Renal outcomes in membranous nephropathy with preexisting diabetes mellitus

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Abstract

Background: Previous studies have described prognostic factors for worse renal outcomes in membranous nephropathy (MN). The impact of preexisting diabetes mellitus (DM) on renal outcomes in membranous nephropathy is less well characterized. The present study explored the influence of preexisting DM on renal outcomes in patients with MN.

Methods: This is a single-center retrospective cohort study that included all adult patients with biopsy proven MN between 1 January 2001 to 31 December 2020. Patients were categorized into 2 groups according to the presence or the absence of DM. The composite outcomes of end-stage kidney disease, the decline in estimated glomerular filtration rate ≥40% and death due to renal causes were compared between the 2 groups.

Results: A total of 114 patients with biopsy proven MN were identified. Most patients (70%) were diagnosed with idiopathic MN. Sixteen patients (14%) had preexisting DM. Diabetic patients were older (60.6±10.5 years vs. 51.1±16.2 years, *P=0.025*) and had lower prevalence of hypertension (2% vs 50%, *P=0.005*). At baseline, the amount of urine protein, pathological findings, and the rate of remission were not significantly different between the two groups. The median follow-up time was 2.9 years. The composite renal outcomes occurred in 27 patients (18.8%). Univariate cox proportional hazards regression analysis revealed pre-existing DM as a predictor of higher composite renal outcomes (Hazard Ratio: 2.60; 95% CI: 1.09-6.22; *P=0.032*). The association between preexisting DM and outcome was lost after adjustments for age, sex, hypertension and renal remission status (Hazard Ratio: 2.24; 95% CI: 0.89–5.67; *P= 0.09*). Subgroup analysis according to the etiologies of MN demonstrated that pre-existing DM was a predictor of poor renal outcome among idiopathic MN (Hazard Ratio: 3.27; 95% CI: 1.22 – 8.78; *P = 0.019*) but not in secondary MN.

Conclusion: Preexisting DM in patients with MN might be associated with worse long-term renal outcomes. A larger population-based study is required to ascertain these findings.

Keywords: nephrotic syndrome; kidney failure; renal failure; CKD; proteinuria; glomerular disease

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ผลลัพธ์ทางไตของผู้ป่วย membranous nephropathy ที่มีโรคเบาหวานร่วมด้วย

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บทคัดย่อ

บทนำ: ปัจจุบันมีงานวิจัยจำนวนมากที่รายงานปัจจัยที่สัมพันธ์กับการดำเนินโรคเข้าสู่โรคไตเรื้อรังระยะสุดท้ายของโรคไตชนิด membranous nephropathy (MN) อย่างไรก็ตามปัจจัยที่เกี่ยวข้องกับการดำเนินโรคของผู้ป่วย MN ที่มีโรคเบาหวานร่วมด้วยยังมีการรายงานน้อย การวิจัยนี้มีวัตถุประสงค์เพื่อประเมินความสัมพันธ์ระหว่างการมีโรคเบาหวานร่วมด้วยต่อผลลัพธ์ทางไตของผู้ป่วยโรคไตชนิด MN

วิธีการศึกษา: การศึกษาย้อนหลังที่รวบรวมข้อมูลผู้ป่วยจากโรงพยาบาลเดียวที่ได้รับการเจาะตรวจชิ้นเนื้อไตระหว่างวันที่ 1 มกราคม 2554 ถึง 31 ธ.ค. 2563 และมีผลการตรวจทางพยาธิวิทยาเข้าได้กับโรค MN ผู้ป่วยทั้งหมดจะถูกแบ่งออกเป็น 2 กลุ่มตามการมีโรคเบาหวานร่วมด้วย ผลลัพธ์ที่สนใจ ได้แก่ การเกิดโรคไตเรื้อรังระยะสุดท้าย การทำงานของไตลดลงอย่างน้อยร้อยละ 40 และ การเสียชีวิตจากโรคไต

