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RESEARCH ARTICLE

Positive impacts of universal newborn screening on the outcome of children with sickle cell disease in the province of Quebec: A retrospective cohort study

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Abstract

A universal newborn screening program for sickle cell disease (uNS-SCD) was implemented in the province of Québec (Qc) in November 2013, close in time to the recommendation of early initiation of hydroxyurea (HU) therapy for children. This retrospective cohort study evaluated the impact of such a program on children first seen between January 2000 and December 2019. Cohorts pre-SCD-uNS in Qc (pre-QcNS) (n = 253) and post-QcNS (n = 157) for patients seen prior to or after Nov 2013 were compared. Kaplan-Meier curves, Poisson regression, and logistic regressions were used for statistical analysis, using Software R version 4.2.1. Median age at first visit decreased significantly from 14.4 [interquartile range: 2.4–72.0] to 1.2 months [1.2–57.6] ($p < 0.001$). The percentage of children born in Qc undiagnosed at birth and referred after a first SCD-related complication dropped from 42.6% to 0.0% ($p < 0.0001$). The median age of HU introduction for patients with SS/Sβ°-thalassemia decreased from 56.4 [31.2–96.0] to 9.0 months post-QcNS [8.0–12.1] ($p < 0.001$). Event-free survival improved significantly for any type of hospitalization as well as for vaso-occlusive crisis (VOC) (140–257 days ($p < 0.001$) and 1320 vs. 573 days ($p < 0.002$), respectively), resulting in a reduction from 2 [interquartile range: 1.0–3.0] to 1.0 hospitalizations/patient-year [0.6–1.4] ($p < 0.001$). Children with SS/Sβ°-thalassemia referred post-QcNS also had fewer emergency department visits for VOC (RR: 0.69, 95% confidence interval: 0.54–0.88). The Universal NS program allows early detection and referral of children with SCD to comprehensive care centers. Earlier access ensures that children benefit from essential preventive interventions, reducing disease burden. This cohort study highlights that uNS-SCD is an essential public health measure.

KEYWORDS
hemoglobinopathies, neonatal screening, newborn screening, sickle cell anemia, sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD) is a severe autosomal recessive blood disorder due to beta-globin gene mutation. Although the prevalence is greater in Africa, India, and South America, SCD is also the most prevalent genetic disease in most European countries and North America. Worldwide 300,000 infants are born yearly with hemoglobin disorders such as SCD [1–3]

The use of penicillin prophylaxis was found to decrease life-threatening infections in infants with SCD by 84% [4]. This study was instrumental in including SCD in the universal newborn screening (uNS) program. Advocated by the National Institutes of Health Consensus Development Conference in 1987 [5], this led to its implementation in all American states by 2006 [6], some European countries, the United Kingdom, and later in Canada [7, 8]. In the province of Québec (Qc), a targeted SCD screening began in 1988 [9] but was limited to a few Montréal hospitals. In 2013, the Ministry of Health and Social Service introduced SCD-uNS in the greater Montréal area, which expanded to Qc in 2016.

Allowing the use of preventive interventions and diagnostic tests, SCD-uNS resulted in the survival of almost all children into adulthood in a well-resourced multidisciplinary care system [10–12]. In 2014, the US National Heart, Lung, and Blood Institute (NHLBI) recommended that hydroxyurea (HU) be offered preventively in children of 9–12 months of age regardless of clinical severity [13]. To our knowledge, there has been no study evaluating the impact of SCD-uNS in Canada, and the inclusion of early HU therapy. The primary objective of this study was to evaluate the impact of SCD-uNS in Qc (QcNS) on access to specific SCD care and disease severity during a 5-year follow-up period, a program that was introduced in Qc concomitantly to the 2014 NHLBI recommendation on early HU use.

2 | METHODOLOGY

2.1 | Study design and setting

We conducted a retrospective cohort study of patients referred to Centre Hospitalier Universitaire Sainte-Justine (CHUSJ) (Montréal, Canada). In November 2013, our specialized multidisciplinary program was officially designated as one of the referral centers for infants with SCD identified through QcNS.

Reasons for referral were regrouped into two categories: patients referred following NS in Qc (either targeted or SCD-uNS), and patients unscreened at birth in whom a diagnosis was performed following SCD-related complication (DRC).

