Venous Thromboembolism in Patients with Membranous Nephropathy

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Summary

Background and objectives The aims of this study were to determine the frequency of venous thromboembolic events in a large cohort of patients with idiopathic membranous nephropathy and to identify predisposing risk factors.

Design, setting, participants, & measurements We studied patients with biopsy-proven membranous nephropathy from the Glomerular Disease Collaborative Network (n=412) and the Toronto Glomerulonephritis Registry (n=486) inception cohorts. The cohorts were pooled after establishing similar baseline characteristics (total n=898). Clinically apparent and radiologically confirmed venous thromboembolic events were identified. Potential risk factors were evaluated using multivariable logistic regression models.

Results Sixty-five (7.2%) subjects had at least one venous thromboembolic event, and this rate did not differ significantly between registries. Most venous thromboembolic events occurred within 2 years of first clinical assessment (median time to VTE = 3.8 months). After adjusting for age, sex, proteinuria, and immunosuppressive therapy, hypoalbuminemia at diagnosis was the only independent predictor of a venous thromboembolic event. Each 1.0 g/dl reduction in serum albumin was associated with a 2.13-fold increased risk of VTE. An albumin level <2.8 g/dl was the threshold below which risk for a venous thromboembolic event was greatest.

Conclusions We conclude that clinically apparent venous thromboembolic events occur in about 7% of patients with membranous nephropathy. Hypoalbuminemia, particularly <2.8 g/dl, is the most significant independent predictor of venous thrombotic risk.

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Introduction

Thromboembolic events, a recognized complication of the nephrotic syndrome, occur with a frequency between <10% and 45% (1) depending upon the underlying disease and the screening method. Deep vein thrombosis, especially renal vein thrombosis, is reported to occur more frequently among patients with membranous nephropathy (MN) than other nephrotic diseases (2–9). Given the impact of thrombotic events on morbidity and mortality of patients with nephrotic syndrome, the question of prophylactic anticoagulation presents an important clinical dilemma for which no evidence-based guidelines are available.

The aim of this study was to assess the frequency, character, and risk factors of venous thromboembolic events (VTEs) diagnosed in the course of typical clinical care in well-characterized inception cohorts of patients with MN from the Glomerular Disease Collaborative Network (GDCN) and the Toronto Glomerulonephritis Registry (TGNR). We conducted a retrospective analysis of clinically apparent thromboembolic events in 898 patients with biopsy-proven MN diagnosed between 1969 and 2007 (10,11).

Materials and Methods

Study Population

We studied a large pooled inception cohort of patients identified at the time of biopsy diagnosis of GN and followed by prospective accrual of data from each clinic visit (10,11). For both registries, medical records were collected from the initial biopsy diagnosis or earliest available clinical presentation. All patients over age 16 with MN diagnosed and followed between 1969 and 2007 in the GDCN and between 1974 and 2005 in the TGNR were included. Patients with SLE, hepatitis B, hepatitis C, or HIV infection or with another underlying disease (*e.g.*, monoclonal gammopathy) were excluded.

Observation Period

The start of the follow-up period was the time proteinuria was first documented, the first evaluation by a nephrologist, or the date of kidney biopsy. For patients who experienced a VTE prior to the first nephrology evaluation, the date of VTE was considered the first symptom of MN and the start of follow-up. Patient information was reviewed through the most recent clinic date until end-stage kidney disease or death.

Thromboembolic Events

We identified all clinically apparent VTEs, including pulmonary emboli (PE), deep vein thrombosis (DVT) of the lower extremities, renal vein thrombosis (RVT), and other less frequent sites of DVT. Thrombi diagnosed simultaneously at different sites were considered as a single event. PE was confirmed by ventilation-perfusion scanning, spiral computed tomography, or angiography; DVT by compression ultrasound or venography; and RVT by renal venogram, Doppler ultrasound, or magnetic resonance angiography. Other types of VTE were diagnosed by venogram.

Variables Considered

Data extracted from medical records included demographics, clinical variables, medication exposures, and information regarding malignancy, smoking, previous VTE, immobilization within 6 weeks or pregnancy within 3 months of VTE, or use of hormone therapy at the time of VTE.