ผลการศึกษา: ผู้ป่วยที่มีผลการตรวจทางพยาธิวิทยาเข้าได้กับโรคไตชนิด MN มีทั้งหมด 114 ราย โดยร้อยละ 70 ได้รับการวินิจฉัยเป็น idiopathic MN มีผู้ป่วยที่เป็นโรคเบาหวานร่วมด้วยจำนวนทั้งหมด 16 ราย (14%) ผู้ป่วยที่เป็นเบาหวานมีอายุมากกว่า (60.6±10.5 ปี vs. 51.1±16.2 ปี, *P=0.025*) และมีความดันโลหิตสูงน้อยกว่า (2% vs. 50%, *P=0.005*) ในขณะที่ปริมาณโปรตีนในปัสสาวะ อัตราการเข้าสู่ภาวะสงบของโรค รวมถึงลักษณะทางพยาธิวิทยาไม่มีความแตกต่างกันระหว่างผู้ป่วยที่มี และ ไม่มีเบาหวาน ระยะเวลาการติดตามผู้ป่วยมีค่ามัธยฐาน 2.9 ปี พบการเกิดผลลัพธ์รวมทางไตทั้งหมด 27 ราย (18.8 %) โดยผู้ที่เป็นเบาหวานเกิดผลลัพธ์รวมทางไตมากกว่าผู้ที่ไม่ได้เป็นเบาหวานอย่างมีนัยสำคัญ (Hazard Ratio: 2.60; 95% CI: 1.09-6.22; *P=0.032*) เมื่อนำปัจจัยที่เกี่ยวข้องเข้ามาปรับในการวิเคราะห์ ได้แก่ อายุ เพศ ความดันโลหิตสูง และภาวะสงบของตัวโรค พบว่าความสัมพันธ์ระหว่างโรคเบาหวานกับผลลัพธ์ไม่มีนัยสำคัญทางสถิติ (Hazard Ratio: 2.24; 95% CI: 0.89–5.67; *P=0.09*) การวิเคราะห์กลุ่มย่อยเฉพาะผู้ป่วยโรคไตชนิด idiopathic MN พบว่าผู้ป่วยที่มีโรคเบาหวานร่วมด้วยเกิดผลลัพธ์ทางไตมากกว่าอย่างมีนัยสำคัญ (Hazard Ratio: 3.27; 95% CI: 1.22–8.78; *P=0.019*) ในขณะที่ไม่พบความสัมพันธ์ดังกล่าวในผู้ป่วยโรคไตชนิด secondary MN

สรุป: ผู้ป่วยที่มีโรคไตชนิด MN และมีโรคเบาหวานร่วมด้วยอาจมีความเสี่ยงเพิ่มขึ้นต่อการเกิดผลลัพธ์รวมทางไต การศึกษาในประชากรจำนวนมากในอนาคตจะสามารถช่วยยืนยันผลลัพธ์ที่พบในการศึกษานี้

คำสำคัญ: ไตอักเสบ; โปรตีนรั่ว; บวม; ไตวายเรื้อรัง; ไตวาย; ไตเสื่อม

Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in an adult. The incidence of MN is increasing for the time being and represents about 30% of nephrotic syndrome patients second to only IgA nephropathy[1]. In Thailand, native kidney biopsies of 3,555 Thai kidney patients revealed that 15.8% was MN[2]. The breakthrough anti phospholipase A2 receptor (PLA2R)

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discovery by Beck and colleagues turned the page on MN diagnosis. Not only does this marker help us understand the autoimmune natures of primary MN[3] but it is also used as a diagnostic tool instead of a kidney biopsy due to its less invasive nature and high positive results at 70-80%. Although nearly 30% of untreated MN patients could have become spontaneous complete or partial remissions of proteinuria over a 10-year follow-up period, approximately 20 – 30% had remained persistent nephrotic range proteinuria and progressed to end-stage kidney disease (ESKD) thereafter[4]. Therefore, it is essential to identify groups at substantial risk of developing poor renal outcomes. Nowadays, many factors were identified as prognostic markers of disease progression, for example, age, baseline serum creatinine, and remission rate[5-7]. However, Diabetes mellitus (DM), one of the prevailing causes of chronic kidney disease (CKD) and ESKD world-wild[8-10], was less to be known in terms of its effects on kidney outcomes in patients simultaneous MN. Additionally, MN in the diabetic population is not uncommon. A retrospective study of kidney biopsies in 1,604 Chinese patients with diabetes found that MN was the most common kidney disease other than diabetic nephropathy[11]. This condition might pose a therapeutic challenge regarding glucocorticoid administration due to the risks of hyperglycemia and infection. In Thailand, diabetic nephropathy was the second most common cause of ESKD and hemodialysis[12]. The findings raised concern that MN patients with DM may have a greater detrimental effect on renal survival than MN alone.