To be included patients had to: have a first appointment between January 1, 2000, and December 31, 2019, receive a diagnosis of SCD, with a documented quantitative hemoglobin electrophoresis, and have a follow-up for at least 2 years. Two cohorts were defined based on historical periods: pre-QcNS included patients referred prior to the implementation of the QcNS (until Oct 2013), a period where patients were not screened or eventually had a targeted NS; post-QcNS included patients referred after November 1, 2013.

2.2 | Data collection

Data were collected via the CHUSJ archives, available from 2000 to 2014 from paper medical charts, and from 2014 from digital files ("Chartmax" file). Data included gender, birthplace, SCD genotype, age at the first visit to the SCD clinic program, reason for referral, time of first hospitalization for any cause as well as specifically for vaso-occlusive crisis (VOC), and emergency visits for any cause and VOC. Use of medications such as antibiotic prophylaxis, and age of introduction of HU were also recorded, as well as age at first Transcranial Doppler (TCD) and TCD results when available.

2.3 | Outcomes definition

Emergency visits included all visits to our emergency department as well as unplanned emergency visits to our SCD clinic. The following definitions were used for major SCD-related events: VOC defined as acute non-infectious, non-traumatic pain requiring analgesics for > 12 h and/or hospital admission; acute chest syndrome (ACS) defined as a new pulmonary infiltrate on chest X-ray, with pain, cough, fever (≥38.5°C) or hypoxemia. Given the overlapping definition of pneumonia in young children, the latter events were pooled with ACS. In all patients assessed by TCD at ages 2 and 5 years old (patients with Hb SS or S β°-thalassemia), TCD velocities were considered abnormal when they were ≥200 cm/s and conditional when they were ≥170 cm/s but < 200 cm/s [14].

Given that patients with HbSS or Sβ^0-thalassemia usually have a more severe course than those with HbSC or Sβ^+-thalassemia, we further stratified our analysis into two main SCD subgroups: HbSS/Sβ^0-thalassemia (SS/Sβ^0) and SC/Sβ^+-thalassemia (SC/Sβ^+).

To limit the variability related to reference age at the first visit and other factors between cohorts by period, event-free survival (EFS) analyses were limited to a group of patients referred and managed before the age of 5 and followed for 5 years. Considering that SS/Sβ^0 patients were at greater risk of early complications than SC/Sβ^+patients, analysis was performed by subgroups.

2.4 | Statistical analysis

Descriptive analyses were initially performed on both cohorts. Summary statistics were presented as frequencies and percentages for categorical variables, and median, interquartile range, mean, and standard deviation for continuous variables. Chi-square or t-tests were used for group comparisons. Odds ratios (ORs) for the logistic model, hazard ratios (HRs) for Cox proportional models, and incidence rate ratios or differences in incidence rate (IRR or DR) for the Poisson model

were presented with their 95% confidence intervals. Kaplan-Meier curves were generated to evaluate event-free survival (EFS). The event was defined as the time of first hospitalization for any cause, as well as the time of first hospitalization for VOC. Censoring occurred when the event of interest was not observed up to a 5-year follow-up. Cox model was then used for multivariate analysis adjusting for age at the first visit, gender, place of birth, follow-up period, and identification through the QcNS. We also evaluated the number of visits to the emergency room for any cause as well as for pain crisis using multivariate analysis by Poisson regression adjusting for the same variables. For each SCD complication (acute chest syndrome/pneumonia, abnormal TCD), we also adjusted the same variables in a multivariable logistic regression. Statistical analysis was performed using the software R version 4.2.1. A *p*-value of 0.05 was used as the threshold for statistical significance. Given that our main event was the first occurrence of hospitalization, no adjustment to account for multiplicity was made on all secondary outcomes.

3 | RESULTS

3.1 | Patient characteristics

Our single-center study evaluated patients referred to the CHUSJ hemoglobinopathy program. To our knowledge, two-thirds of pediatric patients with hemoglobinopathies in the province of Quebec are being followed to our center.

