ORIGINAL ARTICLE

RISK OF VENOUS THROMBOSIS IN THE PRIMARY CARE SETTING DURING THE COVID-19 PANDEMIC

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Abstract

Aims: *This study aimed to evaluate the variability of risk factors among patients with lower limb venous thrombosis, either Deep Vein Thrombosis (DVT) or Superficial Vein Thrombosis (SVT) in community patients with recent or current SARS-CoV-2 infection compared to a historical cohort..*

Methods: *We performed a historical retrospective analysis of all patients who presented to a primary health care unit and were diagnosed with DVT or SVT from January 2020 to December 2021. Historic controls were selected from January 2018 to December 2019. Demographic and clinical data were collected, including BMI, use of oral combined contraception, smoking status and date of COVID-19 infection diagnosis. Univariate analysis was performed for data assessment, including Chi-Square and ANOVA tests.*

Results: *Of the 8547 patients who attended a non-programmed consultation in the timeframe, seventy-nine patients (0.9%) were diagnosed with DVT (19) or SVT (60) and were included in the study. Their mean age was 57.3 ± 15.93 years, with a female-to-male ratio of 3.2 to 1. There was no significant association between COVID-19 and the development of DVT or SVT (p=0.151). However, there was a trend observed indicating a shift in the predominant gender in patients diagnosed with these conditions (85% females in 2018 versus 53.8% in 2021; p=0.077).*

Conclusions: *Outpatients seen by general practitioners during the pandemic of COVID-19 appear to present a trend towards an increased risk of combined DVT and SVT compared with patients of a historical cohort. Further studies are necessary to shed some light on this issue since robust evidence enables clinicians and policymakers to minimize venous thromboembolism risk in patients with SARS-CoV-2 infection.*

INTRODUCTION

Since the emergence of Coronavirus disease 2019 (COVID-19), several systemic complications have been associated, implicating cardiovascular, gastrointestinal, hematopoietic, neurological and immune systems.[1–3]

Infection is an established trigger for thrombotic events. Following respiratory and other infections, patients have a 3–6-fold increased risk of arterial thrombosis, including myocardial infarction and ischaemic stroke, and a 2–3-fold increased risk of venous thromboses, such as deep vein thrombosis of the legs and pulmonary embolism.[4,5] The risk declines weeks after infection, although a higher risk can persist for a year or longer, particularly for venous thrombosis.[5]

Investigation on the matter of a potential hypercoagulable state induced by COVID-19 has been carried out. Several studies have reported that severe SARS-CoV-2 infection is frequently complicated by coagulopathy and thromboembolic events.[6,7]

Many factors predisposing to thrombotic events in these patients have been identified, including endothelial injury, stasis, coagulation abnormalities and inflammation.[8–10] The hypercoagulable state associated with COVID-19 is accompanied by acute inflammatory changes and laboratory findings, including modest prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), increased fibrinogen and D-dimers and mild thrombocytosis or thrombocytopenia. The pathogenesis behind these

abnormalities is not entirely understood, and other contributing factors may be related to the acute inflammatory response to the disease.[11,12]

A study that reported the 90-day cumulative incidences of venous or arterial thromboembolism and death after a COVID-19 diagnosis in primary care datasets from five countries: the Netherlands, Italy, Spain, the UK, and Germany [13] showed that the incidence of venous and arterial events was higher in older people, and the risk of death after venous and arterial events was higher in people who had been diagnosed with or tested positive for COVID-19 than in people without COVID-19.

There is scarce data on the incidence of thrombosis among COVID-19 cases. Almost all the studies showing an increase in thrombotic risk were conducted in a hospital setting. [6–9] It remains to be demonstrated what happens in outpatients, who constitute the majority of COVID-19 patients.

This scientific manuscript investigates the variance of risk factors associated with deep vein thrombosis (DVT) and Superficial Vein Thrombosis (SVT) before and during the COVID-19 pandemic.