Therefore, we conducted a retrospective cohort study to demonstrate clinical profile and compare adverse renal outcomes between MN with preexisting DM and MN without DM in Thai population.

Methods

Study participants

This is a single-center retrospective cohort study in a tertiary care center, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The study included adult patients aged 18 years old or above with biopsy-proven MN performed between January 2011 and December 2020. The biopsy results were confirmed by the renal pathologist. Patients who had secondary MN from lupus nephritis, underwent a kidney transplant, or a follow-up period of fewer than 3 months were excluded from this study. The Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, approved the study protocol (approval number: MURA2021/315) and the study was performed following the principles in the declaration of Helsinki.

Outcomes

Primary outcome of the present study was the difference in the composite renal outcomes of ESKD, eGFR decline ≥40%, and death from renal causes between patients with and without preexisting DM.

Data collection

Baseline clinical profiles and the pathological result were collected manually from electronic medical records. The clinical profile included age, sex, body mass index (BMI), systolic and diastolic blood pressure, cause of MN, and clinical manifestations. Laboratory data also collected, including serum fasting glucose, HbA1c, serum creatinine, estimated Glomerular Filtration Rate (eGFR) calculated by using the 2009 chronic kidney disease-EPI creatinine equation, glomerular hematuria defined as red blood cell in urine ≥ 3/HPF, 24 hours urine protein, urine protein creatinine ratio (UPCR), serum cholesterol, serum total protein, serum albumin and anti-PLA2R antibody (aPLA2Rab) at baseline. Serum thrombospondin type I domain-containing 7A (THSD7A) antigen was tested in patients who still had been followed up at the hospital.

DM was defined as fasting blood glucose more than or equal to 126 mg/dl, or HbA1c above or equal to 6.5%, or treated with the hypoglycemic agents. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or treated with the antihypertensive agents. Complete remission was defined urine protein less than 0.3 grams a day and a serum albumin level over 3.5 g/dL. Partial remission was defined as a decline of urine protein more than 50% from baseline and the amount of urine protein does not fall between

0.3 and 3.5 g/day regardless of serum albumin level. ESKD was defined as eGFR < 15 ml/min per 1.73m^2 or requiring renal replacement therapy.

Pathological data included light microscopy, immunofluorescence, and electron microscopy. Characteristic pathology of MN, including glomerular sclerosis (global sclerosis and segmental sclerosis), as well as mesangial or endocapillary hypercellularity, was collected. Glomerulosclerosis was defined as the presence of global or segmental glomerulosclerosis in the pathological section. Mesangial hypercellularity was defined as the number of cells in the mesangial area greater than or equal to 4. Endocapillary hypercellularity was defined as cell proliferation within the glomerular capillary lumina, which caused lumen narrowing.

Statistical Analysis

The descriptive data with normal distribution were presented as mean and standard deviation (SD) while non-normal distribution data were presented as the median and interquartile range (IQR, 25th, 75th percentiles). Continuous variables were to be compared by independent samples t-test or Wilcoxon signed-rank sum test for normal and non-normal distribution respectively. Categorical variables were presented as numbers and percentages in which were to be compared by Fisher's exact test or Chi-square test. Time to composite renal outcomes was analyzed using the Kaplan-Meier curve. The primary objective of this study was to determine the effect of DM on composite renal outcomes among MN patients. If patients experience more than one event in composite endpoint, only one outcome was counted for that patient. This objective was tested by using Cox proportional hazards model. Three covariates, including age, hypertension[13, 14], and remission status[5], were a priori decisions made based on literature review to adjusting in the final model[15]. The proportional hazard assumption was tested by time-dependent coefficients. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI) and two-sided p-values. Statistically significant differences were indicated if P<0.05 for all analyses. All measurements were analyzed using Stata version 16 (StataCorp, LLC, College Station, TX, USA).