A total of 658 patients' medical charts were reviewed; of the 248 excluded patients, most were excluded as they had their first visit prior to January 1, 2000, or after Dec 31, 2019. 410 met the inclusion criteria, of which 253/410 (61.7%) were in pre-QcNS and 157/410 (38.3%) in the post-QcNS cohort (Figure 1). Although there were no differences between genotypes subgroups (SS/Sβ^0 vs. SC/Sβ^+), fewer SC patients were found in the post-QcNS period. Of the 157 patients referred post-QcNS, 102 were born in the province of Qc; 95 of them (95/157 = 60.5%) were directly referred to our program, while seven (4.4%) were seen in a different program and later referred for follow-up care.

3.2 | Positive impact of QcNS

The introduction of universal QcNS markedly increased the percentage of patients seen early in life (Table 1) and reduced the median age at the first visit from 14.4 [interquartile range: 2.4–72] to 1.2 months [1.2–57.6] ($p < 0.001$), the difference is particularly marked for patients born in Qc. Consequently, the percentage of children born in Qc unscreened at birth and presenting later in life with DRC, decreased from 42.6% to 0% ($p < 0.001$). 24.7% of children born in Qc pre-QcNS failed to receive antibiotic prophylaxis and recommended vaccination for asplenic patients before the age of 5 years, in contrast to all children post-QcNS ($p < 0.001$). There was no death among the 410 patients evaluated.

3.3 | Impacts of QcNS in the population of children with SS/Sβ°thalassemia

3.3.1 | Age at introduction of HU

Since 2014, it has been recommended that all SS/Sβ^0 patients be offered HU at an early age. In this subgroup, the median age of HU-introduction decreased from a median of 54.0 (range, 31.2–96.0) pre-QcNS to 9 months (range, 8–12) post-QcNS ($p < 0.001$) (Figure 2). Similarly, the percentage of this patient's subgroup receiving HU by the age of 2 years old increased from 28.6% to 59.3% ($p = 0.003$). The overall percentage of patients with SS/Sβ° on HU was nevertheless statistically not different (82.8% [80/97] pre-QcNS vs. 89.7% [61/68] post-QcNS). The median time elapsed between the first visit and HU introduction for all patients with SS/Sβ°-thalassemia furthermore decreased after 2013 from 3.7 (range, 1.8–6.3) to 1.2 years (0.5–2.3) ($p < 0.001$).

3.3.2 | Hospitalizations

Given the relative youth of the QcNS, we chose to evaluate disease severity, we further carried out our analysis in the cohort of patients known to suffer from the most severe form of SCD (SS/Sβ^0) within the first 5 years of life. The number of hospitalizations decreased from 2 to 1.0 hospital/pt-year (95% confidence interval [95% CI] = 1.2–3.1; $p < 0.001$). Kaplan-Meier evaluating EFS for the median time to first hospitalization from the first day of referral significantly improved from 140 days pre-QcNS to 257 days post-QcNS versus ($p = 0.005$) (Figure 3A). Patients who benefited from NS also had better EFS compared to those unscreened (NS vs. DRC: 1047 vs. 292 days, $p = 0.034$) (Figure 3C).

We then used the Cox Proportional Hazard model. Hospitalization risk was lower for screened children versus unscreened children (DRC) born in Qc (HR 0.32, 95% CI 0.13–0.75, $p = 0.008$). The risk of hospitalization was lower for children born in Qc (HR 0.79, 95% CI 0.45–1.37, $p = 0.395$) although statistically not significant. The risk of hospitalization for children SS/Sβ° first seen before the age of 6 months vs seen later was nevertheless greater (HR 0.28, 95% CI 0.12–0.67, $p = 0.004$). Boys were at greater risk of hospitalization (HR 1.37, 95% CI 1.01–1.85, $p = 0.04$) (Appendix A and Table 2).

Hospitalizations for VOC

Median time to VOC-hospitalization EFS was significantly longer post-QcNS (573 days vs. 1320 days, $p = 0.002$) (Figure 2B) and for those who benefited from NS (NS vs. DRC: 1047 vs 292 days, p = 0.039) (Figure 3D).

On multivariable analysis, children diagnosed with NS born in Qc also had a lower risk of VOC hospitalization (HR 0.86, 95% CI 0.45–1.65, $p = 0.66$). Such risk was also higher for children pre-QcNS (HR 2.19, 95% CI 1.45-3.30, $p < 0.001$). Children referred before the age of 6 months tended to have improved VOC-hospitalization EFS (HR 0.51, 95% CI 0.25–0.1.05, $p = 0.07$) (Appendix A and Table 3).

