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Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis

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The risk of venous thromboembolic events is thought to be highest in patients with membranous nephropathy. This association has been recently questioned, and it is not known whether this simply reflects the severity of proteinuria. To better understand the relationship between histologic diagnosis and the risk of venous thromboembolic events we evaluated patients in the Toronto Glomerulonephritis Registry. Of 1313 patients with idiopathic glomerulonephritis, 395 were diagnosed with membranous nephropathy, 370 with focal segmental glomerulosclerosis (FSGS), and 548 with immunoglobulin-A nephropathy (IgAN). Risk factors were evaluated by Cox proportional hazards for 53 image-confirmed venous thromboembolic events in 44 patients during a median follow-up of 63 months. The risk was highest in patients with membranous nephropathy and FSGS (hazard ratios of 22 and 7.8, respectively) referenced to patients with IgAN. Following adjustment for gender, cancer history, proteinuria, and serum albumin by multivariable analysis, the histologic subtype remained an independent risk for venous thromboembolic events. This risk was still highest in patients with membranous nephropathy followed by FSGS with adjusted hazard ratios of 10.8 and 5.9, respectively. Thus, in this large cohort, histologic diagnosis was an independent risk factor for venous thromboembolic events. Further studies are needed to discover mechanisms responsible for this high risk in patients with membranous nephropathy.

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Complications of the nephrotic syndrome are an important cause of morbidity in patients with idiopathic glomerulonephritis (GN).[1] One such complication is venous thromboembolic events (VTEs) including deep and renal vein thromboses (RVTs), as well as pulmonary emboli. The reported risk of VTEs in patients with nephrotic syndrome is highly variable, due to diverse patient populations and variable screening practices. The risk of VTE is not well defined, and is reported to range from 3 to 48%, depending upon the site of the VTE and the intensity of diagnostic screening.[2,3] Given the potentially significant morbidity and mortality associated with these events,[4] a better understanding of the frequency of clinically detected VTEs would help to guide therapy.

The nephrotic syndrome is considered to be a thrombophilic milieu due to a variety of elements including measurable changes in coagulation factors due to protein loss in the urine, altered platelet activity, intravascular volume contraction, venous stasis accompanying edema, and chronic inflammation.[5] Historically, the cause of the underlying glomerular disease was proposed to be an important risk for VTE, with membranous nephropathy (MN) implicated as a risk factor for these events.[3] However, studies that implicated MN as a risk factor for VTE primarily diagnosed asymptomatic thrombotic events on routine screening of uncertain clinical impact; did not adjust for the level of proteinuria or hypoalbuminemia, population age, or cancer; and did not compare with disease-specific controls.[5–9] In contrast to historical tenets, the largest study to address this topic showed an annual incidence rate of VTE in MN similar to that seen in other glomerular diseases.[10] Therefore, the disease-specific risk of VTE in patients with idiopathic GN remains an area of significant uncertainty.

Accordingly, we sought to define the disease-specific risk of clinically evident VTEs in patients with idiopathic GN after adjusting for thrombophilic risk factors common in glomerular diseases such as proteinuria, hypoalbuminemia, and malignancy. We studied a large cohort of patients with idiopathic immunoglobulin-A nephropathy (IgAN), focal and segmental glomerulosclerosis (FSGS), and MN, who

were followed up longitudinally in the Toronto Glomerulonephritis Registry in order to better understand the disease-specific risk of VTE in patients with idiopathic GN.

RESULTS

Patient characteristics

The study cohort comprised 1313 patients, including 370 subjects with FSGS, 548 with IgAN, and 395 with MN. Reasons for exclusion from the study are outlined in Supplementary Figure S1 online. Baseline characteristics are described in Table 1. The cohort comprised 63% male patients, followed up for a median of 63 months with baseline proteinuria of 3.1 g/day and albumin of 32.9 g/l.

