

High Risk of Venous Thromboembolism in Klinefelter Syndrome

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Background—Klinefelter syndrome (KS) is the most common sex chromosome disorder. The genetic background is the extra X chromosome. Venous thromboembolism (VTE) has been observed among KS patients. The aim of the present study was to examine whether KS is associated with VTE.

Methods and Results—We followed up all hospital in- and outpatients (N=1085) in Sweden with a diagnosis of KS between January 1, 1969, and December 31, 2010, for diagnosis of VTE. The reference population was the total male populace of Sweden. We calculated standardized incidence ratios for VTE, adjusted for age, sex, education, time period, and region of residence. The standardized incidence ratio for KS was 6.43 (95% CI 5.15–7.93), with the highest ratio observed at young age. The standardized incidence ratios for VTE were 12.10 (95% CI 6.22–21.21) before age 30 years, 11.00 (95% CI 7.86–14.99) between ages 30 and 49 years, 4.83 (95% CI 3.23–6.95) between ages 50 and 69 years, and 2.07 (95% CI 0.74–4.53) for ages \geq 70 years. The cumulative incidence of VTE for KS patients was 8.6% at age 50 years and 20.8% at age 70 years.

Conclusions—KS is associated with high risk of VTE. KS could be considered a genetic hypercoagulable state. This has clinical implications for the prevention and diagnosis of VTE among patients with KS. (*J Am Heart Assoc.* 2016;5:e003567 doi: 10.1161/JAHA.116.003567)

Key Words: embolism • epidemiology • genetics • risk factors • thrombosis

Klinefelter syndrome (KS) is one of the most common chromosomal disorders and occurs in 1:500 to 1:1000 newborn male infants.^{1–3} KS, also known as 47,XXY, is the set of symptoms that result from \geq 2 X chromosomes in male persons. Gene dosage effects of the supernumerary X chromosome determine the clinical picture of KS.^{3,4} The primary features are hypogonadism and sterility.^{1–3} Symptoms are often subtle; only 25% of male persons with KS are diagnosed. Symptoms are sometimes more prominent and may include greater than average height, learning disabilities, less body hair, gynecomastia, and lack of libido. KS is often accompanied by other disturbances such as epilepsy, varicose veins, osteoporosis, abdominal obesity, metabolic syndrome, glucose intolerance, and type 2 diabetes mellitus.^{1–3} Venous thromboembolism (VTE) has also been described in a number

of case reports.^{5–7} In a cohort study of cause-specific mortality in 3518 KS patients, 8 cases of fatal pulmonary embolism were observed.⁸ The authors estimated a standardized mortality rate of 5.7 (95% CI 2.5–11.3).⁸ In another series of 412 patients with KS, 11 were affected by deep venous thrombosis.⁹ The incidence of deep venous thrombosis was 22.8 cases per 10 000 patient-years at risk. In the same study, 8 KS patients had pulmonary embolism. The frequency of pulmonary embolism was 16 cases per 10 000 patient-years at risk.⁹ Although these previous studies suggested an increased preponderance of VTE in KS patients, few VTE cases have been reported. It remains to be confirmed in a larger number of cases whether or not KS is a risk factor for VTE.

We hypothesized that KS may increase the risk of VTE. In this nationwide follow-up study, the risk of VTE in patients with KS was analyzed with the aim of determining whether KS is associated with VTE. The study used data from the total Swedish male population linked to the Swedish Hospital Register.

Methods

This study was approved by the ethics committee of Lund University, Sweden. The ethics committee waived informed consent as a requirement. Data used in this study represented information on all persons registered as residents of Sweden between 1969 and 2010. It included individual-level

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information on age, sex, socioeconomic occupational status, geographic region of residence, hospital and outpatient diagnoses, dates of hospital admissions, date of emigration, and date and cause of death. The data sources were multiple national Swedish data registers including the Swedish National Population and Housing Census, the Total Population Register, and the Swedish Hospital Register (the Hospital Discharge Register and the Hospital Outpatient Register).^{10–14} These registers were provided to us by Statistics Sweden and the National Board of Health and Welfare. Using the Swedish Hospital Register, we identified hospital inpatients and outpatients with diagnoses of KS in Sweden between January 1, 1969, and December 31, 2010. Data were linked using the individual personal identification numbers that are assigned to all persons in Sweden for their lifetimes. These numbers were replaced with serial numbers to maintain anonymity. The serial numbers were used to check that each person was entered only once for his or her first diagnosis of VTE diagnosis (in- or outpatient and death registers). The follow-up period ran from January 1, 1969, until a VTE event, death, emigration, or the end of follow-up on December 31, 2010, whichever came first. This register does not include data for hospital outpatients or patients treated at primary health care centers. Because KS is inborn, diagnosis of KS anytime during follow-up was taken into account.