Results

There were 151 cases with kidney biopsy-proven MN during a ten-year period at Ramathibodi Hospital. After excluding 25 cases with systemic lupus erythematosus, 10 with a follow-up period of fewer than 3 months, one with unable to access electronic medical records and one with kidney transplant status, therefore, 114 cases were left to be analyzed. Baseline clinical characteristic was summarized as shown in **Table 1**. There are 16 MN cases with preexisting DM and 98 cases without preexisting DM. The mean age was 52. MN cases with preexisting DM were older than non-DM, with the mean age of 60.6±10.5 and 51.1±16.2, P 0.025, respectively. HT at baseline was 45%. Although the number was higher in MN without preexisting DM, systolic and diastolic blood pressure did not significantly differ between two groups. Serum fasting glucose and serum HbA1c were higher in the preexisting DM group than non-DM as expected (125 vs 95 mg/dL and 6.9 vs 5.5% respectively). Primary or idiopathic membranous nephropathy was a majority in this cohort, accounting for 70% of this population. The rest were secondary MN, which is 30%. The number of primary and secondary MN cases were equally distributed between two groups. Baseline urine protein as well as kidney function did not significantly differ between two groups. There were no statistical differences between two groups in terms of clinical presentation (edema, foamy urine, acute kidney injury), other laboratory results (total cholesterol, total protein, baseline serum albumin, baseline aPLA2Rab, and treatment strategies) or pathological finding. The results of the THSD7A antigen that had been performed in patients, who still had been followed up at the Ramathibodi Hospital, were negative in all 29 patients.

Table 1 Baseline characteristics of all patients

Characteristic	Total (N = 114)	Patients with diabetes mellitus (n = 16)	Patients without diabetes mellitus (n = 98)	P-value
Age, mean (SD), years	52.0 (15.9)	60.6 (10.5)	51.1 (16.2)	0.025
Male	69 (60%)	9 (56%)	60 (61%)	0.71
BMI, mean (SD)	24.2 (4.0)	25.2 (3.9)	24.0 (4.0)	0.31
Underlying disease				
Hypertension	51 (45%)	2 (12%)	49 (50%)	0.005
SBP, mean (SD), mmHg	138.9 (22.4)	141.9 (21.9)	138.4 (22.5)	0.57
DBP, mean (SD), mmHg	81.7 (11.6)	80.9 (9.6)	81.8 (12.0)	0.78
Cause of membranous nephropathy				1.00
Idiopathic membranous nephropathy	83 (73%)	12 (75%)	71 (73%)	
Secondary membranous nephropathy • Biopsy • Cancer • Hepatitis B • Autoimmune disease • Other	30 (27%) 12 (40.0%) 7 (23.3%) 6 (20.0%) 4 (13.0%) 1 (3.3%)	4 (25%)	26 (27%)	
Clinical at first presentation				
Edema	80 (71%)	13 (81%)	67 (69%)	0.39
Foamy urine	80 (71%)	14 (88%)	66 (68%)	0.14
AKI	6 (5%)	2 (13%)	4 (4%)	0.18
Laboratories result on the first visit				
Serum fasting glucose, median (IQR), mg/dL	97.0 (88, 113)	125 (105,147)	95.0 (88, 105)	0.005
Serum HbA1c, median (IQR), mg%	5.64 (5.2, 6.4)	6.9 (6.4, 7.7)	5.5 (5.1, 5.8)	<0.001
Serum creatinine, median (IQR), mg/dL	1.02 (0.8, 1.4)	1.1 (0.8, 1.6)	1.0 (0.8, 1.3)	0.32
eGFR, mean (SD), mg/dL	76.4 (30.0)	65.2 (25.0)	78.2 (30.4)	0.11
Glomerular hematuria	60 (53.1%)	5 (31%)	55 (57%)	0.059
Urine protein, median (IQR), g/24h	5.57 (3.1, 9.0)	8.5 (4.5, 10.4)	5.4 (2.9, 8.3)	0.10
Total cholesterol, median (IQR), mg/dL	316 (239,405)	303 (227,381)	321 (240,406)	0.57
Serum total protein, median (IQR), mg/dL	53.9 (46.3, 61.1)	51.1 (44.5, 60.6)	54.2 (47.2, 61.0)	0.48
Serum albumin, mean (SD), mg/dL	21.5 (7.8)	20.5 (6.8)	21.7 (8.0)	0.63
Positive aPLA2Rab (n=27)	12 (44.4%)	3 (50%)	9 (43%)	1.00