Several clinical parameters differed across diagnostic categories: patients with MN tended to be older, were more likely men and of Caucasian background, had more severe proteinuria and hypoalbuminemia, and better renal function at the time of first presentation. Cancer, either before presentation or during the follow-up period, occurred in 3.7% of patients. There was a trend toward a higher number of cancer events in patients with MN; however, this did not reach statistical significance ($P = 0.06$ across groups).

The distribution of proteinuria at presentation and during the follow-up (the time-averaged (TA) proteinuria) across diagnostic categories is illustrated in Figure 1. A greater proportion of patients with MN had high-grade proteinuria (>8 g/day) at presentation, and sustained over time, compared with other GN subtypes ($P<0.0001$).

Venous thromboembolic events: frequency

There were 53 VTEs in 44 patients, with the types of events described in Table 2. A greater proportion of patients with MN developed VTEs, compared with FSGS or IgAN (7.85% vs. 2.97% vs. 0.36%, respectively, $P<0.0001$). Even when isolated RVT was excluded from the analysis, a larger proportion of patients with MN experienced a VTE compared with patients with FSGS or IgAN (4.8% vs. 2.7% vs. 0.36%, $P<0.0001$).

Venous thromboses occurred at a median of 272 days after first presentation. Overall, 57% of VTEs occurred within 1 year and 70% within 2 years of presentation. The VTEs tended to occur closer to the time of GN diagnosis in patients with MN; however, there was a wide range in the timing of the event, and this did not reach statistical significance. The risk of VTE over time is illustrated in the Kaplan–Meier curve in Figure 2. The risk of thrombosis during the follow-up period differed across all three groups, with the lowest risk in IgAN patients and the highest in MN patients ($P<0.0001$ across groups). The characteristics of patients at the time of VTE according to underlying GN diagnosis are summarized in Table 3; at the time of the VTE, patients with MN

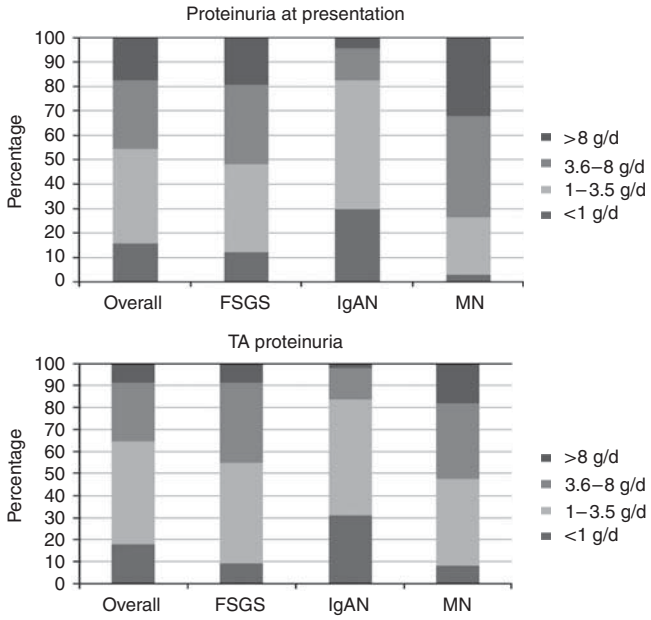

Figure 1 | Percentage of patients with each category of proteinuria at presentation, and time-averaged proteinuria (TA proteinuria). FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin-A nephropathy; MN, membranous nephropathy.

Table 1 | Baseline (within 6 months of presentation) and longitudinal characteristics