Longitudinal clinical and laboratory parameters considered included serum creatinine, albumin, cholesterol and triglycerides, and 24-hour urine protein excretion and estimated GFR (eGFR) using the four-variable Modification of Diet in renal Disease equation (12).

Medications considered included immunosuppressants, anticoagulants, and antiplatelet (aspirin, clopidogrel, dipyridamole) agents. All use of warfarin was reviewed, and no patient received prophylactic anticoagulation because of the nephrotic syndrome. We reviewed hepatic hydroxymethyl glutaryl-CoA (HMG-CoA) reductase inhibitor exposure, as these agents have been associated with a reduced risk of VTE in the general population (13–15). Patients subjected to biopsy before the date of approval of HMG-CoA reductase inhibitors (August 31, 1987) were considered as not having received these medications.

Statistical Analyses

Comparisons between the characteristics of patients enrolled in the GDCN and the TGNR cohorts and the characteristics of patients with and without VTE events were performed using Fisher's exact test for categorical measures and Wilcoxon two-samples tests for continuous variables. Exact P values are reported with two-sided P value of <0.05 considered statistically significant. Incidence of VTE is reported as per person-year of follow-up. Logistic regression was used to assess risk factors–associated VTE and reported as odds ratio (OR) with 95% confidence interval (95% CI). Analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC). Initial univariable and multivariable logistic regression models were constructed including only subjects with complete data for each variable. Imputations were not done for missing data.

Variables related to VTE risk by univariate analysis and clinically relevant parameters were included in the multivariable models. We first considered albumin as a continuous measure, in conjunction with age at MN diagnosis, sex, 24-hour protein excretion, registry site, and immunosuppressive therapy of any type. We also performed multivariable analyses with albumin considered as a categorical variable to search for possible changes of the VTE risk after controlling for age at diagnosis, sex, 24-hour protein excretion, registry site, and treatment with immunosuppressants. This model was further analyzed by adding smoking as a potential predisposing factor. Because smoking history was only available for 65% of patients, these models had lower statistical power than that of the full sample for predicting VTE and were used as a sensitivity analysis for the effects seen in the primary models.

To describe better the association between albumin and VTE risk, we estimated a threshold of albumin below which the risk for VTE is increased. We categorized our patients by baseline albumin concentration <2.0 g/dl, and then by 0.2 g/dl increments to ≥ 3.0 g/dl, with this highest concentration used as the reference group. We evaluated ORs and 95% CIs for each group of patients to estimate the cut point where the risk increased, adjusting for age, sex, proteinuria, immunosuppressive therapy, and registry site.

To assess whether duration of hypoalbuminemia was independently associated with the risk of VTE, we analyzed logistic regression models controlling for age at biopsy, sex, proteinuria, immunosuppressive treatment, and registry site using an interaction term for serum albumin and duration of albuminemia ≤ 2.8 g/dl. In this analysis, all patients with available albumin concentration data were included (n=732). Patients who were never below the threshold of albumin <2.8 g/dl were assigned a duration of hypoalbuminemia of zero. We also compared risk of VTE among three categories: those with a duration of albuminemia ≤ 2.8 g/dl for <6 months and those with a duration of albuminemia ≤ 2.8 g/dl for >6 months compared with the reference group of those with albumin >2.8 g/dl.

Results

Study Population

A total of 898 patients were included: 412 from the GDCN and 486 from the TGNR (Figure 1 and Table 1). Patients within the GDCN were slightly older than those in the TGNR (50.9 versus 47.5 years; P=0.001). Caucasians composed the majority of patients in both registries (64.6% and 77.6%), but the proportion of African Americans and Asians differed in the two registries ($P<0.001$).

There were minor but statistically significant differences between the two cohorts in albumin at the time of MN diagnosis (2.5 ± 0.8 versus 2.7 ± 0.7 g/dl, $P<0.001$), eGFR (70.6 ± 37.8 versus 75.3 ± 29.8, ml/min per 1.73 m^2, $P<0.001$), and 24-hour urine protein excretion (median interquartile range [IQR] 7.3 [4.4, 11.7] versus 5.6 [3.4, 9.7], $P<0.001$). Smoking exposure at the time of biopsy was similar between cohorts (P=0.34). Use of cyclophosphamide/chlorambucil or cyclosporine was similar in the two registries; however, GDCN patients were more likely to receive glucocorticoids ($P<0.001$). Other therapies (*e.g.*, mycophenolate mofetil, azathioprine, methotrexate, or rituximab) were infrequent in both registries (Table 1).