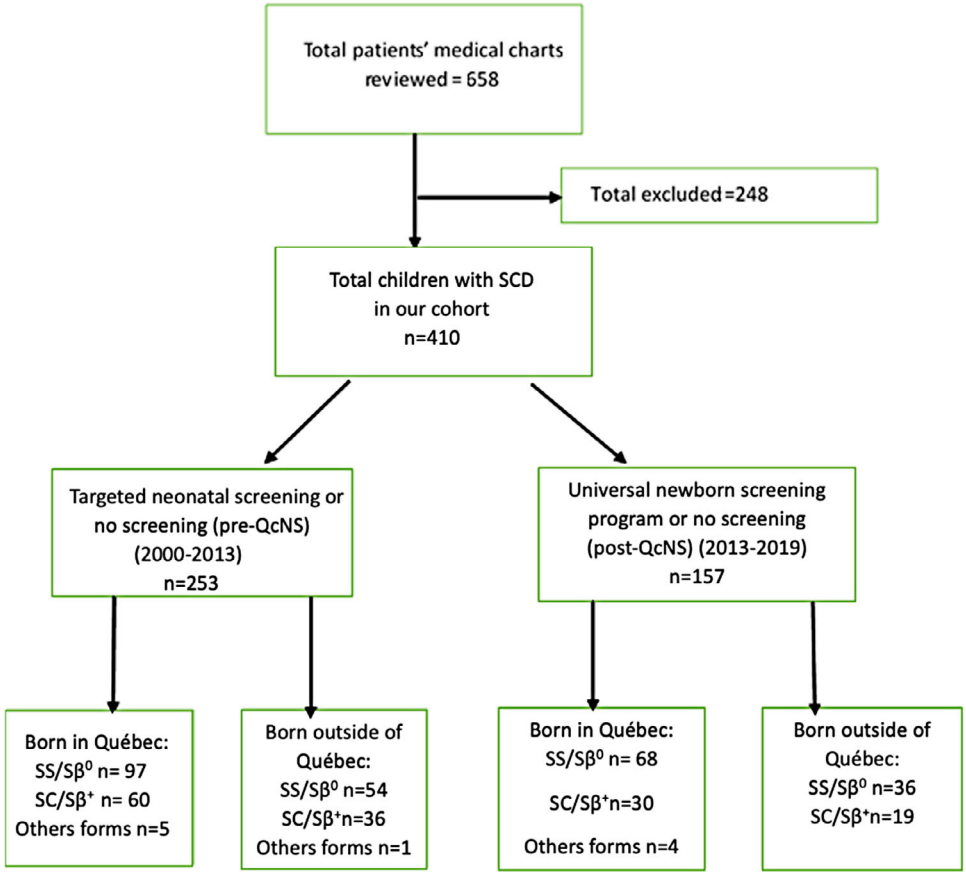

FIGURE 1 Flow diagram of our cohort.

Visit to the Emergency Department for all causes

Poisson regression was performed for the number of emergency visits (including Emergency Department [ED] visits and unscheduled visits to the hematology clinic), adjusting for the same variables. Children who benefited from NS required significantly fewer ED visits (NS vs. DRC, IR −0.18, 95%CI −0.30–0.06, $p = 0.003$). The number of ED visits was also higher in the pre-QcNS cohort (IR 0.91, 95%CI 0.81–1.00, $p < 0.001$). Similar to EFS, boys had a significantly higher number of ED visits (0.24, 95%CI 0.17-0.32, $p < 0.001$). Finally, children referred prior to the age of 6 months had more ED visits (all causes combined) (IR −0.41, 95%CI −0.54–0.28, $p < 0.001$) (Appendix B and Table 4).

Visit to the Emergency Department for VOC

Similarly, children unscreened at birth and diagnosed later in life had a significantly greater risk of ED visits for VOC (IR −0.25, 95%CI −0.48-0.02, $p = 0.03$). Children referred to pre-QcNS also had a greater number of ED visits (IR 1.44, 95%CI 1.22–1.67, $p < 0.001$). Boys had again a significantly higher number of ED visits (IR 0.38, 95%CI 0.23-0.54, $p < 0.001$). Children first seen after the age of 6 months had fewer ED visits for VOC (Appendix B and Table 5).