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, aPLA2Rab = anti-PLA2 receptor antibody, SD = standard deviation, IQR = interquartile range, mg = milligram, dL = deciliter

During a median follow-up period of 2.9 years, seventy-nine cases achieved clinical remission **(Figure1)**. Twenty-six cases had reached renal composite endpoints which were ESKD (3 cases), a decline of eGFR more than 40% (18 cases), and renal death (5 cases). These composite outcomes were commonly occurred in MN with preexisting than non-DM, 7 cases (43.8%) and 19 cases (19.4%), respectively. Cox proportional hazards model showed that DM was a predictive factor of composite renal outcomes (Hazard Ratio: 2.60; 95% CI: 1.09 - 6.22; P 0.032) **(Figure 2a).** However, after adjusting with age in Model 2 **(Figure 2b)** and age, hypertension, and remission status in Model 3 **(Figure 2c)**, the results did not reach a statistically significant, (Hazard Ratio: 2.42; 95% CI: 1.00 – 5.87; P 0.05) and (Hazard Ratio: 2.24; 95% CI: 0.89 – 5.67; P 0.09), respectively. Further subgroup analysis showed that the effect of DM on the renal outcomes was significant (Hazard Ratio: 3.27; 95% CI: 1.22 – 8.78; P = 0.019) in idiopathic MN **(Figure 3a)** but not secondary MN **(Figure 3b)**