	Overall	FSGS	IgAN	MN	*P*-value
Number of patients	1313	370	548	395	
Length of follow-up (months; median (LQ, UQ))	63.0 (33.3, 108.0)	67.8 (35.9, 110.1)	62.6 (33.4, 105.5)	59.6 (30.3, 104.9)	0.3
Age at presentation (years; mean (s.d.))	42.2 (15.2)	42.5 (15.8)	38.1 (13.1)	45.6 (15.6)	<0.0001
Sex (% male)	63.1	62.4	61.3	66.1	0.3
Race (%)					<0.0001
Caucasian	67.6	69.0	58.6	78.5	
African American	5.6	9.0	3.2	5.4	
Asian	15.3	11.0	26.6	4.0	
Other	11.6	11.0	11.6	12.0	
Estimated CrCl at presentation (ml/min per 1.73 m^2; mean (s.d.))	74.4 (30.0)	71.6 (30.9)	73.5 (29.2)	78.4 (30.0)	0.0007
Proteinuria at presentation (g/day; median (LQ, UQ))	3.1 (1.5, 6.5)	3.7 (1.8, 6.8)	1.6 (0.8, 2.9)	5.6 (3.3, 9.9)	<0.0001
TA proteinuria during follow-up (g/day; median (LQ, UQ))	2.6 (1.4, 4.6)	3.3 (1.8, 4.9)	1.8 (0.8, 2.9)	3.9 (2.0, 6.5)	<0.0001
Albumin at presentation (g/l; mean (s.d.))	32.9 (9.1)	33.1 (9.7)	38.2 (6.6)	26.8 (7.1)	<0.0001
TA albumin during follow-up (g/l; mean (s.d.))	36.5 (6.2)	36.6 (6.8)	39.1 (4.5)	33.0 (6.0)	<0.0001
Cancer history prior to or during follow-up period (number (%))	48 (3.7)	14 (3.8)	13 (2.4)	21 (5.3)	0.06

Abbreviations: FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin-A nephropathy; LQ, lower quartile; MN, membranous nephropathy; TA, time averaged; UQ, upper quartile.

Table 2 | The number and nature of VTEs

	Overall, *N*=1313	FSGS, *N*=370	IgAN, *N*=548	MN, *N*=395	*P*-value
Patients with a VTE (number (%))	44 (3.4)	11 (3.0)	2 (0.4)	31 (7.9)	<0.0001
Number of VTEs of each type					
DVT	10	4	1	5	
PE	20	8	1	11	
RVT	19	2	0	17	
Other	4	0	0	4	
Days to first VTE (median (LQ, UQ))	272 (0, 1080)	1094 (401, 1604)	453 (363, 542)	151 (0, 447)	0.07

Abbreviations: DVT, deep vein thrombosis; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin-A nephropathy; LQ, lower quartile; MN, membranous nephropathy; PE, pulmonary embolism; RVT, renal vein thrombosis; UQ, upper quartile; VTE, venous thromboembolic event.

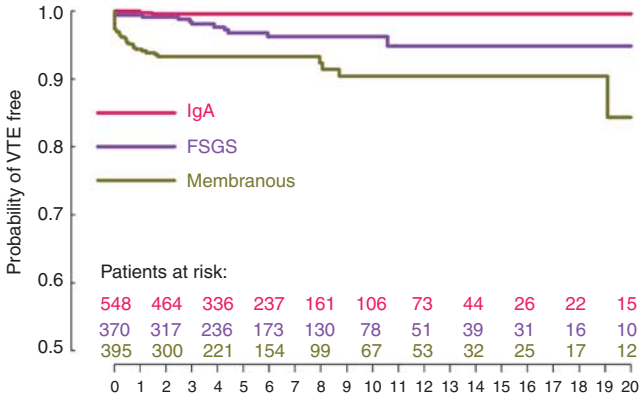

Figure 2 | The risk of VTE over time by type of GN ($P<0.0001$ across groups). FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgA, immunoglobulin A; VTE, venous thromboembolic event.

and FSGS were hypoalbuminemic and had nephrotic-range proteinuria.

Venous thromboembolic events: risk factors

The results of univariable analyses to identify clinical features associated with the development of VTE are shown in Table 4. The underlying histological diagnosis was closely associated with VTE risk; the risk was highest in patients with MN (unadjusted hazard ratio 22.0, 95% confidence interval 5.3–92.1, $P<0.01$) and FSGS (hazard ratio 7.8, 95% confidence interval 1.7–35.2, $P<0.01$) compared with IgAN (reference group). Male sex, proteinuria at presentation, TA proteinuria, albumin at presentation, and TA albumin were all associated with VTEs (see Table 4).