The length of follow-up was calculated from the time of first assessment. The overall median follow-up time was 37.0 months (IQR: 14.6, 78.6): median 24.2 months (IQR: 8.6, 55.5) for the GDCN cohort and 52.8 months (IQR: 21.1, 92.1) for the TGNR cohort ($P<0.001$). The median time of observation for patients with a VTE was 67.9 months (IQR: 25.5, 119.8). All subsequent analyses were based on the combined cohort with multivariate models controlling for registry site.

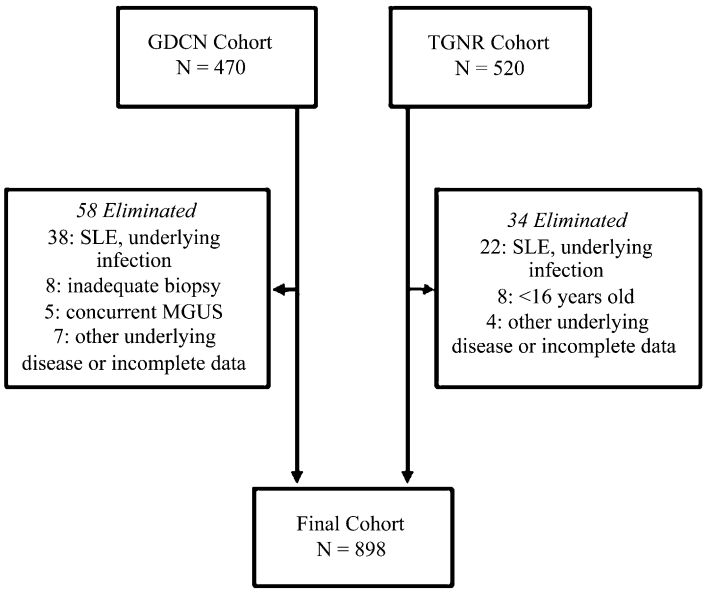

Figure 1. | Derivation of the membranous nephropathy (MN) cohort.

Frequency and Character of VTE

A total of 65 of 898 patients had at least one VTE, which occurred during a mean observation time of 79.4±63.4 months. The frequency of VTE for the entire cohort was 7.2% (7.04% and 7.8% for GDCN and TGNR respectively, P=0.9), and the incidence was 0.017 per person-year (95% CI: 0.013, 0.021). Four patients had a recurrent VTE typically at the time of a relapse of proteinuria. The incidence of VTE including these four additional events was 0.018 per patient-year (95% CI: 0.014, 0.022).

At the time of VTE, patients had a median protein excretion of 9.9 g/d (min, max, 1.1, 40.0), a mean serum albumin of 2.2±0.6 g/dl (min, max, 0.6, 3.7), and mean eGFR of 70.5±27.8 ml/min per 1.73 m^2 (Table 2). Thromboembolic events included 26 cases of RVT, 21 cases of DVT, 27 cases of PE, and 7 cases of venous thrombosis at other sites. Ten patients had simultaneous VTEs in more than one anatomic site. PE were diagnosed in association with RVT in six cases and DVT in two cases.

Time to VTE. The median time to the first VTE calculated from the time of first assessment of proteinuria was 3.8 months (IQR: 0, 12.1) (Figure 2, Table 2). In 16 cases, the VTE occurred prior to the kidney biopsy. Of these, 11 patients had documented nephrotic syndrome but had not yet undergone kidney biopsy, whereas proteinuria was first discovered at the time of VTE in four patients. Seventy-four percent of VTEs occurred within the first 2 years after onset of disease and 86% within 3 years. None of the VTEs was fatal.

Renal Survival. The proportion of patients who reached ESRD was similar between those who experienced a VTE and those who did not (P=0.4) (Figure 3).

