Incidence, Risk Factors, and Outcomes of Neonatal Renal Vein Thrombosis in Ontario: Population-Based Cohort Study

Allison C. Ouellette,1 Elizabeth K. Darling,2,3 Branavan Sivapathasundaram,2 Glenda Babe,2 Richard Perez,2 Anthony K.C. Chan,4 and Rahul Chanchlani2,5,6

Abstract

Background There are limited data at a population level on the burden, risk factors, and long-term outcomes of neonatal renal vein thrombosis (nRVT). We conducted a population-based cohort study to understand the epidemiology and outcomes of nRVT over a 25-year period in Ontario.

Methods Using linked administrative health databases, all hospitalized neonates ≤28 days born in Ontario between 1992 and 2016 with nRVT were identified. The primary outcome was to calculate the incidence of nRVT and trend over time in Ontario. We also determined the risk factors associated with nRVT as well as the risk of long-term outcomes after nRVT, including CKD, ESKD, all-cause mortality, and hypertension (HTN) compared with the healthy neonatal population without nRVT.

Results The annual incidence rate of nRVT was 2.6 per 100,000 live births (n=85). Presence of respiratory distress syndrome (OR, 8.01; 95% CI, 4.90 to 13.1), congenital heart disease (OR, 9.1; 95% CI, 5.05 to 16.4), central venous catheterization (OR, 3.9; 95% CI, 1.89 to 7.93), maternal preeclampsia (OR, 2.8; 95% CI, 1.6 to 4.79), and maternal diabetes (OR, 2.36; 95% CI, 1.36 to 4.07) conferred the highest risk for nRVT. Over a median follow-up of 15 years and after adjusting for confounders, neonates with nRVT versus the comparator cohort had a 15.5-fold risk of CKD, HTN, or death (n=49 [58%] versus n=90,050 [3%]; 95% CI, 11.7 to 20.6); 12.3-fold increased risk of CKD or death (n=39 [46%] versus n=32,016 [1%]; 95% CI, 8.9 to 16.8); and a 15.7-fold increased risk of HTN (n=33 [39%] versus n=64,458 [2%]; 95% CI, 11.1 to 21.1). None of the nRVT cohort developed ESKD. The median time to composite outcome of CKD, HTN, or death was 11.1 years.

Conclusions Patients with a history of nRVT remain at higher risk than the general population for long-term morbidity or mortality, indicating the need for long-term follow-up.

Introduction Neonatal renal vein thrombosis (nRVT), although rare, is the most common form of noncatheter-related venous thrombosis in neonates outside of the central nervous system (1–3). It is thought to be related to postglomerular hemocoencentration, and therefore can present with hypovolemia, nephrotic syndrome, and coagulopathies (4).

The incidence of nRVT is unclear and has been estimated as 2.2 per 100,000 live births based on data from voluntary case registries (5). Poor outcomes have been reported, including hypertension (HTN), CKD, and ESKD (5–8). Several risk factors have been associated with nRVT, including thrombophilias, birth asphyxia, sepsis, maternal diabetes, and volume contraction (9–11). There is a known preponderance for males to be affected (1–3). Indwelling intravascular catheters are also a risk factor for neonatal thrombosis (2,3).

Epidemiologic studies of nRVT have been conducted as case series (7,8,12) or voluntary registries (2,3,5,9), rather than population-based studies, and are limited by the inability to control for selection bias. Additionally, these studies have been limited by small sample size and lack of adequate follow-up to characterize long-term outcomes. A longitudinal population-based approach is warranted to better understand the risk factors, incidence, and outcomes of nRVT.

The province of Ontario, Canada (population 13.6 million) is well suited for evaluating longitudinal population health data. All children who are born and reside in Ontario have universal health insurance through a public single-payer system for all medically 

1Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
2ICES McMaster, Hamilton, Ontario, Canada
3Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada
4Division of Hematology/Oncology, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
5Division of Nephrology, Department of Pediatrics, McMaster Children’s Hospital, McMaster University, Hamilton, Ontario, Canada
6Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Correspondence: Dr. Rahul Chanchlani, Division of Nephrology, Department of Pediatrics, McMaster Children’s Hospital, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada. Email: chanchlr@mcmaster.ca

www.kidney360.org Vol 1 July, 2020
necessary health services through the Ontario Health Insurance Plan (OHIP). Ontario’s low annual emigration rate of <0.25% (13–15) makes it well suited to study long-term health outcomes. We performed a longitudinal population-based study to determine the incidence and temporal trend of nRVT, as well as identify risk factors and long-term adverse outcomes of nRVT, using administrative health databases.