METHODS

We performed a retrospective review and analysis of all patients who presented to a primary health care unit in northern Portugal and were diagnosed with DVT or SVT on a non-programmed consultation from January 2018 to December 2021. First, the patients with DVT or SVT were selected, resorting to MIMUF® and SIARS® primary care tools, which allowed the exportation of the patient's list by a diagnostic code. In this case, the K94 (Flebite e Tromboflebite) of the International Classification of Primary Care -2 (ICPC-2) classification was used. Then, each patient file was consulted to confirm the clinical diagnosis of DVT or SVT. Patients whose diagnosis was unclear or not confirmed by imaging were excluded. The ecological approach was adopted to investigate the impact of COVID-19 on the incidence of deep vein thrombosis (DVT) in Portugal between 2020 and 2021. Despite the implementation of aggressive diagnostic policies, a significant proportion of DVT cases may have gone unnoticed due to COVID-19. Additionally, asymptomatic instances of thrombosis may have gone undiagnosed. To address these potential limitations, all diagnosed cases of DVT and COVID-19 were analyzed in this study.

A doppler ultrasound diagnosed each DVT or SVT. The analysis only included episodes within 1-30 days after the covid-19 infection diagnosis.

Data were collected and analyzed using SPSS (IBM Corp., release 2019. IBM SPSS Statistics for Windows, version 26.0, Armonk, NY, USA). Clinical data collected included BMI, use of oral combined contraception (COC), smoking status and date of diagnosis of COVID-19 infection.

The descriptive characteristics were presented as means and standard deviations when continuous and normally distributed, and categorical were expressed as the number of cases and percentages. Univariate analysis was performed for data assessment, including ANOVA Tests and Chi-Square analysis, respectively. The significance level was set to P value <0.05. A linear logistic regression analysis was performed to determine independent clinical and demographic factors associated with increased DVT across the years. The stepwise dimension reduction method was used, and variables with $p < 0.10$ were included.

RESULTS

Of the 8547 patients who attended a non-programmed consultation in the timeframe, seventy-nine patients (0.9%) were diagnosed with DVT (19) or SVT (60) and included in the study. The mean cohort age was 57.3 ± 15. Ninety-three years, with a female-to-male ratio of 3.2 to 1.

There was no significant association between COVID-19 and the combined risk of DVT or SVT (p=0.793). It was verified that a shift in the predominant gender was diagnosed with these conditions (85% females in 2018 versus 52.9% in 2021; p=0.047). (Table 1)

The mean age of diagnosis of DVT and TVS also

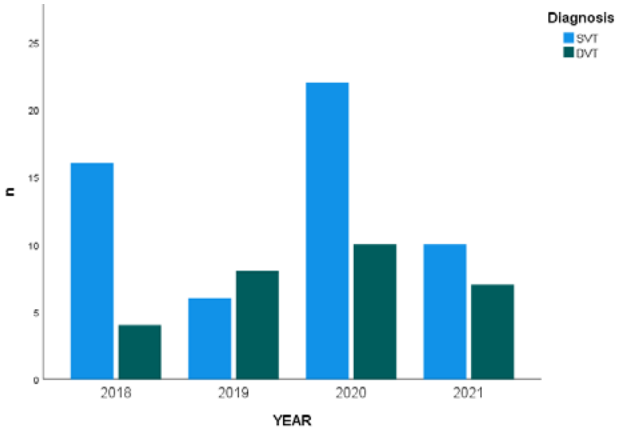

Figure 1 *DVT – Deep Venous Thrombosis; SVT – Superficial Venous Thrombosis.*

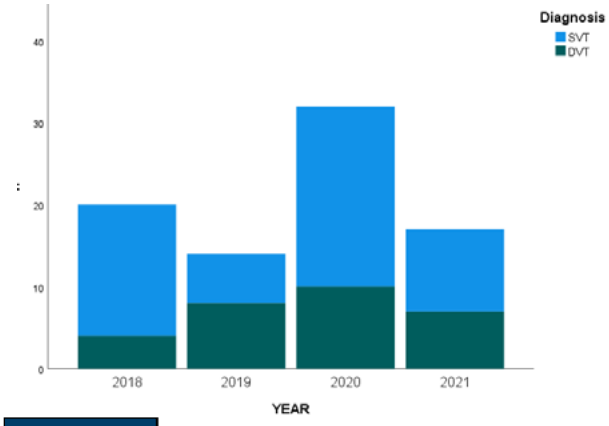

Figure 2 *DVT – Deep Venous Thrombosis; SVT – Superficial Venous Thrombosis.*

Table 1 **Demographics and risk factors of patients with lower limb thrombosis – 2018-2021**

