中 國 醫 藥 大 學

臨床醫學研究所

碩士學位論文

重症糖尿病患者與較低腹主動脈瘤破裂機率關係探討

Advanced Diabetes is Associated with Lower Risk of Abdominal Aortic Aneurysms Rupture: A Population-Based Cohort Study

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論文題目

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本論文係 蔡忠霖 於中國醫藥大學臨床醫學研究所完成之碩士論文，經考試委員審查及口試合格，特此證明。

考試委員

吳怡瑩

謝世榮

趙四里

所長：

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摘　要

中　文　摘　要

背景

糖尿病往往引發血管硬化阻塞及日後致命的併發症。近期系列文獻提出糖尿病提供了腹主動脈瘤的保護作用。然而，更重症的糖尿病狀態往往反映了持續性的體內高血糖環境，是否能更進一步提供腹主動脈瘤的保護作用。此文獻，我們探討了重症糖尿病與腹主動脈瘤發生及破裂之相關性研究。

方法及結果

資料來源為台灣健保資料庫，資料中有 206,685 位為糖尿病患者，配對了 826,740 位非糖尿病患者，平均年齡為 65.8 歲。重症糖尿病為根據糖尿病併發症所定義，腹主動脈瘤總發生率，糖尿病組低於非糖尿病組病患 22%，男性、高血壓及慢性病為腹主動脈瘤高危險因子，男性糖尿病病患比女性糖尿病病患呈現較高的保護作用。重症糖尿病患者有低於 33%比率的腹主動脈瘤危險機率及較佳的腹主動脈瘤破裂保護作用。

結論

本研究顯示出糖尿病與腹主動脈瘤逆向關連性；另外，糖尿病嚴重度與腹主動脈瘤破裂機率之比較，於本研究呈現的結果令人印象深刻且是首先於亞洲文獻中提出；且研究結果顯示，更重症的糖尿病狀態有較低的腹主動脈瘤破裂機率，更進階的相關機轉探討仍須進一步於未來作探討。

英 文 摘 要

Background

Diabetes (DM) can induce “atherosclerotic” change of vessels and some lethal complications. Current series of studies suggest a protective role of diabetes in the development of abdominal aortic aneurysms (AAAs). However, the more advanced complicated, reflect persistent hyperglycemia status, than well-controlled diabetic patients could offer more protective effect in aneurysm progression? We sought to determine the relationship between advanced diabetic condition and incidence of abdominal aortic aneurysm, and rupture event.

Methods and Results

Data analyzed in this study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD). The 206,685 patients with DM and 826,740 comparisons were similar in sex and age distribution, with a mean age of 65.8 (SD, 12.0) years. The severity of diabetes partitioned as advanced and uncomplicated status according to coexist DM-related disease. The overall incidence rate of AAA was 22% lower in the DM cohort than in the non-DM cohort (1.88 vs. 2.41). DM patients had a 19% lower risk of abdominal aortic aneurysm than non-DM patients (unadjusted HR=0.81). Male gender (adjusted HR=3.75), hypertension (adjusted HR=1.98), chronic kidney disease (adjusted HR=1.91) and ischemic heart disease (adjusted HR=1.60) were associated with increased risk of developing AAA. Sex-specific analysis showed higher beneficial effect from DM patients in men than in women (IRR=0.71 vs. IRR=0.99,) Age-specific analysis showed the incidence increasing with age in both cohorts. Compared to the severity of diabetes in association with AAA, the advanced DM patients had a 33% lower risk in un-ruptured abdominal aortic aneurysm (adjusted HR = 0.67). Compared to the non-DM cohort, the uncomplicated DM patients had a beneficial effect in abdominal aneurysm without rupture group (adjusted HR = 0.44,). Moreover, the advanced DM patients had a more significant protective effect in aneurysm rupture group (adjusted HR = 0.51).

Conclusions

The inverse relationship between DM and AAA was determinate in our study. And the implication of diabetic severity comparison to AAA rupture event is impressive and first addressed in documented articles. Our study revealed that the more advanced diabetic condition was related to lower risk of aneurysm rupture. Further research is required to demarcate the underlying mechanisms for this association.