Materials and Methods

Study Design and Setting
This was a longitudinal retrospective cohort study using linked administrative health databases to compare hospitalized neonates in Ontario who developed nRVT versus the general neonatal population of Ontario between 1992 and 2016. Only de-identified administrative health data were used and the study was exempt from institutional research ethics board review under Section 45 of Ontario’s Personal Health Information Protection Act. The reporting of this study complies with the Reporting of Studies Conducted Using Observational Routinely-Collected Data statement (16).

Study Population
All neonates (≤28 days of age) born in Ontario between April 1, 1992 and March 31, 2016 were identified. The occurrence of nRVT was determined by the presence of codes (Supplemental Table 1) including International Classification of Diseases, Ninth Edition (ICD-9) code 453.3 (renal vein thrombosis) and ICD-10 code I82.3 (embolism and thrombosis of renal vein), which are suggestive of nRVT as a discharge diagnosis in hospitalized neonates. The comparator cohort comprised all neonates born in Ontario during the study period without a diagnosis of nRVT. Exclusion criteria included absence of a valid health card number, mortality on or before index date, and missing birth weight. The index date for the nRVT cohort was date of admission to hospitalization for nRVT. The index dates for the comparator cohort were assigned randomly based on the distribution of index dates of the nRVT cohort. All neonates were followed for at least 1 year.

Data Sources
The study used provincial administrative health databases housed at ICES. Hospitalization records were obtained from the Canadian Institute for Health Information Discharge Abstract Database and were used to identify hospitalizations, comorbidities, and procedures. The OHIP database contains records of all physician billings for outpatient and inpatient services, including a service date and a single diagnosis. The Registered Persons Database contains demographic data for all individuals with OHIP coverage, periods of coverage, and date of death. The Canadian Organ Replacement Register contains information on chronic dialysis treatments and transplantation. The ICES-derived MOMBABY cohort contains delivery records for mothers and their newborns, linked deterministically. The Ontario Marginalization Index Database (from Public Health Ontario) reports neighborhood-level indices of marginalization, derived from census data. The material deprivation quintile component of the index was used. Data for total births in Ontario was derived from the Statistics Canada Canadian Socio-Economic Information Management System database.

Outcome Assessment
The primary outcome was to determine the incidence and temporal trend of nRVT over a period of two decades in Ontario. Secondary outcomes were to determine the neonatal and maternal risk factors associated with nRVT as well as the risk of long-term outcomes after nRVT including CKD, ESKD (defined as receipt of chronic dialysis or kidney transplant), all-cause mortality, or HTN. These adverse outcomes were assigned using diagnosis, procedure, and billing codes (Supplemental Appendix). Diagnoses and procedures were identified by ICD codes from the ICD-9 and ICD-10 or the Canadian Classification of Health Interventions (Supplemental Table 1).

Covariates
We assessed the following demographic risk factors: age, sex, birth weight, gestational age, neonatal comorbidities (congenital heart disease, sepsis, respiratory distress syndrome, and use of central venous catheters), maternal factors (maternal age, marginalization, rural status), and maternal comorbidities (preeclampsia or eclampsia and diabetes mellitus during the pregnancy). Codes used to identify these conditions are explained in Supplemental Table 1. To identify maternal pregnancy complications, maternal health records were accessed for 280 days before the birth, as early as June 26, 1991. The 2001 version of the Ontario Marginalization Index was used for neonates born between 1992 and 2003, the 2006 version for neonates born between 2004 and 2008, and the 2011 data for neonates born between 2009 and 2016 (17). Rurality was defined as a community of <10,000 persons.

Statistical Analyses
All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Because we expected all continuous baseline variables to be non-normally distributed, we presented all continuous variables using medians (interquartile range [IQR]). Categorical and binary variables were reported as numbers and percentages. Standardized differences were used to measure effect size between the nRVT and comparator cohort due to the difference in sample sizes between the cohorts (18).