Proteinuria at presentation and TA proteinuria, when expressed as either continuous (log transformed) or categorical variables, were both significantly associated with VTEs, as were albumin at presentation and TA albumin. The risk of VTE was directly proportional to the severity of proteinuria and inversely related to the albumin level, for both at presentation and TA values.

A diagnosis of cancer at any time during the patient course was found to be a risk factor for the development of VTE in this cohort. There were a total of 48 cancers in the cohort. Approximately 11% of the patients with VTE ($n=5$ of 44 patients with VTE) had a diagnosis of cancer prior to diagnosis or during follow-up, compared to 3.7% in the total cohort.

Age and self-reported race were not associated with thrombotic events (data not shown).

To determine the independent relationship between histological diagnoses and VTE risk, a multivariable model, including the covariates such as male sex, cancer history, proteinuria, and albumin levels, was considered. As indicated in Table 5, sex and serum albumin were associated with increased risk of VTE, whereas cancer and proteinuria were not. Similar results were obtained when considering TA albumin and TA proteinuria (data not shown). Even after adjustment for these important clinical variables, the underlying histological diagnosis remained independently associated with thrombotic events, with the higher risk in MN and FSGS compared with IgAN (adjusted hazard ratio = 10.8, $P=0.002$, for patients with MN and adjusted hazard ratio = 5.9, $P=0.02$, for patients with FSGS).

DISCUSSION

VTEs are a potentially life-threatening complication of the nephrotic syndrome. The risk of VTE has traditionally been thought to be highest in patients with MN; however, it is not clear whether this disease-specific risk is independent of clinical variables such as patient age or degree of proteinuria. In this study, we sought to determine whether the underlying histological diagnosis is an independent risk factor for the development of clinically evident VTE.

We have shown that the risk of clinically evident VTE in patients with idiopathic GN is closely related to the underlying histological diagnosis, with the highest risk in MN, the lowest in IgAN, and an intermediate risk in FSGS. The higher frequency of VTEs was not uniquely attributable to a higher frequency of RVT events; a higher frequency of VTEs was observed in patients with MN even when RVTs were excluded. In our cohort, when considered in isolation, both proteinuria and hypoalbuminemia increased the risk of VTE; however, the disease-specific risk of VTE was independent of the degree of proteinuria, serum albumin levels, and cancer history. Although patients with MN were more likely to have higher levels of proteinuria and lower albumin levels, as well as high rates of cancer, these differences did not fully account for differences in VTE risk.

Table 3 | Description of patients with (VTE+) and without (VTE−) VTEs

	FSGS, *N*=11 events		MN, *N*=31 events		IgAN, *N*=2 events	
	VTE+	VTE−	VTE+	VTE−	VTE+	VTE−
Albumin at presentation (g/l)	26.1 (8.7)	33.2 (9.7)	21.9 (6.1)	27.2 (7.1)	40, 46[a]	38.2 (6.6)
TA albumin over entire follow-up (g/l)	33.3 (5.4)	36.7 (6.8)	32.7 (6.1)	33.0 (5.9)	44.0, 46.0	39.1 (4.5)
Proteinuria at presentation (g/day)	8.2 (3.0, 13.7)	3.6 (1.8, 6.7)	6.5 (4.4, 11.2)	5.6 (3.2, 9.7)	3.5, 0.5[a]	1.6 (0.8, 2.9)
TA proteinuria over entire follow-up (g/day)	5.9 (4.1, 7.0)	3.1 (1.8, 4.9)	4.9 (2.7, 9.3)	3.7 (1.9, 6.5)	0.5, 2.8	1.8 (0.8, 2.9)
Albumin at time of VTE (g/l)	32.8 (8.2)	NA	25.5 (7.4)	NA	40.0[b]	NA
Proteinuria at time of VTE (g/day)	6.2 (3.9, 10.7)	NA	9.8 (3.7, 11.7)	NA	3.4, 0.5	NA
Days to first VTE	1094 (401, 1604)	NA	151 (0, 447)	NA	363, 542	NA