Risk Factors of VTE

Univariate Analysis. Patients with a VTE had a lower serum albumin level at the time of diagnosis (2.2 versus 2.6 g/dl, P<0.001). There were no significant differences with respect to age, sex, race, smoking exposure, serum creatinine, eGFR, or proteinuria at the time of diagnosis of MN. Compared with patients without a VTE, those who had an event were more frequently treated with immunosuppressive therapy (76.9% versus 55.9%, P=0.001), including corticosteroids (69.2% versus 50.8%, P=0.004) and cytotoxic agents (33.9% versus 18.1%, P=0.005) but not cyclosporine (13.9% versus 7.2%, P=0.08); however, the majority (90% in GDCN and 68% in TGNR) received these medications after the VTE event.

We identified 64 (7.1%) patients with a diagnosis of cancer, six of who had a VTE. The difference in the frequency of VTE between patients who did and did not have a cancer was not significant (9.4% versus 7.2%, P=0.46). The incidence of VTE among patients with cancer (0.024 events per person-year, 95% CI: 0.005, 0.04) was not significantly different from that in patients without cancer (0.017 events per person-year, 95% CI: 0.013, 0.021).

Other traditional risk factors for VTE were identified in six patients who experienced an event; three with recent immobilization, two with recent pregnancy, and one on oral contraceptives. None of the seven females on hormone replacement therapy had a VTE. Venous thrombotic events occurred in 12 of 163 (7.4%) patients taking an HMG-CoA reductase inhibitor after the onset of MN, compared with 48 of 659 (7.3%) patients not taking such medication (P=1.00). None of the patients who experienced a VTE was taking warfarin prior to the time of event, but 46% (n=30) were on antiplatelet agents (20 on aspirin, 1 on aspirin and clopidogrel, and 9 on dipyridamole).

Multivariable Analysis. The initial model of multivariate analysis included albumin, age, sex, 24-hour proteinuria, immunosuppressive treatment, and registry. Each 1.0 g/dl decrease in albumin level was associated with a 2.13-fold increased risk of VTE (95% CI for adjusted OR: 1.32, 3.46; P=0.002; Table 3).

The threshold for serum albumin, below which the risk for VTE significantly increases, was estimated by calculating the OR for patients categorized for an albumin

Table 1. Comparison of the GDCN and TGNR cohorts

Parameter	All Patients with MN		
	GDCN (n=412)	TGNR (n=487)	P Value[a]
Age at MN diagnosis (yr, mean ± SD)	50.9±16	47.5±15.8	0.001
Males, *N* (%)	238 (57.8)	317 (65.1)	0.03
Race, *N* (%)			<0.0001
Caucasian	266 (64.6)	332 (77.6)	
African American	82 (19.9)	25 (5.8)	
other	64 (15.5)	71 (16.6)	
History of smoking, *N* (%)[b]			0.34
never	100 (42.2)	131 (37.3)	
ex-smoker	72 (30.4)	105 (29.9)	
smoker at MN diagnosis	65 (27.4)	115 (32.8)	
Laboratory values at MN diagnosis (mean ± SD)			
albumin (g/dl)	2.5±0.8	2.7±0.7	0.0004
eGFR (ml/min per 1.73 m^2)	70.6±37.8	75.3±29.8	0.001
24-hour proteinuria (g)	8.6±6	6.9±5.0	<0.0001
Immunosuppressive treatment, *N* (%)			
glucocorticoids	261 (63.4)	207 (42.5)	<0.0001
cyclophosphamide/chlorambucil	88 (21.4)	85 (17.5)	0.15
cyclosporine	26 (6.3)	43 (8.8)	0.17
MMF, MTX, or AZA	21 (5.1)	15 (3.1)	0.13
rituximab	3 (0.7)		
any immunosuppressive therapy	269 (65.3)	247 (50.7)	<0.0001
	Patients with VTE		
	GDCN (n=29)	TGNR (n=38)	P Value[a]
History of smoking, *N* (%)[c]			1.00
never	5 (29.4)	8 (28.6)	
ex-smoker	5 (29.4)	8 (28.6)	
smoker	7 (41.2)	12 (42.9)	
Laboratory values at MN diagnosis[d] (mean ± SD)			
serum albumin (g/dl)	2.2±0.5	2.25±0.6	0.52
eGFR (ml/min per 1.73 m^2)	69±31.3	74.0±26.0	0.23
24-hour proteinuria (g)	9.9±5.0	7.1±4.9	0.02
Immunosuppressive treatment, *N* (%)			
glucocorticoids	24 (82.8)	21 (55.3)	0.02
Cytoxan/chlorambucil	9 (31.0)	13 (34.2)	1.00
cyclosporine	5 (17.2)	4 (10.5)	0.49
MMF, MTX, or AZA	1 (3.4)	3 (7.9)	0.63
rituximab	0 (0)		
any immunosuppressive therapy	24 (82.8)	26 (68.4)	0.26