誌　謝　辭

寫論文、分析資料這段日子為我的生活帶來的壓力，而此論文得以完成要感謝的人很多，以字句聊表心中無限的感激。

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最後感謝所有幫助過我的研究與論文的人，期許碩士生涯的結束也是我持續投入研究的開始。

忠霖謹誌

102 年 7 月 於台中

目　錄

圖 表 目 錄

第一章 前言

第一節 研究背景

Diabetes mellitus carry some lethal complicated disease even during intensive blood sugar control. The epidemic database revealed that diabetes mellitusaffects around 4% of the UK population.[1]Abdominal aortic aneurysm (AAA) is defined asa permanent aortic wall dilatation of the abdominal aorta. That is considered traditionally as aging disease, pathologic artery wall atherosclerotic change and mainly occurs in men over 60 year-old groups. In older men, studies figure that is thetenth leading cause of death.[2] As the aging process contributed to development of AAA, the prevalence of diagnosed type 2 diabetes is most at risk of developing abdominal aorticaneurysms (AAAs) and is estimated between 10 to15%.[3,4,5,6] However, even thought theoretical pathogenic mechanisms,the association between AAA and diabetes remains limited and conflicting. A negative association between diabetes and AAA was observed first in a 1997 report of a large abdominal aortic aneurysm (AAA) screening study.[7]A negative association was demonstrated between diabetes and AAA measuring between 3.0 - 3.9 cm and ≥4 cm. The same group published further results using 52,745 new subjectsrecruited to the same trial.[8] These evidences provide a challenge to the traditional view of AAA as a manifestation of atherosclerosis contrasts with its causal role inocclusive vascular disease. Furthermore, series of researches focused on a protective effect and summarized that the paradoxical confuting can be distinguished as changes in the aortic wall and characteristics of the mural thrombus.[9,10,11] Moreover, advanced diabetic condition always reflected more blood sugar concentration than simple diabetic status. The persistent hyperglycemia might theoretically pave the way for biologic changes in the aortic wall and fibrolytic characteristics then alter the pathophysiological course in DM patients with AAA.

We retrieved Taiwan National Health Insurance Research Database (NHIRD) in this study. The insurance program was set up since the beginning of 1995, by the end of 2009 and covered approximately 99% of the population (23.74 million). We analyze the link and outline possible factors between abdominal aortic aneurysm without rupture (AAAW), aneurysm with rupture (AAAR) and diabetes from the evidence. Different severity of diabetes, uncomplicated and advanced DM, associations between the risks of AAAW and AAAR were determinate.

第二節 研究目的

The primary discharge diagnosis of diabetes mellitus (DM) (ICD-9 code 250) was used to identify in whom new-onset diabetes mellitus had been diagnosed during the period 1998-2008. The index date for patients with DM was the date of their first medical visit. Patients with a history of abdominal aortic aneurysm (AAA) (ICD-9 code 441.3-441.4)diagnosed before the index date, those with missing information for age or sex, and those younger than 40 years were excluded. For the comparison cohort, we used a simple random sampling method and selected 4 insured people with non-DM status for every person with DM during thee same period. Patients and controls were frequency matched for age 5 years each, sex, and index year. We conducted the method of 1:4 matching design to increase the statistical power and control the potential confounding.

第二章 研究方法

第一節 研究材料

Data analyzed in this study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD). The Bureau of National Health Insurance (BNHI) provided the medical claims data and this study was exempted by the Institutional Review Board (CMU-REC-101-012). With approval from the NHRI, we were able to use the scrambled patient identification numbers to interlink files, including inpatients care claims and the registry for beneficiaries. The National Health Research Institute, which maintains and updates the NHIRD. The insurance program was set up since the beginning of 1995, and by the end of 2009 this program covered approximately 99% of the population (23.74 million) and contracts with 97% of the hospitals and clinics in Taiwan (Cheng, 2009). The accuracy and high validity of diagnosis in NHIRD also has been demonstrated (Cheng, 2011; Kang 2010).The International Classification of Disease, Ninth Revision (ICD-9) was used for the diagnosis codes.

第二節 研究設計

The follow-up time began on the index date and lasted until the AAA diagnosis; withdrawal from the insurance system; death; or December 31, 2010; whichever came first. AAA was identified using hospital discharge diagnosis. The history of hypertension (ICD-9 code 401-405), chronic kidney disease (ICD-9 code 582.9, 585.3-585.9, 586) and ischemic heart disease (ICD-9 code 412, 414.00-414.07, 414.2-414.9) were identified as diagnosed by hospital admissions before the index date.