The incidence of nRVT was calculated per 100,000 live births per fiscal year. The incidence of nRVT was stratified by 5-year intervals and by two ICD eras (April 1, 1992 to March 31, 2003 and April 1, 2003 to March 31, 2016) associated with the transition from ICD-9 to ICD-10 coding. Univariate logistic regression models were created to determine the neonatal and maternal risk factors associated with nRVT. Neonatal variables included sex, age at presentation, birth weight, congenital heart disease, respiratory distress syndrome, sepsis, and use of central venous catheter. Maternal factors included maternal age, marginalization index, rural status, presence of preeclampsia or eclampsia, and maternal diabetes. Variables with $P$ values <0.05 in the univariate model were included in the final multivariable logistic regression model.
The Kaplan–Meier product-limit method was used to calculate the cumulative incidence of long-term outcomes. All neonates were followed until one of the following events occurred: all-cause mortality, loss of OHIP coverage for a period >3 months, a period of >2 years passed without health care contact, or until administrative censoring (March 31, 2017). Incidence rates (IRs) were reported per 1000 person-years and Cox proportional hazards models were created to calculate hazard ratios (HRs) for long-term outcomes. Proportionality was confirmed by plotting Schoenfeld residuals for each model (19).

As a sensitivity analysis, we created Kaplan–Meier curves only for those neonates who survived the first year of life without any outcomes to better understand their risk of long-term outcomes. Although prematurity is a known risk factor for nRVT and adverse long-term outcomes of CKD and HTN, we did not include prematurity in the main analysis because our databases lack prematurity data before 2002. As a sensitivity analysis, we included prematurity as a covariate in the multivariate Cox model for the subgroup of neonates born after 2002.

Any analyses with a cell count of five or fewer study participants was reported as “<6” in accordance with ICES data privacy policies.

Results
Of 3,055,075 births registered in Ontario between April 1, 1992 to March 31, 2016, 3,010,610 neonates were included in our study (99%) based on inclusion and exclusion criteria (Figure 1). Baseline features among the nRVT and the comparator cohorts are shown in Table 1. Median age at diagnosis was 1 day (IQR, 0–4 days). A greater proportion of the nRVT cohort were premature and had lower birth weight compared to the comparator cohort. A higher proportion of the nRVT cohort had maternal (preeclampsia, diabetes affecting pregnancy) and neonatal comorbidities (congenital heart disease, sepsis, respiratory distress syndrome, central venous catheterization). The rest of the baseline characteristics were similar between cohorts. No nRVT cases had missing data. Of the comparator cohort, only 2991 neonates (0.1%) were missing rurality status.

Incidence
There was a total of 85 cases of nRVT diagnosed in Ontario between April 1, 1992 and March 31, 2016, with an IR of 2.6 cases of nRVT per 100,000 live births. The incidence was stable over time (Figure 2) and between the two ICD eras (2.8/100,000 live births between 1992 and 2003 versus 2.4/100,000 live births between 2003 and 2016).

Risk Factors for nRVT
Among the risk factors assessed for development of nRVT, respiratory distress syndrome (odds ratio [OR], 8.01; 95% CI, 4.90 to 13.1), congenital heart disease (OR, 9.1; 95% CI, 5.05 to 16.4), central venous catheterization (OR,
3.9; 95% CI, 1.89 to 7.93), maternal preeclampsia (OR, 2.8; 95% CI, 1.6 to 4.79), and maternal diabetes (OR, 2.36; 95% CI, 1.36 to 4.07) conferred the highest risk (Table 2).

Unexpectedly, multivariate analysis showed an increase in birth weight per 100 g was associated with a 4% increase in nRVT. However, in the univariate analysis, higher birth weight was associated with lower odds of nRVT.

**Long-Term Outcomes**

After a total of 1316 person-years of follow-up among children with nRVT, the IR of the composite outcome of CKD, all-cause mortality, or HTN was 111.8 per 1000 person-years, compared with an IR of 2.6 per 1000 person-years in the comparator cohort (Table 3). The median time to first outcome was 11.1 years. The median time to HTN was 11.1 years and the median time to CKD was 11.3 years.