GDCN, Glomerular Disease Collaborative Network; TGNR, Toronto Glomerulonephritis Registry; MN, membranous nephropathy; eGFR, estimated GFR; MMF, mycophenolate mofetil; MTX, methotrexate; AZA, azathioprine; VTE, venous thromboembolic event.
[a]*P* value was calculated by Fisher's exact test for categorical variables and Wilcoxon two-samples test for continuous variables.
[b]Information was available in 237 and 350 patients, respectively.
[c]Laboratory values from the time of diagnostic biopsy for the overall cohort and at the time of first VTE for thrombotic patients.
[d]Information was available in 17 and 26 patients, respectively.

<2.0 g/dl, then by increments of 0.2 g/dl to a concentration of ≥3.0 g/dl (Table 4). This analysis showed a consistent trend of increased risk with a serum albumin <2.8 g/dl. Compared with patients with albumin ≥2.8 g/dl, those with an albumin <2.8 g/dl had a 2.5-fold increased risk of VTE (95% CI: 1.17, 5.47; P=0.02), controlling for the same parameters as described earlier. Thromboembolic events occurred in 9.4% of patients with an albumin <2.8 g/dl compared with only 3.2% of those with an albumin ≥2.8 g/dl.

Of the other variables tested, only male sex was independently associated with an increased risk of VTE (OR: 2.13; 95% CI: 1.02, 4.44; P=0.04). The addition of smoking to the multivariable analysis model eliminated male sex as an independent risk factor for VTE, whereas serum albumin remained strongly associated with VTEs (OR = 3.07

Table 2. Characteristics of the patients with VTE at the time of the first event

Characteristic at First VTE[a]	*N*	Mean ± SD	Median (Min, Max)
Albumin (g/dl)	41	2.2±0.6	2.1 (0.6, 3.7)
eGFR (ml/min per 1.73 m^2 by MDRD)	57	70.5±27.8	70.8 (12.7, 132.4)
24-hour proteinuria (g)	54	10.3±6.8	9.9 (1.1, 40.0)
Time to VTE (mo) ≥ 0	64	24.2±59.8	3.8 (0.0, 338.7)
Age at event (yr)	63	49.2±15.5	51.0 (20.0, 84.0)

MDRD, Modification of Diet in Renal Disease.
[a]From the date of first assessment of proteinuria.