Abbreviations: FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin-A nephropathy; MN, membranous nephropathy; NA, not applicable; TA, time averaged; VTE, venous thromboembolic event.
Data are provided as median (lower quartile, upper quartile) or mean (standard deviation), except for IgAN where individual data are provided, as there were only 2 VTEs.
[a]Values presented are first available.
[b]Albumin at time of VTE was not available for one patient.

Table 4 | Univariable analyses: clinical variables associated with risk of venous thromboembolic events

	HR	95% CI	*P*-value
Underlying disease			0.0001
IgAN	Reference		
FSGS	7.8	1.7–35.2	0.008
MN	22.0	5.3–92.1	<0.0001
Male sex	2.6	1.2–5.6	0.01
Proteinuria at presentation by categories			0.0003
<1 g/day	Reference		
1–3.5 g/day	3.0	0.4–24.4	0.3
3.6–8 g/day	8.2	1.1–62.8	0.04
>8 g/day	17.0	2.3–127.6	0.006
TA proteinuria by categories			0.0002
<1 g/day	Reference		
1–3.5 g/day	5.7	0.8–42.8	0.09
3.6–8 g/day	13.3	1.8–99.9	0.01
>8 g/day	25.3	3.2–198.7	0.002
Albumin at presentation by categories			<0.0001
>38 g/l	Reference		
29–38 g/l	4.3	0.5–37.1	0.2
<29 g/l	27.7	2.8–203.9	<0.0001
TA albumin by categories			0.002
>39 g/l	Reference		
35–39 g/l	3.4	1.3–8.9	0.01
<35 g/l	5.5	2.2–13.5	<0.0001

Abbreviations: CI, confidence interval; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; IgAN, immunoglobulin-A nephropathy; MN, membranous nephropathy; TA, time averaged.
Albumin and proteinuria metrics are given both as continuous variables and by categories.

Table 5 | Multivariable analysis of risk of venous thromboembolism

	HR	95% CI	*P*-value
Male sex	2.4	1.1–5.3	0.02
Cancer history	2.4	0.9–6.3	0.07
Albumin at presentation			0.02
>38 g/l	Reference		
29–38 g/l	2.7	0.3–23.9	0.4
<29 g/l	9.6	1.2–76.4	0.03
Proteinuria at presentation			0.7
<1 g/day	Reference		
1–3.5 g/day	1.6	0.2–13.9	0.6
3.6–8 g/day	1.9	0.2–14.9	0.5
>8 g/day	2.6	0.3–20.2	0.4
Underlying disease			0.006
IgAN	Reference		
FSGS	5.9	1.3–27.9	0.02
MN	10.8	2.4–49.4	0.002

Abbreviations: CI, confidence interval; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; IgAN, immunoglobulin-A nephropathy; MN, membranous nephropathy.

Data regarding the disease-specific risk of VTE in patients with the nephrotic syndrome are divergent. Historically, MN has been associated with a particularly high risk of VTE. This was supported by studies that used screening renal venograms, and a substantial proportion of VTEs captured in the patient population were asymptomatic RVTs; in these studies, the risk of VTE was reported to be as high as 86%.[5–7,9,11] However, the clinical impact of these asymptomatic VTEs is unclear. Furthermore, not all studies uniformly found a similarly high frequency of VTE in MN.[3] In addition, previous studies did not adjust for proteinuria or albumin level; therefore, the question of the independent disease-specific risk of VTE remained unanswered.[5,11,12] The largest study to date, to address disease-specific risk included 298 patients with nephrotic-range proteinuria, of whom 157 had idiopathic primary GN.[10] In this study, there was no observed difference in the incidence of VTE between MN, FSGS, and minimal change disease, and only proteinuria above 8.2 g/day was associated with increased VTE risk.[10] Our study findings differ likely because of the fact that our large sample size of over 1300 patients may be better powered to detect disease-specific differences in risk.