In the nRVT cohort, 49 children (58%) developed the composite outcome. None of the nRVT cohort developed ESKD during the study period. The combined outcome of CKD or all-cause mortality was reported in 39 children (46%)—of which fewer than five children died. A total of 33 children (39%) developed HTN. In the comparator cohort, only 3% (n=90,050) developed the composite outcome, 1% (n=32,016) developed CKD or mortality, and 2% (n=64,458) developed HTN. The median follow-up per patient was 14.8 (IQR, 9.7–20.9) years. The first year after nRVT holds the greatest risk of developing these adverse outcomes (Figure 3). The adjusted HR of the composite outcome was 15.5 (95% CI, 11.7 to 20.6; P<0.001) compared with the comparator cohort. nRVT was associated with an increased risk of CKD or all-cause mortality with an adjusted HR of 12.3 (95% CI, 8.9 to 16.8; P<0.001) (Table 3). nRVT was also associated with an increased risk of HTN (adjusted HR, 15.7; 95% CI, 11.1 to 21.1; P<0.001).

| Table 1. Baseline demographic and clinical characteristics of the nRVT cohort and comparator cohort in Ontario between 1992 and 2016 |
|-----------------|-------------------|-------------------|
| Baseline Characteristics | nRVT (n=85) | Comparator (n=3,010,525) |
|-----------------|-------------------|-------------------|
| Age (d) at index, median (IQR) | 1 (0–4) | 1 (0–4) | 0.01 |
| Males, n (%) | 54 (64%) | 1,544,959 (51%) | 0.25 |
| Duration of index hospitalization, median (IQR) | 20 (9–34) | NA | |
| Birth weight (g), median (IQR) | 3226 (2830–3900) | 3400 (3060–3740) | 0.18 |
| Maternal age, median (IQR) | 29 (26–32) | 30 (26–33) | 0.18 |
| Rural status, n (%)a | 7 (8%) | 324,857 (11%) | 0.09 |
| Term (>37 wk gestation), n (%) | 26 (31%) | 1,678,153 (56%) | 0.53 |
| Preterm (<37 wk gestation), n (%) | 21 (25%) | 141,012 (5%) | 0.59 |
| Missing gestational age before 2002, n (%) | 38 (100%) | 1,187,286 (91%) | 0.46 |
| Missing gestational age after 2002, n (%) | 0 (0%) | 683 (<0.1%) | 0.03 |
| Material deprivation index, median (IQR)b | 3 (2–4) | 3 (2–4) | 0.03 |
| **Neonatal comorbidities** | | | |
| Congenital heart disease, n (%) | 25 (30%) | 40,372 (1%) | 0.84 |
| Sepsis, n (%) | 7 (8%) | 64,417 (2%) | 0.28 |
| Respiratory distress syndrome, n (%) | 44 (52%) | 204,192 (7%) | 1.14 |
| Central venous catheters, n (%) | 15 (18%) | 17,260 (0.6%) | 0.62 |
| **Maternal comorbidities** | | | |
| Preeclampsia or eclampsia, n (%) | 17 (20%) | 165,200 (6%) | 0.45 |
| Diabetes (affecting pregnancy), n (%) | 17 (20%) | 199,416 (7%) | 0.40 |
| **Follow-up** | | | |
| Total (person-yr) | 1316 | 45,133,886 | — |
| Median, yr (IQR) | 14.8 (9.7–20.9) | 14.5 (9.2–21) | — |

nRVT, neonatal renal vein thrombosis; Stdiff, standardized difference; IQR, interquartile range; NA, not applicable because only the nRVT cohort had an index hospitalization when diagnosed with nRVT.

aFor baseline characteristics, if urban versus rural status was missing, urban status was assigned.
bMaterial deprivation index values are calculated based on years where data is available (1998–2016). For continuous variables, baseline characteristics are reported as medians with IQR in brackets.
The results of the sensitivity analysis were similar to the main analysis. The Kaplan–Meier curves showed that neonates who survived the first year after nRVT with no adverse outcomes continued to have elevated risk into adolescence (Supplemental Figure 1, A–C). When including prematurity in the Cox models, the HRs of all outcomes reduced slightly but the trend remained similar (Supplemental Table 2).