Other SCD-related events

A total of 108 children with SS/Sβ° developed at least one episode of either ACS and/or pneumonia. Table 6 shows the risk of ACS and/or pneumonia as a function of several variables. We found no difference between ACS/pneumonia and follow-up period even if patients with ACS/ tended to be higher pre-QcNS patients (OR 1.48, 95%CI 0.71–3.10, $p = 0.3$), and that screened children in Quebec tended to have a lower risk of developing acute chest syndrome/pneumonia (OR 0.68, 95%CI 0.15–2.77, $p = 0.6$).

Of the entire cohort of patients with SS/Sβ°-thalassemia, only six children (3.2%) had abnormal and one conditional TCD. Of these, two had confirmed Moya-Moya syndrome on angio-MRI. Median age at first TCD was 2.1 years for children who benefited from NS [interquartile range, 2.0–2.3] versus 5.3 years for unscreened children [interquartile range 2.4–8.5], ($p < 0.001$). Although our analyses tend to show a reduced risk of vasculopathy post-QcNS, as well as for children who benefited from an NS, the small number of patients with such complications limits our analyses.

3.3.3 | Impacts of QcNS in the population of children with SC/Sβ^{+}thalassemia

Patients with SC/Sβ^{+}thalassemia had better EFS than SS/Sβ^{0}-thalassemia (338 vs. 183 days, $p < 0.001$) as well as better EFS for VOC (1825 vs. 851 days, $p < 0.001$). However, we observed no statistical differences in EFS and emergency visits in SC/Sβ^{+}thalassemia cohorts, within the first 5 years of life.

TABLE 1 : Cohort characteristics.

		N (%)	Pre-QcNSP	Post-QcNSP	*p*-Value
# patients	410	253 (61.7)	157 (38.3)		
Gender					
	Male	204 (49.8)	122 (48.2)	82 (52.2)	0.47
	Female	206 (50.2)	131 (51.8)	75 (47.8)	
Birthplace					
	Quebec	264 (64.4)	162 (64)	102 (65)	0.85
	Outside-Qc	146 (35.6)	91 (36)	55 (35)	
Genotype					
	SS/Sβ^0	255 (62.2)	151(59.7)	104(66.2)	0.38
	SC/Sβ^+	145 (35.4)	96(37.9)	49(31.2)	
	Others forms	10 (2.4)	6 (2.4)	4 (2.6)	
Screened in Qc					
	Yes	192 (46.8)	90 (35.6)	102 (64.3)	<0.001
Reason for referral					
	QcNS*	178 (43.4)	83 (32.8)	95 (60.5)	0.002
	DRC*	232 (56.6)	170 (67.2)	62 (39.5)	
Age at 1st visit					
	<3month	176 (42.9)	82 (32.4)	94 (59.9)	<0.001
	3-6month	15 (3.7)	14 (5.5)	1 (0.6)	
	>6month	219 (53.4)	157 (62.1)	62 (39.5)	

Note: Pre-QcNS: targeted newborn screening or no screening in the province of Quebec; Post-QcNS: universal newborn screening program or no screening; DRC: patients unscreened at birth, presenting with SCD-related disease complication and previously unknown.

4 | DISCUSSION

Our research illustrates several positive impacts of the uNS program. As expected, this was associated with a significant reduction in the age of referral, enabling a marked improvement in the use of preventive measures and the introduction of HU. As a result, we observed a significant decrease in disease burden as illustrated by reduced hospitalization rate, EFS, and emergency visits in patients with SS/Sβ^0-thalassemia.

Our study demonstrates a net benefit from the introduction of QcNS in November 2013. As expected, the average age of care for children born in Qc fell drastically. Before November 2013, more than 40% of Qc children were unscreened at birth and presented later in life, with SCD-related complications. Such unscreened children were at greater risk of further hospitalizations and emergency visits, failed to receive early antibiotic prophylaxis, adequate vaccination for asplenic patients as well as systemic detection of early-SCD-related complications.