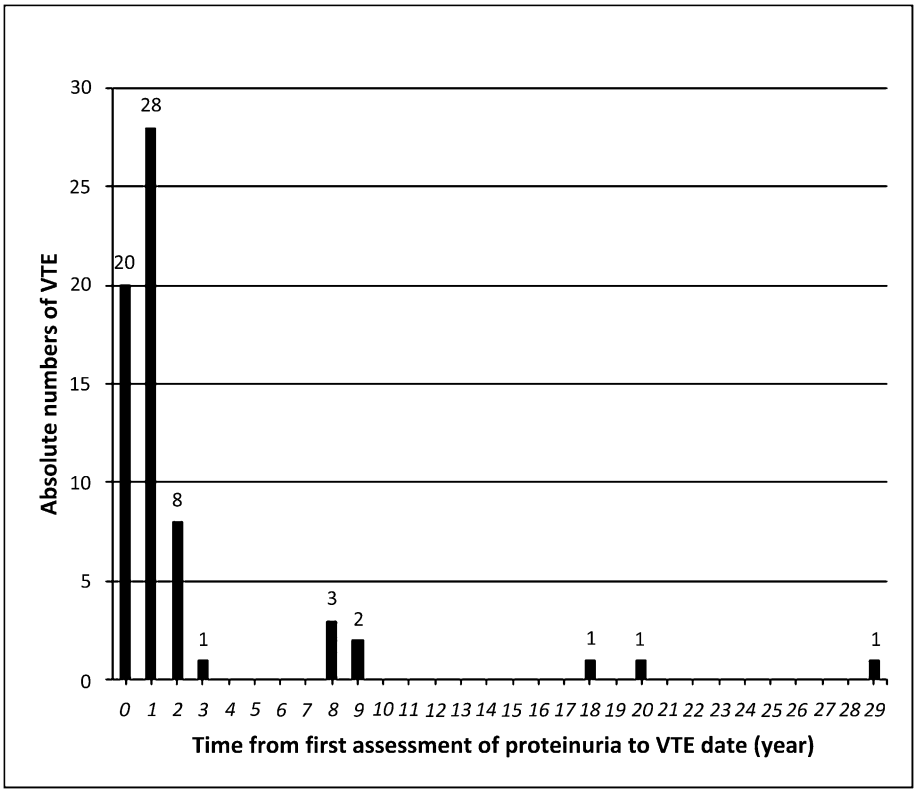

Figure 2. | Distribution of venous thromboembolic event (VTE) during the observation time.

per 1 g/dl decrease in albumin; 95% CI: 1.64, 5.72; $P<0.001$). Adding the use of HMG-CoA reductase inhibitors to the main model did not reveal an association with VTEs (OR=1.3; 95% CI: 0.65, 2.55; $P=0.47$).

We evaluated whether the duration of albuminemia was associated with risk of VTE using two different models. In a multivariable model, the interaction term of albuminemia and duration of hypoalbuminemia was not statistically significant ($P=0.57$). Albuminemia ≤2.8 g/dl remained statistically significantly associated with risk of VTE ($P=0.002$) whereas duration of hypoalbuminemia was not ($P=0.49$). In the categorical modeling of duration, albumin ≤2.8 g/dl with a duration ≤6 months, the OR for VTE was 2.30 (95% CI: 1.06, 5.02; $P=0.04$), and for duration >6 months the OR was 2.35 (95% CI: 1.00, 5.53; $P=0.05$), each compared with the reference group of albuminemia >2.8 g/dl.

Discussion

Thromboembolic events are a preventable cause of morbidity and mortality in patients with the nephrotic syndrome (16), especially MN. A fundamental treatment dilemma pertains to prophylactic anticoagulation. A better understanding of the risk of VTE in patients with MN is critical to balance the risks and benefits of prophylactic anticoagulation. The aim of this study was to describe the frequency of clinically evident VTE in patients with MN and determine clinical variables associated with increased risk of events based on a homogeneous inception cohort of 898 patients.

We found that clinically apparent VTEs are relatively infrequent, affecting about 8% of patients. Although similar to that reported in a smaller retrospective case series (17), this frequency is substantially lower than that previously reported in studies that used systematic screening for