第三章 研究結果

第一節 統計分析

We compared differences in sex, age and baseline comorbidities between the DM cohort and non-DM cohort using the Chi-square test. The mean age between both cohorts was measured and tested using t-test. We compared the incidence rate of AAA between 2 cohorts stratified by sex and age. Poisson regression model was used to estimated incidence rate ratio (IRR) and 95% confidence interval (95% CI) of AAA. To compare the risk of AAA between DM patients and the non-DM cohort, we used Cox proportional-hazards regression models to calculate the hazard ratios (HR) and 95% CI. Multivariate models were also used to assess the AAA risk associated with socio-demographic factors and comorbidities. A further analysis was done to assess whether the associations between different level DM and the risks of AAAW (abdominal aneurysm without mention of rupture) and AAAR (abdominal aneurysm, ruptured). The statistical significance level was set a probability value of < 0.05 (SAS software, version 9.1, SAS Institute Inc, Cary, NC).

第四章 討論

第一節 結果討論

Diabetes is traditionally known to predispose of atherosclerotic pathophysiology with its causal role in occlusive vascular disease. Since the publication of the ADAM by Lederle et al in 1997[7], the evidence of inverse relationship between diabetes and aortic aneurysm development is addressed. It had point out a challenge to the traditional view of AAA as a manifestation since that time. Documented studies focused on a protective effect of diabetes have already increased currently. Several articles had reported that AAAenlargement progresses more slowly in diabetic patients.[15,16,17,18,19] Besides, the patients with carotid artery stenosis or aorto-iliac occlusive disease had significant negative association between the developmentof AAA and diabetes.[20,21,22] Compared to reported researches, the overall incidence of AAA in our study was 23% lower in the DM cohort than in the non-DM cohort (2.76 vs. 3.60), with an adjusted HR of 0.57. Our data also revealed negative association between diabetes and AAA. However, this inverse association also had been challenged, as the consideration of ”competing risk”. The theory described that if AAA were particularly lethal in diabetics, more patients with both conditions might die before they could be identified at AAA screening. Nevertheless, the explanation has been opposed and potential reasons were explained[7]. If diabetics were more likely to have AAA diagnosed prior to screening, fewer AAA would be left for detection at screening. Following these described considerate, the prevalence of diabetes should be increased in patients with previously diagnosed AAA. But the same low rate of diabetes as in those with screening-detected AAA was found. The conclusions strongly suggested that the present ”competing risk” between diabetes and abdominal aortic aneurysm could not contribute the evident difference.[7]

From our population-based data, sex-specific analysis showed higher protective effect from diabetic patients in men than women (IRR=0.68 vs. IRR=1.02). Hence, the adjusted HR was also higher protective benefit in men than in women. The documented similar results had been established. The large, population-based study assessed the relationship between diabetes and AAA in men over the age of 65.[23,24] A recent analysis, AAA events in a cohort of

161,808 post-menopausal women followed-up for a mean of 7.8 years, found that women who suffered an AAA event had a lower prevalence of diabetes and the negative association between diabetes and AAA seen in men is also evident in women.[25] In the United Kingdom Small Aneurysm Trial, the hazard ratio (HR) for risk of rupture was four times higher in women compared with men (HR 4.0, 95% CI 2.0-7.9; P<0.001), but the HR for the primary outcome of all-cause mortality was worse for immediate repair in women (0.99) than in men (0.80)[26] However, data from the ADAM screening program had a contrary result and showed that female sex is a negative risk factor for the presence of AAA (OR 0.17, 95% CI 0.07-0.48).[27] The estrogen of women had also been researched and might occupy a possible role in the against effect of abdominal aortic aneurysm.[28] Different hormone therapy contribute to significantly different abdominal aortic aneurysm events was also documented.[29,30] These reports had offer a explanation in the different association between male and women in the inverse relationship between AAA and DM.

We supposed the reasons of patients with diabetes higher beneficial effect in men, and more significant with increased age through the NHIRD base.

