported in the Louisiana State University Hospital-Based Longitudinal Study;<sup>22</sup> among the patients with known type 2 diabetes and a median diabetic duration of 9 years, the lowest mortality rate in the group with BMI between  $33.2$  and  $39.4 \text{ kg/m}^2$  was reported in the Madrid DIABETES Study with the mortality records of the Spanish National Institute of Statistics.<sup>23</sup> In comparison to subjects with normal glucose regulation, it has been deduced that the optimal BMI was approximately  $1.5 \text{ kg/m}^2$  higher for patients with incident diabetes and approximately  $3 \text{ kg/m}^2$  higher for patients with known diabetes.<sup>13</sup> In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, however, Xing et al<sup>14</sup> reported contrary findings. Among patients with long-standing diabetes, the highest risk of mortality in patients with BMI  $\geq 40 \text{ kg/m}^2$  was observed with no

**Table 2** Hazard Ratio (HR) for All-Cause Mortality, Stratified by Body Mass Index (BMI) for Patients with and Without Diabetic Retinopathy (DR)

BMI (kg/m <sup>2</sup> ) Categories	All			Without DR			With DR		
	HR (95% CI)	P*	P <sup>#</sup>	HR (95% CI)	P*	P <sup>#</sup>	HR (95% CI)	P*	P <sup>#</sup>
BMI <18.5	2.84 (2.04–3.92)	<0.001	<0.001	3.35 (2.11–5.32)	<0.001	<0.001	1.88 (1.09–3.25)	0.022	<0.001
BMI 18.5–23	1.42 (1.12–1.80)	0.003		1.73 (1.21–2.47)	0.002		1.17 (0.82–1.66)	0.364	
BMI 23–25	1.29 (1.01–1.67)	0.046		1.51 (1.03–2.22)	0.033		1.07 (0.72–1.57)	0.725	
BMI 25–27 (Reference)	1			1			1		
BMI 27–30	1.13 (0.84–1.50)	0.384		1.37 (0.91–2.07)	0.121		1.11 (0.71–1.73)	0.680	
BMI >30	1.08 (0.79–1.50)	0.571		1.08 (0.56–1.59)	0.849		1.03 (0.65–1.64)	0.872	

**Notes:** \*Denotes P value for differences compared to the reference group. <sup>#</sup>Denotes P value for differences compared across all BMI groups. Adjusted by age, sex, glycated hemoglobin, estimated glomerular filtration rate, systolic blood pressure, smoking history, and coronary artery disease history.

**Abbreviations:** BMI, body mass index; CI, confidence interval.

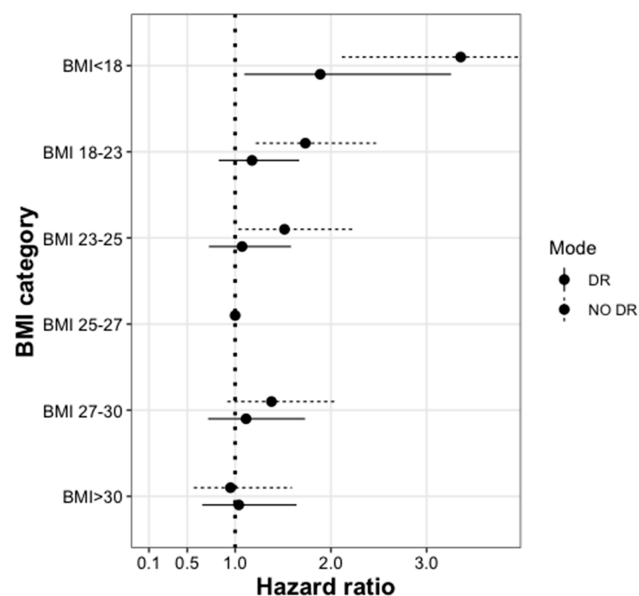
evidence of the obesity paradox, but it should be noted that the ACCORD study was primarily designed for intensive control of blood glucose, blood pressure, and lipids.<sup>14</sup>

In medical science, the term “obesity paradox” still lacks a precise definition.<sup>24</sup> It was first used as an article title for an unexpected higher mortality in CAD patients with normal BMI than those with overweight BMI. In line with our findings that article did not find a significant difference in mortality between subjects with overweight and obesity.<sup>25</sup> Here, we selected BMI of 25–27 kg/m<sup>2</sup> as the reference category because previous reports have shown a low risk of mortality in this BMI range among Taiwanese with type 2 diabetes and among Asians.<sup>26,27</sup> Therefore, we considered the relationship between long-

term mortality and BMI an obesity paradox in the present study, with mortality risk being lowest in overweight patients. Salehidoost et al<sup>28</sup> also reported relatively low mortality risk in overweight Iranians with type 2 diabetes. In Asian patients developing type 2 diabetes, low BMI is associated with predominant  $\beta$ -cell dysfunction.<sup>29</sup> In our cohort composed of inpatients with type 2 diabetes and a mean HbA1c of approximately 10%, these patients might undergo a certain degree of the catabolic effects of hyperglycemia when admission, especially patients with BMI <18.5 kg/m<sup>2</sup>.