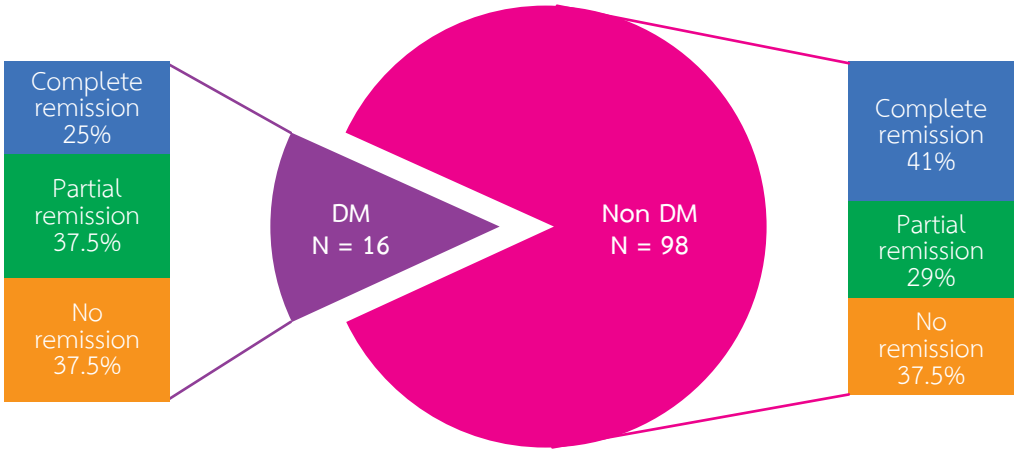

Figure 1 Characteristics of clinical remission during follow-up

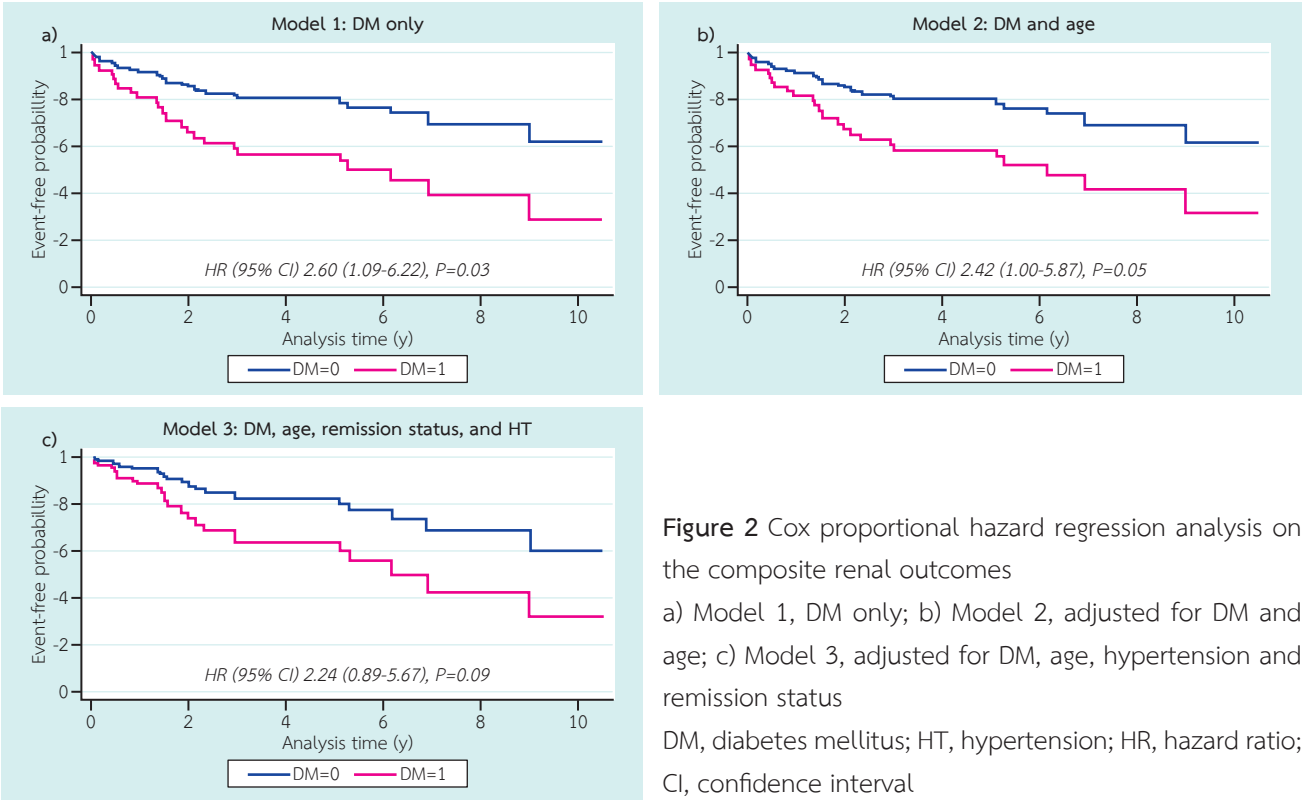

Figure 2 Cox proportional hazard regression analysis on the composite renal outcomes

a) Model 1, DM only; b) Model 2, adjusted for DM and age; c) Model 3, adjusted for DM, age, hypertension and remission status

DM, diabetes mellitus; HT, hypertension; HR, hazard ratio; CI, confidence interval