In our cohort, the median age at first visit decreased drastically from 14.4 to 2 months. In London, a similar study of 252 children also showed that screened patients benefited from early management, with a median age at clinic referral of 2.7 months [11].

The unique aspect of the QcNS is that it was deployed almost simultaneously with the recommendation of early HU use [13]. Therefore, another main benefit of QcNS is to favor the early use of such disease-modifying agents as a primary preventive intervention. We indeed demonstrate a marked decrease in the age of HU introduction and a significant increase in the percentage of patients receiving HU prior to the age of 2 years old. This may also have encouraged the use of HU in other patients, as illustrated by the decrease in the delay between the time of the first visit and the introduction of HU post-QcNS. Furthermore, the median age of introduction of HU decreased remarkably from 56.4 to 9 months, whereas the median age did not vary significantly in non-SS patients. In a Belgian cohort, Le et al. also showed that the age of introduction to HU for screened children was lower (2.6 years, range, 0.6–7.9 years vs. 4.5 years, range, 0.7–31.9 years) [15]. Our study was however not designed to assess the impact of HU use. Moreover, the high percentage of patients now on HU limits our ability to assess it. The benefit of the early introduction of HU on survival, reduction in disease severity, growth, and even socio-economic is however well established [16–18].

We illustrate the impact of the QcNS on disease severity by evaluating the hospitalization rate, EFS, and rate of emergency visits in patients with SS/Sβ^0-thalassemia. We observe a reduction of the hospitalization rate by half, an improvement in EFS and EFS-VOC, as well as a decrease in the number of emergency room visits for VOC. While we have no doubts that early referral of children with inherited diseases such as SCD is key to improving disease outcomes, other factors may also have influenced such outcomes. Improvement in the management of VOC, as well as modification in protocols for febrile illness, may also have contributed to a reduction in hospitalization