Fatty acid oxidation is an important energy source for the heart. An alternative energy source, such as glucose, should be increased when fatty acid utilization is impaired; however, glucotoxicity status with high insulin resistance may result in a lack of glucose uptake into cardiomyocytes.<sup>30</sup> Impaired energy utilization may induce a cardiac damage and increase risk of heart failure.<sup>31</sup> Therefore, the maladaptive cardiac response to energy impairment may explain the high mortality risk in patients with low BMI and poor glucose control. Furthermore, impaired activation of peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ), mostly expressed in adipose tissue, may also be a mechanism for the high mortality rate in patients with low BMI, based on the literature-based discovery.<sup>32</sup> In an animal study, PPAR $\gamma$  agonist-induced fatty acid oxidation and prevented heart failure.<sup>33</sup>

DR was a significant predictor of mortality in the present study. In a meta-analysis of studies on type 2 diabetes, Kramer et al<sup>34</sup> showed that DR was associated with 2.41-fold increased risk of mortality. In Asians with type 2 diabetes, Sabanayagam et al<sup>35</sup> reported that DR was associated with 1.54-fold increased risk of mortality, and this result is consistent with our own previous study in which we found that DR was associated with 1.58-fold increased risk of mortality in patients without albuminuria.<sup>36</sup>



**Figure 3** Hazard ratios with 95% confidence interval for mortality in patients with and without diabetic retinopathy (DR). P = 0.019 for the interaction between body mass index (BMI) and DR.

The role of adiposity is ambiguous in patients with DR.<sup>37</sup> DR has been shown to be associated with obesity.<sup>38,39</sup> On the contrary, several studies have shown that obesity has the potential to diminish the severity of DR in Asians with type 2 diabetes.<sup>40–42</sup> Man et al<sup>40</sup> pointed out that generalized obesity and abdominal obesity may have different effects on DR. Although a high waist-to-hip ratio increased the risk of DR, a high BMI decreased the risk of DR in Asians with type 2 diabetes recruited from the Singapore National Eye Centre.<sup>40</sup> Sasongko et al<sup>41</sup> reported that high BMI was significantly associated with lower risk of DR in Indonesians with type 2 diabetes. Similarly, Chan et al<sup>42</sup> reported an inverse association between BMI and incidence of DR in separate prospective cohorts of Malays and Indians.

Ahlqvist et al<sup>43</sup> reported that patients with low BMI and low insulin secretion were prone to developing DR based on data-driven cluster analysis. A lower DR risk was associated with a better  $\beta$ -cell function, as reflected by high fasting C-peptide levels, in Chinese patients with type 2 diabetes.<sup>44</sup> Furthermore, there are some differences in the mechanism between DR and CAD; for example, vascular endothelial growth factor is an initiator of DR development, but plays a protective role in vascular collateralization for CAD.<sup>45,46</sup> Therefore, patients with DR should be viewed as a different population from those without DR. There appears to be a close relationship between DR, BMI, and mortality. Ours is the first study to demonstrate a difference in the shape of the association between BMI and mortality in patients with and without DR.

The present study has several strengths. First, DR was diagnosed by ophthalmologists. Second, BMI was obtained on admission using standard instruments, avoiding the recall bias of self-reported values. Third, all-cause mortality data were obtained from the national mortality registry, which covers 99.6% of the total population of Taiwan. Nevertheless, this study also has some limitations. First, BMI is known to be a weak surrogate for adiposity as it does not distinguish between muscle and fat. BMI also fails to reflect visceral adiposity, which has more impact on cardiovascular risk than subcutaneous fat.<sup>47</sup> Second, we did not identify the mechanism by which DR influences the relationship between BMI and mortality. Finally, we did not assess the effect of treatments received by patients after discharge.

## Conclusion

A low BMI appears to be associated with a high risk of mortality in patients with poorly controlled type 2 diabetes.

The lowest mortality risk was observed in patients with BMI between 25 and 27 kg/m<sup>2</sup>. The relationship between BMI and mortality in patients with DR differed from that in patients without DR. Compared with the reference group, the curve of obesity paradox became flat and only patients with BMI <18.5 kg/m<sup>2</sup> showed a significantly higher mortality risk.

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## Disclosure

The authors report no conflicts of interest in this work.

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