Outcome Variables and Ascertainment of Cases

Cases of VTE, classified according to the World Health Organization *International Classification of Diseases* (ICD), 8th, 9th, and 10th revisions, were identified in the Hospital Discharge Register and the Hospital Outpatient Register 2001–2010 (Table 1). Only main diagnoses of VTE were considered to ensure high validity and to include mainly primary and not secondary VTE cases. The Swedish Hospital Discharge Register has nearly 90% overall validity or positive predictive values.^{10,14} The positive predictive value for cardiovascular disorders such as VTE, myocardial infarction, and stroke is ≈90% to 95%.^{10,14,15} In a Swedish study of male persons with VTE,

hospital records were available for 304 cases (1970–1998).¹⁵ A total of 289 of 304 cases (95%) of diagnosed VTE were judged to be diagnosed correctly.¹⁵ Only 12 cases (3.9%) were not diagnosed with an objectively verified method but were treated with oral anticoagulation because of strong clinical probability. In total, 277 cases (91%) were objectively diagnosed with methods such as phlebography, ultrasound, computed tomography scan, and pulmonary scintigraphy.¹⁵ The Hospital Outpatient Register has not been validated previously for VTE. Sultan et al recently found that 43% of pregnant VTE patients first recorded as outpatient were not accompanied by anticoagulant prescriptions, whereas this proportion was much lower than those patients first recorded in the inpatient register (9%). Moreover, for cases of nonspecific thrombophlebitis diagnoses, 25% had evidence of glucosaminoglycan polysulfate (C05BA01) prescriptions. We also used ATC (Anatomical Therapeutic Chemical) codes for anticoagulant drugs to validate the entire outpatient and inpatient registers with prescription of anticoagulant drugs after VTE diagnosis (B. Zöller, MD, PhD, H. Ohlsson, PhD, J. Sundquist, MD, PhD, and K. Sundquist, MD, PhD, unpublished data, 2016); however, the prescription register is available only from July 2005. The positive predictive value for inpatient diagnosis of VTE was similar to published data by Rosengren et al and Sultan et al (unpublished data).^{15,16} An outpatient diagnosis of VTE had less validity, similar to Sultan et al,¹⁶ but the presence of a VTE diagnosis on 2 occasions in outpatients was associated with high positive predictive value (ie, anticoagulant prescription), similar to what was observed in the study by Rosengren et al (unpublished data).¹⁵ Consequently, we classified only outpatient diagnosis of VTE if diagnosis had occurred 2 times for outpatients, whereas 1 event of VTE for inpatients was enough to be classified as VTE.

Main Predictor Variable

KS patients were identified from the Swedish Hospital Register (in- and outpatients) by ICD-8 (759.51, 310.53, 311.53, 312.53, 313.53, 314.53, 315.53), ICD-9 (758H),

Table 1. Venous Thromboembolism Manifestations in Klinefelter Syndrome Patients

	International Classification of Diseases codes			Venous Thromboembolism in Klinefelter Syndrome Patients, n (%)
	8th Revision	9th Revision	10th Revision	
Cerebral vein thrombosis	321	437G	I63.6, I67.6	0 (0)
Venous thrombosis of the lower extremities	451	451	I80	37 (43)
Portal vein thrombosis	452	452	I81	0 (0)
Other venous embolism or thrombosis	453	453	I82	27 (31)*
Pulmonary embolism	450	415B, 416W	I26	23 (26)
All venous thromboembolism				87 (100)

*One case was thrombophlebitis migrans, and 26 cases were in an unspecified vein.

and ICD-10 (Q98.0, Q91.1, Q98.2, and Q98.4) codes (main or secondary diagnosis). We did not have access to the mode of diagnosis, but in Sweden, chromosomal testing is a clinical routine when KS is suspected (Stefan Arver, personal communication, 2013).^{17,18}

Adjustment Variables

Adjustments were made for sex, age, education, time period (allowing adjustment for changes in incidence over time), and geographic region of residence. Geographic region of residence was included to adjust for possible regional differences in hospital admissions and was categorized as (1) large cities, (2) southern Sweden, and (3) northern Sweden. Large cities were defined as municipalities with populations >200 000 and comprised the 3 largest cities in Sweden: Stockholm, Gothenburg, and Malmö. Education was used as a proxy for socioeconomic status. Education was classified as completion of compulsory school or less (≤ 9 years), of practical high school (10–11 years), or of theoretical high school and/or college (≥ 12 years).