The diminishing risk of abdominal aortic aneurysm with increasing duration of diabetes was observed in an article[24]: 3-5years (OR 0.50), 6 -12 years (OR 0.57), over 12 years (OR 0.37). The reason may be due to long diabetic duration, the more stiffed aneurysmal wall was expected to against aortic pressure. In this study, we compared the probability free of abdominal aortic aneurysm for patients with and without diabetes mellitus. The Kaplan-Meier survival analysis showed that patients with DM had significantly lower rates in AAA than the comparisons. Invitingly, the curves for AAA become wider starting years 5. According to the prescribed mechanisms, we further analyzed the follow up duration in advanced DM group. During the within five years after advanced DM diagnosis, the incidence rate of AAA was lower in the advanced DM cohort than non-DM cohort (0.63 vs. 0.91) and adjusted HR is 0.54 (95% CI=0.29-0.99) (Table 5). However, when follow-up duration is more than 5 years, the adjusted HR is 0.31, P valve cannot be significant. We considered that the too small rupture event (n=3) might contribute to the potential basis.

The associations between different level diabetic condition and the risks of AAAW and AAAR were presented in our study. The hospital discharge data claimed from New York and Florida showed that diabetics were less likely to have an ruptured abdominal aortic aneurysm at the time of repair.[31] We specific pay attention to the severity of diabetes and partitioned as advanced and uncomplicated status according to coexist DM-related disease. Present diabetic

related complications such as nephropathy, retinopathy, neuropathy were defined as the advanced.

Varieties of studies potentially provide the possible mechanism to find out the relation of aneurysm rupture. Norman et al.[9] described mechanisms involving the aortic wall that result in aneurysmal disease. Intraluminal thrombus (ILT) and ILT growth are also considered to associate with the rate of expansion of AAAs[10,11] In small molecular mechanisms, the advanced glycation has been shown to induce cross-linking of collagen lattices in theaortic media in diabetic patients, and this cross-linking resists proteolysis and inhibits secretion of the matrix metalloproteinases (MMP). They are thought to mediate abdominal aortic aneurysmal formation.[32]Diabetes also suppresses plasmin, itself an activator of matrix metalloproteinases.[33] The effect decrease aortic wall degradation directly and may also explain the thicker abdominal aortic wall observed in diabetes. A thicker aortic wall reduces wall stress by the Law of LaPlace,[34] and wall stress is considered fundamental to abdominal aortic aneurysm progression.[35] We considered that the advanced diabetes has persistent highest quartile of blood sugars. They reflected the existence that higher quartile blood sugar has higher advanced glycation. Under the mentioned description in above articles, lower abdominal aorta ruptured rate could be expected in advanced diabetic status. The results were observed from our study. In un-ruptured abdominal aortic aneurysm group, the advanced DM patients cannot reveal a higher protective effect than uncomplicated DM (adjusted HR = 0.67 vs. 0.44) when compared to the non-DM cohort. However, considering aneurysm rupture, the advanced diabetic patients revealed a lower aneurysm ruptured rate than uncomplicated DM (adjusted HR = 0.51 vs. 0.71).

The advanced diabetic status always react much potency of medication. The doubt focused on medication use rather than diagnoses[19] have a negative effect onAAA growth has been queried. Studies suggest that hyperglycemia itself rather than its treatment retard aneurysm progression. The explanations could be concluded as below. The study reported a negative association between fasting glucose and aortic diameter in 2859 non-diabetics.[24] Investigators at Stanford reported that hyperglycemia in mice was associated with slowerAAA enlargement, and this effect was diminished by insulintherapy.[36]These explanations could further provide a basis of theory in our study. The advanced diabetes itself

not the much potency of medication effect in this advanced disease condition occupy the major protective role in abdominal aortic aneurysm rupture.

第二節　研究限制

The study was subject to some limitations, which must be mentioned. First, the NHIRD does not provide detailed information on patients such as their smoking habits, alcohol consumption, body mass index (BMI), physical activity, socioeconomic status, and family history of systemic diseases. All of these are major risk factors for abdominal aortic aneurysm. Second, the evidence derived from a cohort study is generally of a lower methodological quality than that from randomized trials because a cohort study design is subject to many biases related to adjustment for confounds. Despite our meticulous study design with adequate control of confounding factors, a key limitation was that bias could still remain because of possible unmeasured or unknown confounders. Third, the diagnoses in NHI claims primarily serve the purpose of administrative billing, and do not undergo verification for scientific purposes. We were unable to contact the patients directly to obtain more information because of the anonymity assured by the identification numbers.

Although the data that we obtained on NIDDM and abdominal aortic aneurysm diagnoses were highly reliable, underlying mechanisms must still be explored and identified. Additional large population-based unbiased studies are required, and it would be essential to confirm our current findings before drawing any firm conclusions.