Discussion

This is the first population-based longitudinal cohort study of nRVT describing the epidemiology and long-term outcomes. We assembled the largest described cohort of neonates with RVT that spanned two decades and encompassed the entire Ontario population of >13 million residents. The universal access to publicly funded health care in Ontario provided a unique opportunity to study the changing incidence and outcomes of nRVT among the entire neonatal population in our province. The annual IR of nRVT in Ontario from 1992 to 2016 was 2.6 per 100,000 live births. Respiratory distress syndrome, congenital heart disease, presence of central venous catheters, and maternal pre-eclampsia and diabetes were the most important risk factors for nRVT. We determined that, after a median follow-up of approximately 15 years, patients with nRVT were at a 12-fold increased risk of CKD and/or all-cause mortality and a 16-fold increased risk of HTN compared with patients without nRVT. The first year after nRVT holds the greatest risk of developing adverse outcomes but an increased risk compared with the general pediatric population persists throughout adolescence.

Table 2. Risk factors associated with the development of nRVT

| Variables                     | Univariate Analysis | Multivariate Analysis |
|-------------------------------|---------------------|-----------------------|
|                               | Odds Ratio (95% CI) | P Value               |
| Sex                           | 1.65 (1.06 to 2.57) | 0.03                  |
| Age at index date             | 0.99 (0.97 to 1.03) | 0.95                  |
| Mothers age at birth          | 0.97 (0.94 to 1.01) | 0.15                  |
| Neonate’s weight at birth (/100 g) | 0.95 (0.92 to 0.98) | 0.003                |
| Deprivation quintile          |                     |                       |
| 2                             | 0.64 (0.25 to 1.62) | 0.35                  |
| 3                             | 1.19 (0.62 to 2.27) | 0.60                  |
| 4                             | 1.25 (0.58 to 2.70) | 0.57                  |
| 5                             | 0.87 (0.39 to 1.95) | 0.74                  |
| Rural status                  | 1.35 (0.62 to 2.92) | 0.45                  |
| Comorbidities before nRVT     |                     |                       |
| Congenital heart disease      | 30.7 (19.2 to 48.9) | <0.001                |
| Central venous catheters      | 37.2 (21.3 to 65.0) | <0.001                |
| Respiratory distress syndrome | 14.8 (9.64 to 22.6) | <0.001                |
| Sepsis                        | 4.11 (1.89 to 8.90) | 0.003                 |
| Maternal risk factors         |                     |                       |
| Preeclampsia or eclampsia     | 4.31 (2.53 to 7.33) | <0.001                |
| Diabetes affecting pregnancy  | 3.53 (2.07 to 6.00) | <0.001                |

nRVT, neonatal renal vein thrombosis.

Table 3. Adverse outcomes among patients with nRVT in Ontario from 1992 to 2016

| Long-Term Outcomes          | nRVT (n=85) | Comparator (n=3,010,525) | Stdiff | P Value |
|-----------------------------|-------------|--------------------------|--------|---------|
| Composite outcome, n (%)a   | 49 (58%)    | 90,050 (3%)              | 1.48   |         |
| IR per 1000 person-yr       | 111.8       | 2.56                     |        |         |
| Unadjusted HR (95% CI)      | 42.3 (28.9 to 62.1) | Ref.                     |        | <0.001  |
| Adjusted HR (95% CI)b       | 15.5 (11.7 to 20.6) | Ref.                     |        | <0.001  |
| CKD or mortality, n (%)     | 39 (46%)    | 32,016 (1.1%)            | 1.25   |         |
| IR per 1000 person-yr       | 66.5        | 0.9                      |        |         |
| Unadjusted HR (95% CI)      | 67.5 (46.8 to 97.4) | Ref.                     |        | <0.001  |
| Adjusted HR (95% CI)        | 12.3 (8.9 to 16.8) | Ref.                     |        | <0.001  |
| Hypertension, n (%)         | 33 (39%)    | 64,458 (2.1%)            | 1.02   |         |
| IR per 1000 person-yr       | 53.2        | 1.83                     |        |         |
| Unadjusted HR (95% CI)      | 30.0 (19.8 to 45.5) | Ref.                     |        | <0.001  |
| Adjusted HR (95% CI)        | 15.7 (11.1 to 21.1) | Ref.                     |        | <0.001  |

nRVT, neonatal renal vein thrombosis; Stdiff, standardized difference; IR, incidence rate; HR, hazard ratio; Ref., reference.