Statistical Analysis

Person-years at risk (ie, number of persons at risk multiplied by time at risk) were calculated from the time

at which participants were included in the study until first hospitalization for VTE, death, emigration, or the end of the study period. Age-adjusted incidence rates based on the European standard population for the year 2000 were calculated for the whole follow-up period. Person-years for patients with KS were calculated from birth (if born after 1969) or from the start of the follow-up period (if born before 1969). The expected number of cases was based on the number of cases in the reference group (ie, all Swedish male persons without KS). Standardized incidence ratios (SIRs) were calculated as the ratio of observed and expected numbers of VTE cases, using the indirect standardization method:¹⁹

$$\text{SIR} = \frac{\sum_{j=1}^J o_j}{\sum_{j=1}^J n_j \lambda_j^*} = \frac{O}{E^*}$$

$O = \sum o_j$ denotes the total observed number of cases in the study group; E^* , the expected number of cases, is calculated by applying stratum-specific standard incidence rates (λ_j^*) obtained from the reference group to the stratum-specific person-years (n_j) of risk for the study group; o_j represents the observed number of cases that the cohort participants contributed to the j th stratum; and J represents the strata defined by cross-classification of the different adjustment

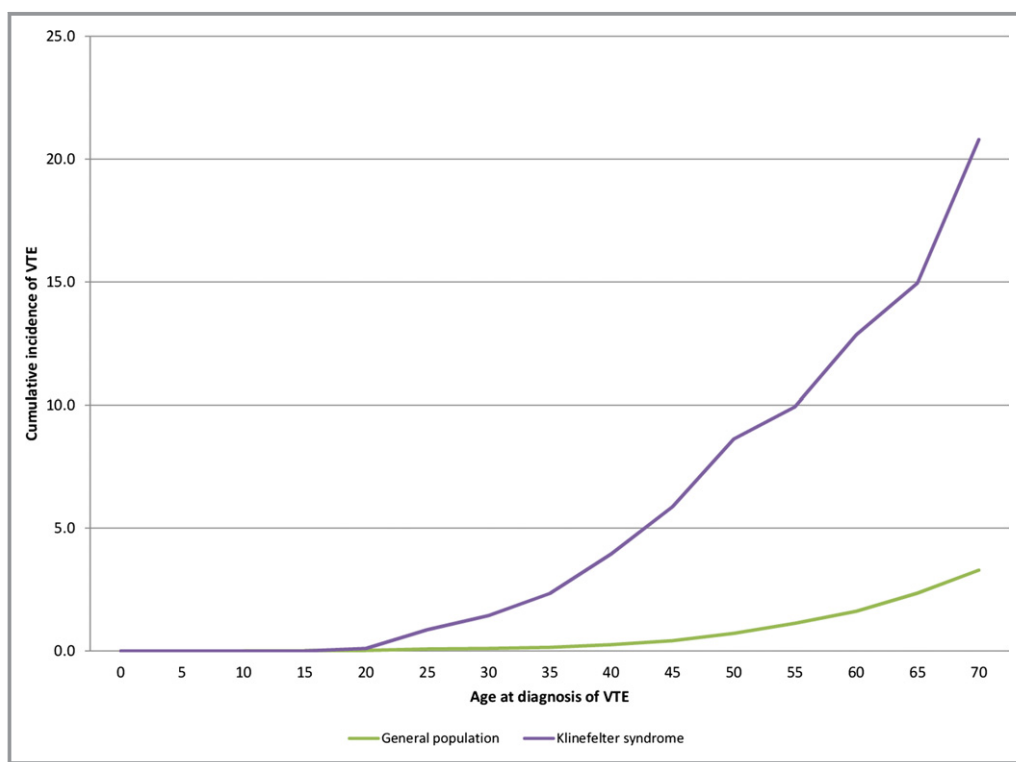


Figure. Cumulative incidence of venous thromboembolism (VTE) among patients with Klinefelter syndrome (KS) and the male population in Sweden. The cumulative incidence for the general population at ages 50, 55, 60, 65, and 70 years was 0.63%, 0.85%, 1.23%, 1.72%, and 2.83%, respectively; for KS patients, the cumulative incidence was 8.6%, 9.3%, 12.8%, 14.9%, and 20.8%, respectively.

variables of age, sex, time period, education, and geographic region of residence.