第五章 結論與建議

第一節 結論

The 206,685 patients with DM and 8,26,740 comparison were similar in sex and age distribution, with a mean age of 65.8 (SD, 12.0) years (Table 1). Among possible comorbidities, hypertension, chronic kidney disease and ischemic heart disease were more prevalent in the DM cohort than in the non-DM cohort (p<0.0001). The overall incidence rate of AAA was 22% lower in the DM cohort than in the non-DM cohort (1.88 vs. 2.41per 10,000 person-years, IRR=0.78, 95% CI = 0.76–0.80), with an adjusted HR of 0.61(95% CI, 0.52–0.72) (Table 2). Sex-specific analysis of IRR showed higher beneficial effect from DM patients in men than in women (IRR=0.71, 95% CI=0.69-0.73 vs. IRR=0.99, 95% CI=0.96-1.02) and the adjusted HR was also higher beneficial effect in men than in women. Age-specific analysis showed the incidence increasing with age in both cohorts. Moreover, it showed significantly highest risk to developing AAA in younger subjects (40-50 years of age) (adjusted HR= 12.4, 95%CI= 2.26–68.2). Furthermore, the beneficial effect was more significant in those age 60 years and elderly (adjusted HR=0.66, 95%CI=0.48-0.91;adjusted HR=0.50, 95% CI=0.39-0.64; adjusted HR =0.55, 95% CI=0.39-0.79, respectively). The results of univariate and multivariate Cox proportional-hazards regression models for association between AAA and DM or other covariates are shown in table 3. DM patients had a 19% lower risk of AAA than non-DM patients (unadjusted HR=0.81, 95% CI=0.69-0.95). The beneficial effect was stronger after adjusted for socio-demographic factors and comorbidities (adjusted HR=0.61, 95% CI=0.52-0.72).

The adjusted HR of AAA was much greater for elderly (adjusted HR=96.9, 95% CI=48.0-195.7), compared with those in 40-50 years of age. Male gender (adjusted HR=3.75, 95% CI=3.35-4.21), hypertension (adjusted HR=1.98, 95% CI=1.75-2.24), chronic kidney disease (adjusted HR=1.91, 95% CI=1.50-2.44) and ischemic heart disease (adjusted HR=1.60, 95% CI=1.38-1.86) were associated with increased risk of developing AAA. The Kaplan-Meier survival analysis showed that patients with DM had significantly lower rates in AAA than the comparisons (Figure 1) and the curves for AAA become wider starting years- 5. The associations between different level DM and the risks of AAAW and AAAR were shown in table 4. Compared to the non-DM cohort, the uncomplicated DM patients had a higher beneficial effect of AAAW (adjusted HR = 0.44, 95% CI = 0.32–0.61) and the advanced DM

patients had an 33% lower risk of AAAW (adjusted HR = 0.67, 95% CI = 0.55–0.83). However, the advanced DM patients had a higher protective role in AAAR (adjusted HR = 0.51, 95% CI = 0.30–0.89). In determination of AAAR in patients aged 60 years or more by follow-up duration, under five years after advanced DM diagnosis, the lower incidence rate of AAAR was observed. (0.63 vs. 0.91 per 10,000 person-years) and adjusted HR is 0.54 (95% CI=0.29-0.99, p<0.05).

Table.1 Demographic characteristics and comorbidity in patient with and without diabetes mellitus

	Diabetes mellitus		
Variable	No	Yes	*p*-value
	N =8026740	N =206685	
Sex	n(%)	n(%)	
Female	416544(50.4)	104136(50.4)	0.99
Male	410196(49.6)	102549(49.6)	
Age, years			
40-50	101236(12.3)	25309(12.3)	0.99
50-60	166773(20.2)	41646(20.2)	
60-70	223291(27.0)	55870(27.0)	
70-80	238876(28.9)	59719(28.9)	
80+	96564(11.7)	24141(11.7)	
Age, mean (SD) [#]	65.1(12.3)	65.8(12.0)	<0.0001
Comorbidity			
Hypertension	106204(12.9)	110694(53.6)	<0.0001
Chronic kidney disease	8566(1.04)	13342(6.46)	<0.0001
Ischemic heart disease	45781(5.54)	38467(18.6)	<0.0001

Chi-Square Test [#]: Two sample T-test

Table.2 Comparison of incidence and hazard ratio of AAA stratified by sex, and age between with and without diabetic mellitus patients