Our study results prompt two important questions for future consideration. First, why is MN independently associated with a particularly high VTE risk? Next, how could these data inform decisions regarding prophylactic anticoagulation?

The mechanisms responsible for the increased VTE risk require further study and elucidation. The nephrotic syndrome itself is purported to cause changes in hemostatic factors that favor thrombosis, including increased fibrinogen and coagulation factor levels and decreased antithrombin III, protein C and S, and plasminogen levels.[4] However, these findings are inconsistent, and less is known about mechanisms by which MN may specifically place patients with nephrotic syndrome at higher risk of VTE. Given that the absolute quantity of proteinuria may not independently explain the VTE risk, the nature of the proteinuria may differ between types of GN. The particular molecular weight of proteins lost in patients with MN may result in disease-specific alterations in proteins that affect susceptibility to thrombosis.[13] Antibodies to α-enolase have been observed in patients with MN, and these may have antifibrinolytic activity.[14,15] There is also a suggestion that factor V Leiden mutation may be associated with MN, providing a second hypercoagulable risk factor in addition to the nephrotic syndrome.[16] A relationship between antibodies to the M-type phospholipase receptor (PLA2R) and VTE risk also requires further exploration.[17]

The next logical stage in analysis is an evaluation of the risks and benefits of prophylactic anticoagulation in patients with GN. Our data suggest several characteristics that may identify patients with proteinuric GN who may be at highest risk of thrombosis, including male gender, significant hypoalbuminemia, and an underlying histological diagnosis of MN. The timing of VTE in MN appeared to be earlier than in those with FSGS (see Table 2), supporting the need for additional analyses to identify disease-specific time periods of highest thrombosis risk. These could then be used in a formal decision analysis to help guide the use of prophylactic anticoagulation.

Several considerations regarding how our study design may have affected our findings merit comment. Patients did not undergo predefined screening tests to diagnose venous thrombotic events. It is therefore possible that patients with more severe nephrotic syndrome or those with a diagnosis of MN may have been more aggressively investigated for VTEs because of their higher perceived risk. One might expect this to have the most impact with respect to detection of RVT; indeed, VTE frequency was disproportionately high even when RVTs were excluded from the analysis. Next, there was a trend suggesting earlier thrombotic events in patients with MN, which needs to be considered in the context of our inclusion of patients with at least 1 year of follow-up in our analysis. We chose 1 year of follow-up in order to assure adequate time to detect events across all GN subtypes, and to accrue sufficient clinical data to identify risk factors associated with VTE. This may have biased our results toward diagnosing fewer events, potentially underestimating the increased risk of VTE in MN. We verified that this was not likely to be a concern, given that only two VTEs were documented in patients with MN who had <1 year of follow-up (see Materials and Methods). In addition, an underestimation of the risk of events would not necessarily alter our findings of the risk factors associated with VTE. Finally, despite the large size of our cohort and the long follow-up period, there were relatively few events, which does limit the ability to identify predisposing risk factors. In conclusion, this underscores the rarity of clinically evident venous thrombotic events in this patient population and the need to identify those patients at highest risk to target clinical interventions.

In summary, we have shown that patients with MN have a greater risk of VTE compared with those with FSGS or IgAN, even after adjustment for differences in degree of proteinuria, hypoalbuminemia, and malignancy. Further research is required to identify reasons for the disease-specific risk of VTE in patients with MN.

MATERIALS AND METHODS

Description of the cohort

Since 1974, all patients with biopsy-proven idiopathic GN in the greater Toronto area have been enrolled in the Toronto Glomerulonephritis Registry.[18] Information is collected prospectively by registrars as of the time of first clinical presentation, and includes demographics, baseline and developing comorbidities, clinical and laboratory parameters, and medication use.