Sensitivity Analysis

The risk of VTE with determination of SIRs before and after diagnosis of KS was estimated to determine whether the diagnosis of KS affected the risk of VTE. A sensitivity analysis was also done with inclusion of all VTE outpatients (even those diagnosed only once).

Cumulative 5-year incidence rates were calculated by *lifetest* in SAS (SAS Institute). The data were transferred to Excel (Microsoft), and Figure was created in Excel.

The 95% CIs were calculated assuming a Poisson distribution. All analyses were performed using SAS version 9.2 (SAS Institute).

Results

Table 1 shows the different manifestations of VTE in KS patients. In total, 646 (60%) of all 1085 KS patients were diagnosed in the outpatient register. The remaining 439 KS patients were diagnosed in the inpatient register. Table 2 shows characteristics for all KS patients in Sweden. The median age for diagnosis was 33 years. Most KS patients were diagnosed during the period 2000–2010. Total person-years of follow-up was 35 171 person-years for KS patients (not shown). The incidence rate was 340.0 per 100 000 person-years for KS patients and 60.5 per 100 000 person-years for the general population, according to the European standard population in 2000.

Risk of VTE for KS Patients

Table 3 shows the adjusted SIR results for VTE risk of KS patients. The SIR was highest in KS patients aged <30 years and declined with age. Young patients with KS had higher SIRs than older patients (aged <30 years, SIR 12.10; aged ≥70 years, SIR 2.07). The overall risk of both pulmonary embolism (SIR 6.56) and deep venous thrombosis (SIR 5.57) were similarly increased. Figure shows the cumulative incidence for KS patients and the general male population. Cumulative incidence for the general male population by ages 50, 55, 60, 65, and 70 years was 0.63%, 0.85%, 1.23%, 1.72%, and 2.83%, respectively; for KS patients, the cumulative incidence was 8.6%, 9.3%, 12.8%, 14.9%, and 20.8%, respectively.

Sensitivity Analysis

The risk of VTE was assessed before and after diagnosis of KS (Table 4). The VTE risk was increased both >1 year before and >1 year after diagnosis of KS, although the risk was highest within 1 year before and after diagnosis of KS.

Table 2. Patients With Klinefelter Syndrome in Sweden

Subtype	No.	%
Total	1085	100.0
Age at diagnosis, y		
0–9	109	10.0
10–19	168	15.5
20–29	183	16.9
≥30	625	57.6
Median	33	
Year of diagnosis		
1969–1979	146	13.5
1980–1989	109	10.0
1990–1999	112	10.3
2000–2010	718	66.2
Median	2003	
Year of birth		
Before 1950	267	24.6
1950–1959	142	13.1
1960–1969	200	18.4
1970–1979	202	18.6
1980–1989	130	12.0
1990–1999	99	9.1
After 2000	45	4.1
Median	1966	
Years of education		
0–9	372	34.3
10–11	296	27.3
≥12	280	25.8
Unknown	137	12.6

A sensitivity analysis was done with inclusion of all VTE outpatients (ie, even those who were diagnosed only once). The risk of VTE was 6.25 (95% CI 5.08–7.61, n=99).

Discussion

This study showed a very high risk of VTE in KS patients. An especially high risk at young age was observed. Our study is in line with previous research^{5–9}; however, the present study showed that the thrombotic risk in KS patients is comparable to inherited thrombophilias.²⁰ Consequently, KS is equivalent to inherited thrombophilias such as factor V Leiden and the prothrombin G20210A mutations with regard to VTE risk.²⁰ The estimated prevalence in the population of KS (1:500 to 1:1000 newborn male infants) is similar to the prevalence of deficiencies of antithrombin, protein C, and protein S.²⁰ This

Table 3. Risk of Venous Thromboembolism in Patients With Klinefelter Syndrome

Age at Diagnosis, y	Venous Thromboembolism			Deep Venous Thrombosis			Pulmonary Embolism		
	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio	95% CI
<30	12	12.10*	6.22–21.21	6	14.64*	5.27–32.07	1	5.19	0.00–29.77
30–49	40	11.00*	7.86–14.99	20	11.59*	7.07–17.94	11	12.46*	6.18–22.37
50–69	29	4.83*	3.23–6.95	8	3.29*	1.40–6.51	9	4.78*	2.17–9.11
≥70	6	2.07	0.74–4.53	3	2.80	0.53–8.28	2	1.71	0.16–6.30
All	87	6.43*	5.15–7.93	37	6.56*	4.62–9.05	23	5.57*	3.53–8.38