	Diabetes mellitus		
	No	Yes	Compared to cohorts without DM

Variables	Event	PY	Rate[#]	Event	PY	Rate[#]	IRR[*](95% CI)	Adjusted HR[†] (95% CI)
All	1351	5610945	2.41	191	1018065	1.88	0.78(0.76, 0.80)***	0.61(0.52, 0.72)***
Sex								
Female	337	2898749	1.16	61	528268	1.15	0.99(0.96, 1.02)	0.76(0.56, 1.01)
Male	1014	2712195	3.74	130	489797	2.65	0.71(0.69, 0.73)***	0.56(0.47, 0.69)***
Age, years								
40-50	2	766265	0.03	6	161130	0.37	14.3(13.5, 15.1)***	12.4(2.26, 68.2)**
50-60	45	1225919	0.37	16	244597	0.65	1.78(1.71, 1.86)***	0.96(0.48, 1.91)
60-70	283	1668779	1.70	55	296640	1.85	1.09(1.05, 1.14)***	0.66(0.48, 0.91)*
70-80	695	1517022	4.58	78	246982	3.16	0.69(0.66, 0.72)***	0.50(0.39, 0.64)***
80+	326	432960	7.53	36	68717	5.24	0.69(0.65, 0.74)***	0.55(0.39, 0.79)**

Rate[#], incidence rate, per 10,000 person-years; IRR[*], incidence rate, ratio

Adjusted HR[†]: multivariable analysis including age, sex, and co-morbidity

*p<0.05, **p<0.01, ***p<0.001

Table.3 Cox model with hazard ratios and 95% confidence intervals of AAA associated with diabetes mellitus and covariates

	Crude		Adjusted[†]	
Variable	HR (95%CI)		HR (95%CI)	
Age, years				
40-50	1	(Reference)	1	(Reference)
50-60	4.86	(2.32, 10.1)***	5.23	(2.51, 10.9)***
60-70	20.0	(9.94, 40.4)***	21.9	(10.9, 44.2)***
70-80	53.8	(26.8, 108.0)***	54.1	(26.9, 108.6)***
80+	98.0	(48.6, 197.6)***	96.9	(48.0, 195.7)***
Sex (female vs. male)	3.11	(2.78, 3.49)***	3.75	(3.35, 4.21)***
Baseline co-morbidities (yes vs. no)				
Diabetes mellitus	0.81	(0.70, 0.94)**	0.61	(0.52, 0.72)***
Hypertension	2.98	(2.67, 3.31)***	1.98	(1.75, 2.24)***
Chronic kidney disease	4.08	(3.22, 5.17)***	1.91	(1.50, 2.44)***
Ischemic heart disease	3.38	(2.95, 3.87)***	1.60	(1.38, 1.86)***