We considered all patients in the Toronto GN Registry with idiopathic IgAN, FSGS, and MN for enrolment in our cohort. We excluded those patients with secondary causes of GN, who were younger than 16 years of age at presentation, had incomplete clinical data, or less than 12 months of follow-up. We included patients with a spectrum of disease severity, including those who had subnephrotic proteinuria, to more completely describe the risk of VTE associated with the underlying histological type of disease. The 12-month period was chosen to ensure that patients were followed up long enough to capture VTEs. There were 2790 patients considered for our cohort, of whom 1477 were excluded resulting in a cohort of 1313 patients, including 370 with FSGS, 548 with IgAN, and 395 with MN. Supplementary Figure S1 online shows the derivation of the cohort and reasons for exclusion. We determined that only two VTEs were detected in 94 MN patients with <1 year of follow-up, supporting the fact that restricting our analyses to patients with longer follow-up would not substantially underestimate the frequency of events.

Definitions

The start of the follow-up period was defined as the time of the first assessment with available clinical and laboratory data. This may have preceded the date of renal biopsy. Baseline parameters were taken as the first available within 6 months of the start of the follow-up period. Secondary causes of GN were defined as the presence of systemic lupus erythematosis, hepatitis B, hepatitis C, HIV, or other coexistent glomerular diseases on biopsy (such as diabetes).

Proteinuria was measured in 24-h urine collections. The follow-up period was broken into 6-month blocks, the average proteinuria during each block was determined, and the mean of all such values was termed the TA proteinuria, and meant to reflect the burden of proteinuria during the follow-up period. Similarly, the TA albumin levels (TA albumin) were calculated. Creatinine clearance was estimated from the Cockroft-Gault formula and standardized to body surface area (ml/min per 1.73 m^2).[19] Race was self-reported.

Comorbidities were prospectively collected by the registrars during routine chart reviews.

Outcomes

We reviewed the longitudinal follow-up data of patients within the Toronto Glomerulonephritis Registry and extracted all venous thrombotic events. Routine screening for asymptomatic events was not performed, although some RVTs were detected on routine pre-biopsy ultrasound tests. Most events were clinically symptomatic, prompting further investigations, and were confirmed by imaging modalities. Pulmonary embolus was confirmed by pulmonary angiography, ventilation–perfusion scans, or computed tomography; deep vein thrombosis by ultrasound; and RVT by ultrasound, computed tomography, or percutaneous renal venograms. To ensure that cases were not missed, the records for all patients on warfarin were identified for repeat review to determine whether VTE may have been the indication for anticoagulation.

Statistical analyses

Data were analyzed using Microsoft Excel and SAS software. Normally distributed variables were described as mean standard deviation and compared across groups using analysis of variance. Nonparametric variables were described as median (lower quartile and upper quartiles), and compared using the Kruskal–Wallis test. Categorical variables were compared using the χ^2-test. All *P*-values are two tailed, with <0.05 considered statistically significant.

The time to event was measured as the time from the start of the follow-up period to the documentation of a VTE. Differences in event-free survival were determined using the Cox proportional hazards test.

The Cox proportional hazards test was used to identify clinical variables associated with the risk of VTE. Covariates considered included histological diagnosis, age, sex, self-reported race, cancer, proteinuria at presentation, TA proteinuria, albumin at presentation, and TA albumin. Because proteinuria is not normally distributed, it was analyzed as a log-transformed variable. All variables found to be significantly associated with VTE risk by univariable models were included in a multivariable model. However, proteinuria at presentation was found to be highly correlated with TA proteinuria; similarly, albumin at presentation was found to be highly correlated with TA albumin. Therefore, we chose to include proteinuria and albumin at presentation in our multivariable models. These were expressed as categorical variables to account for missing values, which were not associated with VTE risk ($P=0.34$ for missing albumin and $P=0.31$ for missing proteinuria). Multivariable analysis was repeated using TA albumin and TA proteinuria as covariates instead of values at presentation, with similar results (data not shown).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Derivation of the cohort.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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