Adjustments were made for sex, age, education, time period (allowing adjustment for changes in incidence over time), and geographic region of residence. *P<0.05.

has important clinical implications for the prevention and diagnosis of VTE among patients with KS. Most important, the risk was increased before diagnosis of KS, indicating that any treatment for KS such as testosterone may not explain the association between KS and VTE.

The mechanism of the association between VTE and KS is unclear but may be multifactorial. The increased VTE risk may be related to X-linked gene dosage as a contributing factor for disease susceptibility.^{1–4} The factor VIII gene, for example, is localized to the X chromosome. Increased factor VIII levels were observed in a KS patient with VTE and may contribute to increased VTE risk and thus warrant further investigation.²¹ Other possible mechanisms are abdominal adiposity, metabolic syndrome, diabetes, and systemic lupus erythematosus, all of which have been associated with KS and could affect the risk of VTE.^{1–4}

The present study has a number of strengths. These include nationwide coverage in a country with high medical standards and surveillance by the Swedish National Board of Health and Welfare, together with inpatient diagnoses of patients by specialist physicians during examinations in clinics. Data in the Swedish registers are almost complete. In 2001, personal numbers were missing for only 0.4% of hospitalizations, and main diagnoses were missing for 0.9% of hospitalizations.¹¹

A limitation is that we did not have access to individual-level data for weight, smoking, blood pressure, karyotyping or other blood tests, and estimated alcohol consumption;

however, we adjusted for education level, which is related to several lifestyle factors. The observed increased thromboembolic risk reported in KS can be worsened by the coexistence of ≥1 well-known thrombophilic conditions (eg, mutations in factor V [FV Leiden] and prothrombin). Because KS often remains undiagnosed,^{1–4} our sample contains only those who received chromosomal testing, which in Sweden is a clinical routine if KS is suspected (Stefan Arver, personal communication, 2013).^{17,18} Undiagnosed persons with KS may not experience VTE to the same extent as the identified KS patients. In fact, our observed incidence rate for VTE (340.2 per 100 000 person years) among KS patients is similar to a UK case series of 412 KS patients in which the incidence rate was 388 per 100 000 person-years (160 per 100 000 person-years for pulmonary embolism and 228 per 100 000 person-years for deep venous thrombosis).⁹ Although associations could be weaker in a completely representative sample, we believe that the large sample size and the robust associations observed indicate a relationship between KS and VTE. Furthermore, it is possible that KS patients are more likely to receive VTE diagnoses because they already have 1 condition and thus have more contact with health care (ascertainment bias). In our sample, however, VTE risk was highly increased both before and after diagnosis of KS. A bias is suggested within 1 year of diagnosis of KS because VTE risk was highest during this period; however, this did not affect the overall VTE risk over the whole follow-up

Table 4. Risk of Venous Thromboembolism in Patients With Klinefelter Syndrome by Time of Diagnosis

Date of Diagnosis Venous Thromboembolism Related to Klinefelter Syndrome	Venous Thromboembolism			Deep Venous Thrombosis			Pulmonary Embolism		
	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio	95% CI
1 year before	26	6.6*	4.31–9.68	12	8.26*	4.25–14.48	4	4.11*	1.07–10.63
Within 1 year	18	12.85*	7.6–20.35	4	6.83*	1.78–17.65	6	13.67*	4.92–29.95
After 1 year	43	5.68*	4.11–7.65	21	6.36*	3.93–9.74	13	5.13*	2.72–8.79

Adjustments were made for sex, age, education, time period (allowing adjustment for changes in incidence over time), and geographic region of residence. *P<0.05.

period. Consequently, we do not believe that ascertainment bias explains the magnitude of the associations to any major degree. Moreover, 646 KS patients (60%) were diagnosed in the outpatient register; therefore, using the hospital inpatient register would result in underestimation of the VTE risk.

In conclusion, KS is associated with high risk for VTE. KS could be considered to be a genetic hypercoagulable state. This has clinical implications for the prevention and diagnosis of VTE among patients with KS.

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Disclosures

None.

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