aComposite of CKD, all-cause mortality, and hypertension.

bAdjusted for sex, congenital heart disease, respiratory distress syndrome, sepsis, maternal preeclampsia or eclampsia, and maternal diabetes.
Figure 3. | The risk of adverse outcomes after nRVT persists over 10 years of follow-up. In each figure, the red line represents the cumulative probability of adverse outcomes among patients with nRVT; the green line represents the risk among general neonatal population over time. Median time to outcome was calculated when at least 50% of the cohort developed the outcome. (A) Cumulative risk of CKD, all-cause mortality, or hypertension. (B) Cumulative risk of CKD and/or all-cause mortality. (C) Cumulative risk of hypertension. HR, hazard ratio; nRVT, neonatal renal vein thrombosis; NE, not estimated.
In the classic description of spontaneous nRVT, the thrombus first forms in the small vessels of the kidney and later extends into the renal vein. This had been identified in autopsy studies that identified reactive changes in cells nearby thrombi in small intrarenal veins that were absent near larger veins, suggesting that the renal vein becomes involved secondary to resultant stasis (20). Kidneys are vulnerable to thrombosis due to slow perfusion through the double capillary network, especially in the context of hemoconcentration or hypercoagulability. This process may occur antenatally, because several cases of nRVT have been diagnosed prenatally (21).

The incidence of nRVT across 24 years in Ontario was found to be 2.6 per 100,000 live births, which is similar to the finding by Bökenkamp et al. (5) that estimated the annual IR in Germany from 1993 to 1994 to be 2.2 per 100,000 live births. Similar to previous findings, the median age of nRVT diagnosis in our cohort was 1 day. Median age of nRVT in term infants has been reported as 1–3 days and in preterm infants has been reported as 8 days (1,3).

The most contributory neonatal risk factors in our study were respiratory distress syndrome, congenital heart disease, and presence of central venous catheters. Both respiratory distress syndrome and congenital heart disease are associated with increased risk of thrombosis through alterations in coagulation systems (22,23). Additionally, congenital heart disease predisposes neonates to thrombosis due to alterations in blood flow (23). We found that central venous catheterization conferred a threefold increased risk of developing nRVT. Indwelling catheters predispose to renal vein thrombosis by endothelial injury of the large vessels. In our study, 18% of the nRVT cohort had central venous catheterization, which is consistent with previous reports of indwelling catheters being associated with 20% of nRVT cases (2). This is unlike other forms of neonatal thromboses, in which 89% of cases are associated with indwelling catheters (3).

Previous studies reported that male sex is associated with nRVT (1–3). We used logistic regression analysis to simultaneously adjust for all potential risk factors and found that male sex was not significantly associated with the development of nRVT. Prematurity has been reported as the most frequently reported comorbidity in neonates with RVT (2). Our databases only had prematurity data from 2002 onward. Only 47 cases of nRVT were identified between the years of 2002–2016 and, therefore, this was not assessed as a risk factor. Unexpectedly, in the multivariate analysis, we found that an increase in birth weight by 100 g was associated with a 4% increase in the risk of nRVT. In contrast, in the univariate analysis, higher birth weight was associated with lower risk of nRVT. We believe that this conflicting finding in the multivariate analysis is attributable to confounding arising from the low number of neonates with RVT. Due to the small number of cases, our data would not support other detailed analyses such as looking for effect modification.

To our knowledge, no previously reported studies have assessed the long-term adverse outcomes after nRVT at a population level. Existing literature comes from studies from single centers with short follow-up times and small sample sizes. In our study, 39% of patients developed HTN after nRVT, which is similar to previous reports of 31% (7) to 34% (8). The proportion of patients that were diagnosed with CKD or all-cause mortality in our study (46%) was slightly higher than the previously reported 29% (8). This may be due to the fact that the median follow-up time in our study was long enough to allow for development of CKD. Because fewer than five deaths occurred, we could not provide mortality data separately due to privacy policies governing the data we used for this study. Notably, no cases developed ESKD during the study period, therefore ESKD was not the cause of death of any of the patients. Prematurity is an important confounder in the link between nRVT and the future risk of CKD and HTN. In our main multivariate analysis for the long-term outcomes, we adjusted for various neonatal and maternal risk factors but did not include prematurity because this data was not available before 2002. However, we performed a sensitivity analysis in which we included prematurity as a covariate and observed a slight reduction in the hazard estimates of all outcomes but the trend remained similar to the main analysis (Supplemental Table 2). Overall, our work and previous studies highlight the important association between nRVT and adverse long-term kidney outcomes.