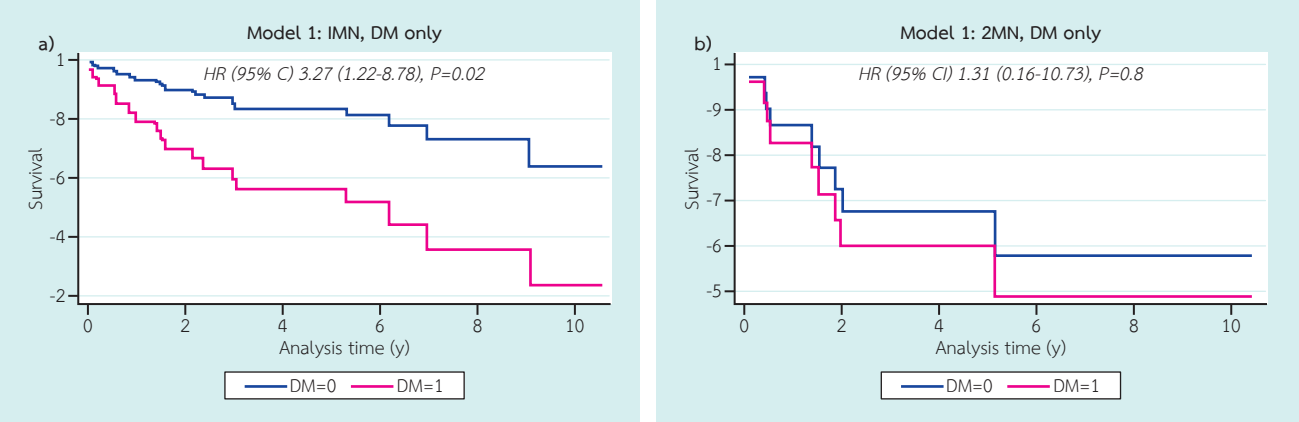

Figure 3 Cox proportional hazard regression analysis on the effect on DM on the composite renal outcomes in subgroup of patients

a) Idiopathic membranous nephropathy; b) secondary membranous nephropathy

DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; IMN = idiopathic membranous nephropathy; 2MN = secondary membranous nephropathy, DM = diabetes mellitus

Discussion

In our study, membranous nephropathy (MN) with preexisting diabetes mellitus (DM) patients were older and lower incidence of hypertension. Preexisting DM correlates with higher renal composite outcomes and similar trends were observed across three adjusted models in this study. However, the small study population and event rates may hamper the statistical power to demonstrate significant findings. These findings similar to the previous study, a retrospective observational in China by Zhiyong Xie and colleague[16], investigated clinical outcomes in 42 idiopathic MN coexisting with DM patients. Their result was shown that coexisting DM was an independent risk factor for renal function deterioration but did not affect the remission rate.

DM is a well-recognized independent risk factor for developing CKD and ESKD [8-10]. Pathogenesis of kidney disease in DM, which was hemodynamic and metabolic pathway[17], may negatively affected clinical outcomes of MN. In terms of hemodynamic pathways, impaired renal vasoregulation was one of the key roles. The elevation of Endothelin-1 as well as the activation of the renin-angiotensin system leading to an increase of angiotensin II levels, caused efferent arteriolar vasoconstriction and endothelial dysfunction. Regarding metabolic pathways, hyperglycemia resulted in an increased risk of renal ischemic-reperfusion injury and the activation of four pathways which were the polyol pathway, hexosamine pathway, production of advanced glycation end products, and activation of protein kinase C. Moreover, data from previous study found that DM patients had less responsive the Modified Ponticelli regimen[18]. These proposed hypotheses may partly explain the effect of pre-existing DM contributing to poor composite renal outcomes in MN patients.

Interestingly, in subgroup analysis for the cause of MN, preexisting DM was found to be a predictive factor of composite renal outcomes only in idiopathic MN but not secondary MN. This result may be explained by the higher disease severity in secondary membranous nephropathy (especially, cancer) and specific treatments in idiopathic MN which reduce the likelihood of composite renal outcomes.

For strengths and limitations, this study is a large cohort over a ten-year period in tertiary care center. In addition, this is the first study that investigates the clinical impact of DM and MN patients in Thailand. All MN diagnosis were confirmed by renal pathology and results were approved by a renal pathologist. In terms of limitation, this study had small sample sizes in MN with preexisting DM groups, as a consequence, limited a power of detection in terms of statistical finding in this study. Lastly, missing data of

some important marker such as aPLA2Rab, is a common feature of a retrospective dataset.

Conclusion

Preexisting DM may predict adverse renal outcomes in MN patients. Large clinical study was required to confirm the finding.

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