DVT and SVT	2018	2019	2020	2021	*p* value	Multivariable aOR
Gender (female)	17 (85)	13 (92.9)	23 (71.9)	9 (52.9)	0.047	-2.186 IC: 95% (-1.092,-0.051, P=0.032) – 0.571
Age (mean+-SD)	56.25+-13.4	52.6+-16.9	55.4+-15.6	70.6+-15.6	0.04**	2.038 IC:95% (0.00- 0.028, P=0.028) + 0.014
BMI (mean+-SD)	28.88+-6.9	31.7+-5.6	28.7+-5.7	28.4+-4.3	0.298**	
Smoking	4 (20)	2 (14.3)	9 (28.1)	0	0.106*	
COC	1 (5)	4 (28.6)	3 (9.4)	0	0.045	NS
Covid19	-	-	3 (9.4)	2 (11.8)	0.793	
SVT	16 (80)	6 (42.9)	22 (68.8)	10 (58.8)	0.140	
DVT	4 (20)	8 (57.1)	10 (31.3)	7 (41.2)		

*Fisher Exact test
**One-way ANOVA
Legend: aOR - adjusted odds ratio; BMI – Body mass index; COC – Combined oral contraception; DVT – Deep Venous Thrombosis; NS – Not Significant; SD – Standard Deviation; SVT – Superficial Venous Thrombosis.

increased (56.25 ± 13.4 in 2018 to 70.6 ± 15.6 in 2021). Associated with this finding, COC lost its relevance as a risk factor (p=0.045). Smoking demonstrated a similar trend (p=0.106).

Regarding the population who presented DVT, the predominant gender of patients has also changed during the timeframe (p=0.011) (Table 1). In 2020 the female gender was no longer as dominant. In 2021 28.6% (2) were female patients, while in 2018 and 2019, 100% (4 and 8, respectively) corresponded to female patients. COC did not reveal to be a relevant risk factor (p=0.129) for DVT in this cohort. (Table 2)

DISCUSSION

Outpatients seen by general practitioners during the pandemic of COVID-19 appear to present a trend towards an increased risk of thrombosis (DVT and SVT) compared with patients of a historical cohort. A trend was also verified to shift the predominant gender diagnosed with these conditions. Regarding DVT, a change in gender preponderance was observed, and the male gender became the leading risk factor.

Several studies have reported a higher incidence of arterial and venous thrombosis in COVID-19 patients. [14–16] However, scarce data has been published about DVT and TVS in the primary care setting.

The present study failed to establish an association between COVID-19 and the development of DVT or SVT. In other studies, cases of venous thrombosis have been observed in COVID-19 patients who were not admitted to the hospital, but VTE appears to be rare in outpatients. A 2022 report from the RECOVER Registry (Registry of Potential COVID-19 in Emergency Care), which included >14,000 patients presenting to the emergency department with symptomatic COVID-19 versus nearly 13,000 controls who tested negative for COVID-19 found similar 30-day rates of VTE (1.4 vs 1.3 per cent)[17]. In the ACTIV-4B trial, a randomized trial of outpatient thromboprophylaxis, there was only a single VTE among 558 participants (0.2 per cent), and there was no arterial thromboembolic events[18]. A single-center cohort study of 198 hospitalized patients with COVID-19 showed that the severity of illness is strongly associated with thrombotic risk and patients admitted to the intensive care unit (ICU) have a 5-fold higher incidence of VTE. [16] Other studies also reached similar conclusions, with the incidence of thrombotic events in patients with severe COVID-19 ranging from 15.2% to 79%.[19–24]