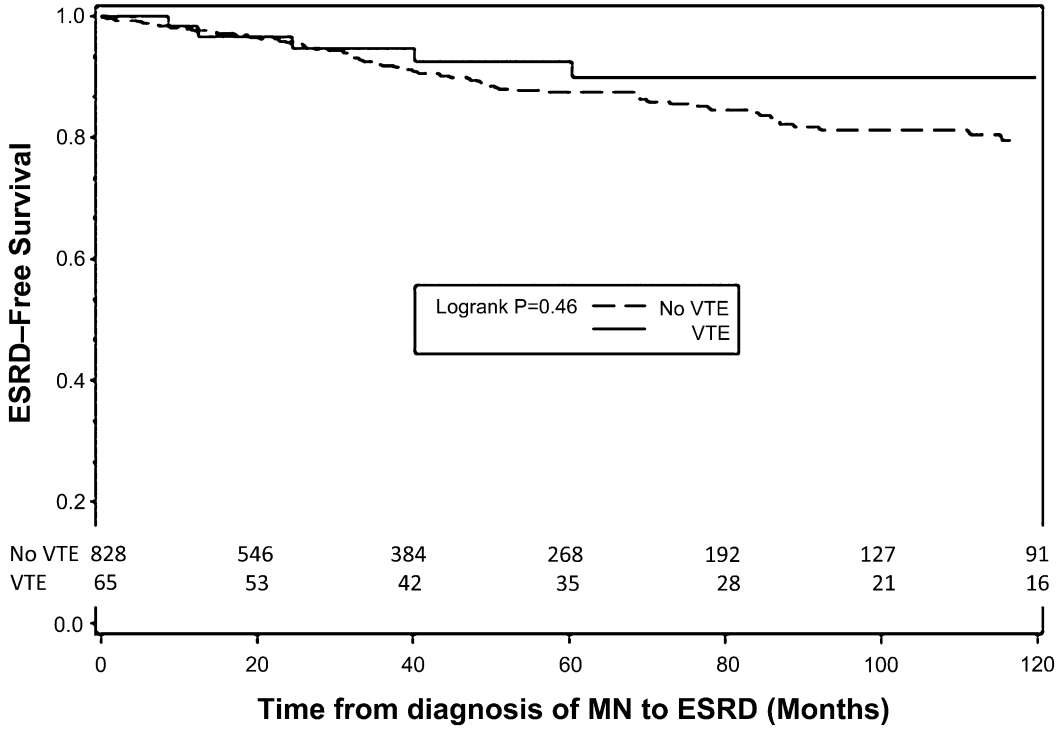

Figure 3. | **Renal survival probability among MN patients with and without VTE.**

Table 3. Multivariate analysis to identify predictors of VTE

Variable	Adjusted Odds Ratio	95% Confidence Interval	*P* Value[a]
Age at diagnostic biopsy (yr)	0.99	0.97, 1.01	0.39
Sex (M/F)	2.13	1.02, 4.44	0.04
24-hour proteinuria (g/d)	0.98	0.93, 1.04	0.59
Immunosuppressive therapy, any	1.72	0.85, 3.47	0.13
Site of registry (GDCN/TGRN)	0.67	0.36, 1.24	0.20
Serum albumin (g/dl)[b]	2.13	1.32, 3.46	0.002

[a]*P* value was calculated by logistic model evaluating the association of serum albumin while controlling for age at diagnostic biopsy, sex, 24-hour proteinuria, immunosuppressive therapy, and site of registry.
[b]Per each g/dl decrease in serum albumin.

VTEs (2,4). The clinical impact of undetected asymptomatic VTE is not known, and the frequency and location of VTEs are highly dependent upon the modality and intensity of clinical screening. In our population, RVT accounted for 30% of VTEs, in the range previously reported (13%−42%) (5,18–20). However, other studies using systematic screening venography reported higher proportions of RVT (50%−80%) (2,4).

We found hypoalbuminemia to be the dominant independent risk factor for VTE, whereas proteinuria was not independently predictive of thrombotic events by multivariable analysis. The relationship between hypoalbuminemia, the nephrotic syndrome, and thrombotic risk is poorly understood. Although hypoalbuminemia does generally correlate with severity of proteinuria, the latter is but one factor determining albumin levels. Recent data suggest that the degree of hypoalbuminemia in relation to proteinuria may be specific to the type of underlying glomerular disease (21). This may represent differences in one of the many determinants of serum albumin, including nutritional status, inflammation, selectivity of protein permeability (22), or other unmeasured factors that may predispose patients to thrombosis. Additional mechanisms include the hepatic overproduction of fibrinogen and factors V and VIII as a compensatory response to hypoalbuminemia (23) and a deficiency in plasma antithrombin III shown to correlate with serum albumin level (24–30). Albumin is a cofactor for the binding of plasminogen to fibrin and their interaction with tissue plasminogen activator (31). Patients with MN have a 6-fold increase in plasminogen activator inhibitor but not plasminogen activator, suggesting suppressed fibrinolytic activity (32). Hypoalbuminemia has also been associated with hyperaggregability of platelets (33–37).

Table 4. Adjusted risk of VTE by the level of serum albumin in 732 patients with available data

Serum Albumin (g/dl)	*N*	Patients with VTE	Odds Ratio	95% Confidence Interval	*P* Value[a]
Reference range ≥3.0[b]	219		1.00		
2.8 to <3.0	66	3	1.41	0.34, 5.87	0.64
2.6 to <2.8	74	2	2.17	0.63, 7.46	0.22
2.4 to <2.6	72	4	2.05	0.59, 7.12	0.26
2.2 to <2.4	77	1	1.31	0.31, 5.62	0.72
2.0 to <2.2	82	8	4.32	1.46, 12.77	0.01
<2.0	142	15	3.56	1.28, 9.88	0.02
<2.8 versus ≥2.8	447/285		2.53	1.17, 5.47	0.02

[a]Logistic regression model with incremental values of serum albumin, adjusted for age at biopsy, sex, 24-hour proteinuria (g/d), immunosuppressive therapy, and registry site.
[b]Logistic regression model with serum albumin as a dichotomous variable. The serum albumin cut-point of 2.8 g/dl was determined from the incremental model (by 0.2 g/dl) reported in this table, with threshold for effect noted for values <2.8 g/dl. Adjusted for age at biopsy, sex, 24-hour proteinuria (g/d), immunosuppressive therapy, and registry site.