This study was limited to analyzing only routinely collected information available in population health databases. Consequently, certain information that would have more fully characterized clinical course was unavailable, including treatments, laboratory investigations, and whether nRVT was unilateral or bilateral. Additionally, certain databases were not available for the entirety of the study period. MOMBABY began reporting gestational age only in 2002 and there is no other linked record of gestational age before 2002 available at ICES. However, beyond 2002, there were no missing gestational ages in the nRVT cohort and only 683 (<0.1%) missing ages in the comparator cohort. Also, the material deprivation index is only available for years beyond 1998. The validity of the codes used to identify nRVT have not been validated—the sensitivity and specificity are unknown. An additional limitation is that the diagnostic codes to report CKD and HTN have not yet been validated in the pediatric population. These codes have been validated in adult populations with a high specificity of >94% but low sensitivity of 33% in adult populations (24). Similarly, ESKD and mortality have been validated in an adult population with a sensitivity of 94% and specificity of 100% (25,26).

In conclusion, patients with nRVT remain at higher risk than the general neonatal population of long-term morbidity and/or mortality, including HTN and CKD or all-cause mortality, suggesting the need for close follow-up over subsequent years after nRVT to monitor and initiate early intervention for these adverse sequelae.

Acknowledgments
We are grateful to Dr. Hsien Seow, senior scientist at ICES for his support of this project.

Author Contributions
G. Babe, A.K.C. Chan, E.K. Darling, A.C. Ouellette, R. Perez, and B. Sivapathasundaram reviewed and edited the manuscript; G. Babe, E.K. Darling, A.C. Ouellette, R. Perez, and B. Sivapathasundaram were responsible for formal analysis; G. Babe, R. Perez, and B. Sivapathasundaram were responsible for data curation;
R. Chanchlani was responsible for investigation; A.K.C. Chan, R. Chanchlani, E.K. Darling, and A.C. Ouellette conceptualized the study; A.K.C. Chan, R. Chanchlani, E.K. Darling, A.C. Ouellette, and R. Perez were responsible for methodology; A.K.C. Chan, R. Chanchlani, E.K. Darling, and R. Perez provided supervision; A.C. Ouellette wrote the original draft; and all authors revised the manuscript.

Disclosures

All authors have nothing to disclose.

Funding

This work was supported by Michael DeGroote School of Medicine McMaster Medical Student Research Excellence Scholarship Awards to A.C. Ouellette, and by a Kidney Foundation of Canada biomedical research grant (KFOC190016) awarded to R. Chanchlani. A.K.C. Chan was supported by the McMaster Children’s Hospital/Hamilton Health Sciences Foundation Chair in Pediatric Thrombosis and Hemostasis. This study was also supported by ICES, a nonprofit research institute sponsored by the Ontario Ministry of Health and Long-Term Care.

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000912019/-/DCSupplemental. 

Supplemental Table 1.
Supplemental Table 2.
Supplemental Appendix.
Supplemental Figure 1.

References

1. Nowak-Göttl U, von Kries R, Göbel U: Neonatal symptomatic thromboembolism in Germany: Two year survey. Arch Dis Child Fetal Neonatal Ed 76: F163–F167, 1997

2. Kühle S, Massicotte P, Chan A, Mitchell L: A case series of 72 neonates with renal vein thrombosis. Data from the 1-800-NO-CLOTS Registry. Thromb Haemost 92: 729–733, 2004

3. Schmidt B, Andrew M: Neonatal thrombosis: Report of a prospective Canadian and international registry. Pediatrics 96: 939–943, 1995

4. Kaplan BS, Chesney RW, Drummond KN: The nephrotic syndrome and renal vein thrombosis. Am J Dis Child 132: 367–370, 1978