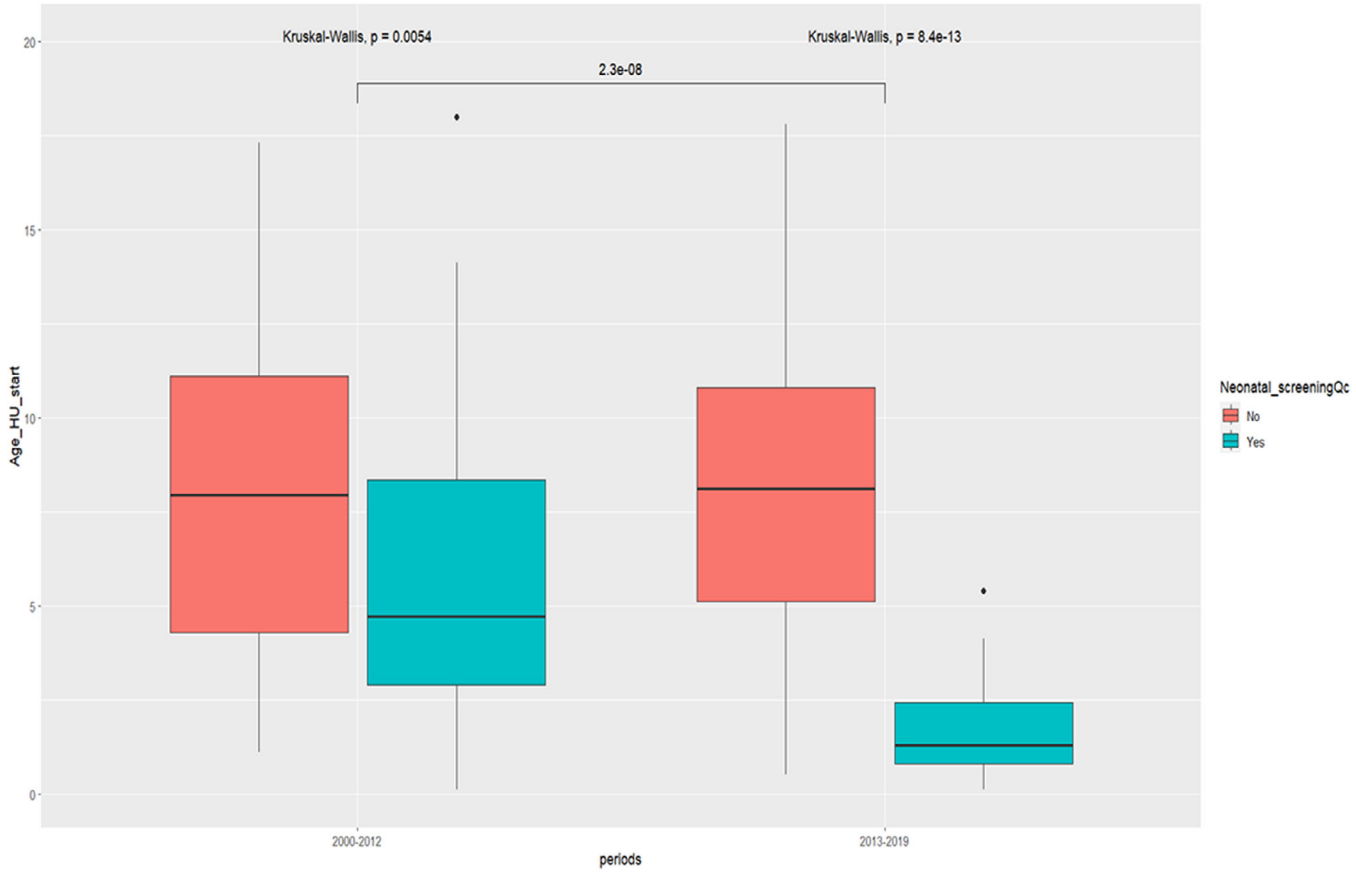

FIGURE 2 Evolution of median age at introduction of hydroxyurea by follow-up period as a function of Quebec universal newborn screening (QcNS).

rate [19, 20]. However, such modifications are less likely to explain a decrease in emergency visits and may therefore likely reflect an impact of the use of preventive measures, such as the use of HU therapy at an earlier age. Le et al. also demonstrated a benefit to NS in Belgium, as children who benefited from NS had better EFS for infectious episodes with bacteremia, and a lower rate of hospitalization as well as hospital days [15]. Earlier, Vichinsky et al. also demonstrated that children who received NS had a lower risk of early death [12].

In contrast, this decrease in post-NS hospitalization rate was nonsignificant for patients with SC/Sβ^+. It is possible that our analyses are limited by our sample size, and lower disease severity, particularly in the early years of life. A longer-term analysis will be needed to determine whether screened SC patients also are at lower risk of acute or chronic complications beyond the age of 5 years.

Our study has limitations. Given the relative youth of the QcNS, our current ability to assess its impact on longer-term complications is restricted. Its retrospective nature limits our capacity to evaluate the impact on patients' quality of life, even though we demonstrate a reduction in EFS without hospitalization. Further research will be needed to determine whether our observations are reproducible for all children screened in our province. However, we believe that our research is representative since more than 2/3 of the children with SCD followed in Qc have been referred to our program.

This work is unique as it is the only one to our knowledge to have studied the impact of universal NS in a Canadian province. Previously, Robitaille et al. had reported on the experience of targeted screening [9]. Our research thus enables us to consolidate the importance of such a universal screening program and its impact on SCD and should further encourage its implementation throughout Canada. Currently, seven provinces and two territories out of 13 currently offer universal NS in Canada.

5 | CONCLUSION

In Qc, a universal NS has enabled early detection and referral of children with SCD to comprehensive care centers. Earlier access to this expertise ensures that children benefit from essential preventive interventions such as adequate vaccination, prophylactic penicillin, early use of HU as well as caregiver education. These combined interventions may explain in part the reduction in acute events. This cohort study highlights that universal NSP of SCD is an essential public health measure.