†Adjusted HR: multivariable analysis including for age, sex, and comorbidities

*p<0.05, **p<0.01, ***p<0.001

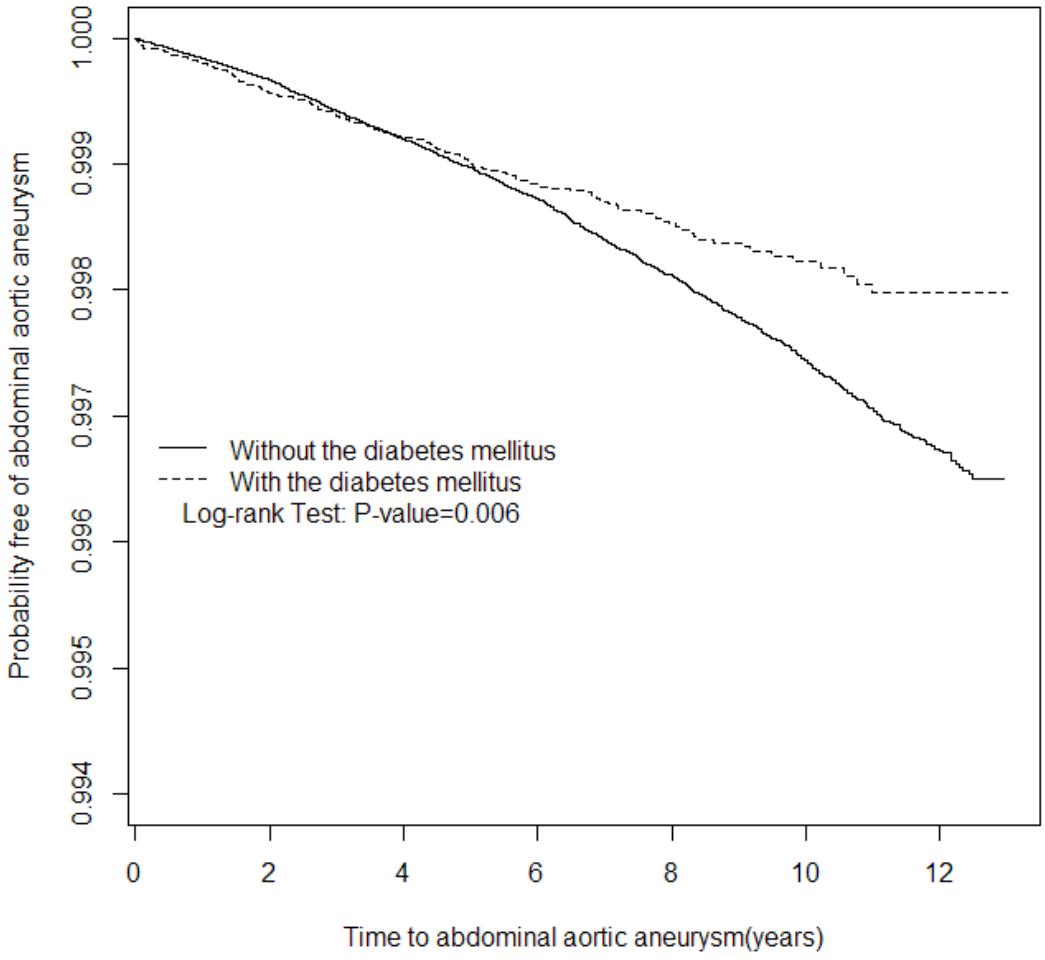

Figure.1 Probability free of abdominal aortic aneurysm for patients with (dashed line) or without (solid line) diabetes mellitus

Table.4 Incidence, and hazard ratios of AAAW and AAAR between different level diabetes mellitus in patients aged 60 years or more

Variables	Event	Rate#	IRR* (95% CI)	Adjusted HR† (95% CI)
AAAW‡				
Non-DM	1096	3.03	1(Reference)	1(Reference)
Uncomplicated DM	39	1.84	0.61(0.58, 0.64)***	0.44(0.32, 0.61)***
Advanced DM	103	2.57	0.86(0.84, 0.89)***	0.67(0.55, 0.83)***

AAAR‡				
Non-DM	209	0.56	1(Reference)	1(Reference)
Uncomplicated DM	12	0.57	0.98(0.94, 1.03)	0.71(0.39, 1.30)
Advanced DM	15	0.37	0.66(0.63, 0.68)***	0.51(0.30, 0.89)*

Rate#, incidence rate, per 10,000 person-years; IRR*, incidence rate ratio

Adjusted HR†: multivariable analysis including age, sex, and co-morbidities

*p<0.05, **p<0.01, ***p<0.001

‡AAAW, abdominal aneurysm without mention of rupture; AAAR, abdominal aneurysm, ruptured

ICD-9-CM: uncomplicated DM, 250.0-250.3; advanced DM, 250.4- 250.9; AAAW, 441.4; AAAR, 441.3

Table.5 Hazard ratio for AAAR compared between advanced diabetes mellitus cohort and non-diabetes mellitus cohort in patients aged 60 years or more by follow-up duration

	non-DM Cohort		Severe DM Cohort		Compared to cohorts without DM	
Follow time	Event	Rate#	Event	Rate#	IRR†(95% CI)	Adjusted HR& (95% CI)
AAAR‡	209	0.56	15	0.37	0.66(0.63, 0.68)***	0.51(0.30, 0.89)*
≤5	124	0.91	12	0.63	0.68(0.66, 0.70)***	0.54(0.29, 0.99)*
>5	85	0.66	3	0.28	0.43(0.40, 0.46)***	0.35(0.11, 1.15)

Rate#, incidence rate, per 10,000 person-years; IRR*, incidence rate ratio; Adjusted HR† :multivariable analysis including age, sex, urbanization, and co-morbidities; *p<0.05, **p<0.01, ***p<0.001

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