5. Bökenkamp A, von Kries R, Nowak-Göttl U, Göbel U, Hoyer PF: Neonatal renal venous thrombosis in Germany between 1992 and 1994: Epidemiology, treatment and outcome. Eur J Pediatr 159: 44–48, 2000

6. Winyard PJ, Bhardwaj A, Bhardwaj R, Dillon MJ, van’t Hoff W, Trompeter R, Lissauer R, Aird W, Rees L: Perinatal renal venous thrombosis: Presenting renal length predicts outcome. Arch Dis Child Fetal Neonatal Ed 91: F273–F278, 2006

7. Mocan H, Beattie TJ, Murphy AV: Renal venous thrombosis in infancy: Long-term follow-up. Pediatr Nephrol 5: 45–49, 1991

8. Marks SD, Massicotte MP, Steele BT, Matsuell DG, Filler G, Shah PS, Perlman M, Rosenblum ND, Shah VS: Neonatal renal venous thrombosis: Clinical outcomes and prevalence of prothrombotic disorders. J Pediatr 146: 811–816, 2005

9. Kosch A, Kuwertz-Bröking E, Heller C, Kurnik K, Schobess R, Nowak-Göttl U: Renal venous thrombosis in neonates: Prothrombotic risk factors and long-term follow-up. Blood 104: 1356–1360, 2004

10. Moudgil A: Renal venous thrombosis in neonates. Curr Pediatr Rev 10: 101–106, 2014

11. Lau KK, Stofman JM, Williams S, McCusker P, Branda L, Patel S, Chan AK: Canadian Pediatric Thrombosis and Hemostasis Network: Neonatal renal vein thrombosis: Review of the English-language literature between 1992 and 2006. Pediatrics 120: e1278–e1284, 2007

12. Duncan RE, Evans AT, Martin LW: Natural history and treatment of renal vein thrombosis in children. J Pediatr Surg 12: 639–645, 1977

13. Government of Canada Statistics Canada: Table 17-10-0040-01 Estimates of the components of international migration, quarterly. 2018. https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1710004001. Accessed June 9, 2020

14. Government of Canada Statistics Canada: Table 17-10-0020-01 Estimates of the components of interprovincial migration, quarterly. 2018. https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1710002001. Accessed June 9, 2020

15. Government of Canada Statistics Canada: Table 17-10-0009-01 Population estimates, quarterly. 2018. https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1710000901. Accessed June 9, 2020

16. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM; RECORD Working Committee: The Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 12: e1001885, 2015

17. Matheson FI, Dunn JR, Smith KIW, Moineddin R, Glazier RH: Development of the Canadian Marginalization index: A new tool for the study of inequality. Can J Public Health 103(Suppl 2): S12–S16, 2012

18. Austin PC: Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 38: 1228–1234, 2009

19. Schoenfield D: Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika 67: 145–153, 1980

20. Morison JE: Renal venous thrombosis and infarction in the newborn. Arch Dis Child 20: 129–134, 1945

21. Moaddah A, Shamshirsaz AA, Ruano R, Salmanian B, Lee W, Belfort MA, Espinoza J: Prenatal diagnosis of renal vein thrombosis: A case report and literature review. Fetal Diagn Ther 39: 228–233, 2016

22. Mahasandanan C, Hathaway WE: Circulating anticoagulants in the newborn: Relation to hypercoagulability and the idiopathic respiratory distress syndrome. Pediatr Res 7: 670–673, 1973

23. Silvey M, Brandão LR: Risk factors, prophylaxis, and treatment of venous thromboembolism in congenital heart disease patients. Front Pediatr 5: 146, 2017

24. Fleet JL, Dixon SN, Shariff SZ, Quinn RR, Nash DM, Harel Z, Garg AX: Detecting chronic kidney disease in population-based administrative databases using an algorithm of hospital encounter and physician claim codes. BMC Nephrol 14: 81, 2013

25. Jha P, Deboer D, Sykora K, Naylor CD: Characteristics and mortality outcomes of thrombolysis trial participants and non-participants: A population-based comparison. J Am Coll Cardiol 27: 1335–1342, 1996

26. Tu K, Campbell NR, Chen Z-L, Cauch-Dudek KJ, McAlister FA: Accuracy of administrative databases in identifying patients with hypertension. Open Med 1: e18–e26, 2007

Received: December 11, 2019 Accepted: May 26, 2020