Given the close association between hypoalbuminemia and VTE risk in our cohort, we identified 2.8 g/dl as the threshold of serum albumin below which the risk of VTE increases 3.9-fold compared with patients with an albumin ≥2.8 g/dl. The risk of VTE increases to 5.8-fold with a serum albumin level <2.2 g/dl.

We did not detect a statistically significant increase in the risk of VTE in association with malignancy. However, because of the relative infrequency of both malignancies and VTEs in our cohort, an association between the two cannot be excluded. Although we did not find an association between smoking and an increased risk of VTE, its inclusion in the multivariate analysis model eliminated male sex as a risk factor for VTE. Our inability to establish a statistically significant impact of smoking on the risk of VTE may be attributable to the fact that information regarding smoking was available on only 65% of the cohort. The consistent risks of smoking for VTE in the general population were established by studies with much larger sample sizes (4000 to 1.1 million individuals) (38–43). Likewise, the lack of a protective association between antiplatelet or HMG-CoA reductase inhibitor use and VTE risk may relate to the sample size. Compared with patients without a VTE, affected patients were significantly more likely to be treated with an immunosuppressant. This difference is likely attributable to the greater severity of proteinuria and hypoalbuminemia among patients prone to VTE prompting the immunotherapy, rather than medications contributing to the risk of thrombosis. This is supported by fact that immunosuppression was initiated subsequent to the VTE event in the vast majority of cases.

The occurrence of VTE did not affect renal or patient survival in our cohort, and none of the patients who suffered a VTE or PE died as a direct consequence. This result is not likely due to underestimating the frequency of events without the use of systematic screening. In fact, reporting only clinically evident VTE would skew the data in favor of more severe events, which would be associated with a higher rate of death.

Several study limitations merit discussion. Based on a retrospective analysis of passively captured clinical events, our findings may underestimate their true frequency. However, the similar event rates in our two independent cohorts make site-specific systematic underreporting and underdiagnosis of cases unlikely.

The specific aim of this study was to describe the occurrence of venous but not arterial thrombotic events. Arterial thromboses are predominantly cardiac and cerebrovascular events (20), which are common in the general population, are largely attributable to atherosclerosis or atrial fibrillation, and are greatly affected by traditional cardiovascular risk factors. As a result, determining the independent risk of arterial thrombotic events attributable to the nephrotic syndrome would require a careful assessment of the incidence ratio compared with a control population matched for age, sex, race, blood pressure, and smoking.

A primary reason for quantifying the risk of VTE in this patient population is to assist balancing the risks and benefits of anticoagulation. This study is not sufficient to resolve this dilemma as it does not address the risk of complications of anticoagulation. In the absence of direct clinical evidence, one would have to rely on decision analysis modeling to identify in which group of patients, if any, prophylactic anticoagulant therapy would be beneficial. It is noteworthy that the incidence of VTE in our cohort (0.016 event per person-year) is substantially lower than estimates used by Sarasin and Schifferli (44) (0.0025–0.0175 event per person-month) in their decision analysis modeling based on data derived from much smaller patient populations. Furthermore, because events are associated with relatively severe nephrosis, the probability of VTE should be based on the incidence of events during the periods of profound hypoalbuminemia. A decision analysis is further complicated by the lack of primary data on the efficacy and risks of anticoagulation in patients with the nephrotic syndrome (45–48). A decision analysis taking these factors into account is currently under way.

In summary, we detected clinically apparent VTE events in about 7% of patients with MN and confirmed the importance of hypoalbuminemia as the major risk factor. The risk of VTE increases significantly below an albumin level of 2.8 g/dl. Whether such patients should receive prophylactic anticoagulation awaits a more elaborate analysis of risk and benefit of such therapy.

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Disclosures

None.

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