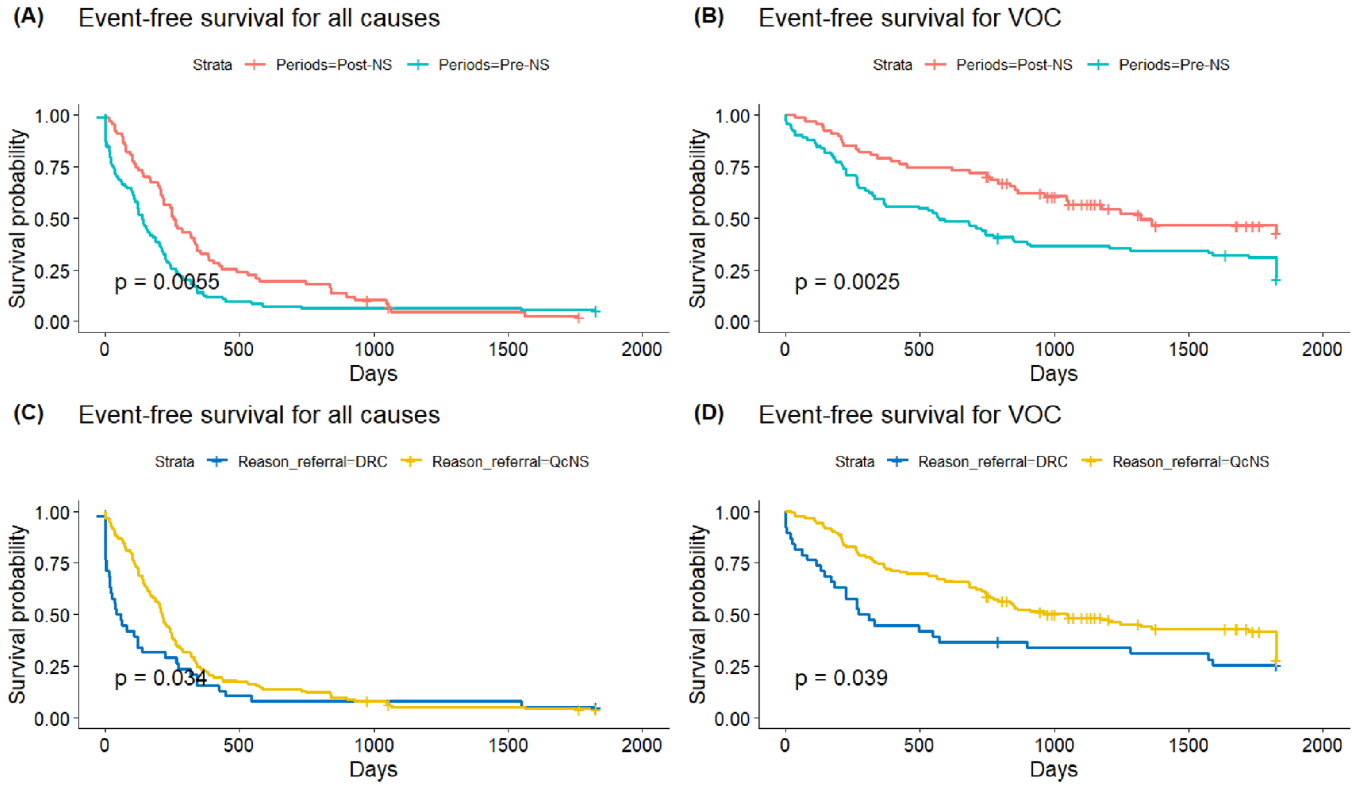

FIGURE 3 Univariable analyses for event-free survival (EFS); the event is defined as any cause of hospitalizations (A and C), or specifically as hospitalization for vaso-occlusive crisis (VOC) treatment (B and D). We compared EFS for patients with SS/Sβ^0thalassemia phenotype pre-QcNS (*turquoise*) versus post-QcNS (red) (A and B), as well as those who benefited from NS (yellow) versus unscreened children referred after first-disease complication (blue) (C and D).

AUTHOR CONTRIBUTIONS

Costa Kazadi was involved in the study design, chart review, data collection, analysis of the data, and writing of the manuscript. Thierry Ducruet was involved in data interpretation and statistical analysis and reviewed the manuscript. Stéphanie Forté and Nancy Robitaille were involved in the study design and supervision and reviewed the manuscript. Yves Pastore designed the study, supervised C Kazadi, and was involved in data interpretation, manuscript preparation, and review.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

FUNDING INFORMATION

Not applicable.

ETHICS STATEMENT

The study has been approved by our local IRB.

PATIENT CONSENT STATEMENT

Given the retrospective nature of the study, patient consent was waived in agreement with the local IRB.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

DATA AVAILABILITY STATEMENT

Research data are not shared. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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