Previous studies showed an interaction between age, covid infection and risk of venous thrombosis. [13,25] In the present study, there was an increase in the age of thrombosis diagnosis, consistent with other studies. One explanation for this could be the increased sedentarism during the pandemic, as entire populations have been asked to self-isolate and live in home confinement for several months, with the older population better complying with these recommendations. Another explanation could be the presence of SARS-CoV-2 infection as age presents a greater risk of serious illness and severe infection has been associated with a higher risk of thrombosis. [25,26]

Regarding sex, in 2020 the female gender was no longer so predominant. Previous studies also showed an increased incidence in the male gender in COVID-19 series. [13,25,27–29] Cohen et al. [29] in an observational study with data sourced from electronic medical records from over 200 United States hospital systems to determine the extent that the elevated thrombotic risk in males relative to females contributes to excess COVID-19 mortality in males. The investigators concluded that compared with females with COVID-19, males with COVID-19 had a rate of receiving a thrombotic diagnosis during their hospital stay that was 35.8% higher (an absolute difference of 4.9%, OR=1.34 (1.28 to 1.40), p<0.001), confirming the higher rate of thrombotic diagnoses in males.[29] The higher thrombotic risk of males compared to females was well established in the literature long before COVID-19. In multiple studies of unprovoked DVT where hereditary thrombophilia was excluded, the rate of recurrent thrombosis in males has been reported to be anywhere from two to more than three times

Table 2 **Demographics and risk factors of patients with DVT – 2018-2021**

DVT	2018 (n%)	2019 (n%)	2020 (n%)	2021 (n%)	*p* value	Multivariable aOR
Gender (female)	4 (100)	8 (100)	6 (60)	2 (28.6)	0.011	3.787 IC:95% (-1.936- 0.575, P=0.001) -1.256
Age (mean+-SD)	58.3+-11.1	56.1+-21.0	52.4+-16.2	72.14+-17.3	0.159	
BMI (mean+-SD)	33.2+-11.1	30.8+-6.1	27.0+-5.1	26.2+-2.5	0.183	
Smoking	1 (25)	2 (25)	2 (20)	0	0.569	
COC	0	3 (37.5)	1 (10)	0	0.129	
Covid19	-	-	1 (10)	2 (40)	0.323	

Legend: aOR - adjusted odds ratio; BMI – Body mass index; COC – Combined Oral Contraception; DVT – Deep Venous Thrombosis; SD – Standard Deviation.

higher than in females.[30–34] The cause for this sex difference in the thrombotic risk of males remains unknown. Body height is a well-established risk factor for venous thromboembolism but only seems to contribute partially to the observed higher venous thromboembolism risk in men.[35] In the present study, the DVT and SVT rate was higher in females before the start COVID-19 pandemic. One possible partial explanation is that females attend more non-programmed appointments than males, although other possible explanations are lacking.[36]

Thrombosis with COC decreased, one possible explanation could be the decrease in incidence of venous thrombosis in women due to reverse causality. Another explanation could be the dramatic reduction in the number of family planning appointments made by the family doctor or family nurse after the emergence of COVID-19 (in 2020 and part of 2021). This could have led to less access to COC.

Difficulties in accessing primary healthcare consultations due to the constraints caused by the pandemic may have impacted the results as people may have avoided healthcare facilities after minor vascular events due to fear of COVID-19.

While the strength of this study is its access to population-based physician claim and hospital discharge data, the single-center with only 12000 patients to construct this cohort is a limitation. This limits the generalizability of the study and should be addressed with further external validation using a national or regional registry in future research. Moreover, there is a substantial overlap between risk factors for vascular disease and COVID-19 that can bias the results. For example, several months of the study period were characterized by successive confinements, which conditioned extensive modifications in the population's lifestyle, namely an increase in sedentary behaviour, which is a risk factor for DVT. Besides, risk factors for vascular events (e.g., body mass index) are not systematically recorded for all patients and are subject to measurement error. Another potential limitation of this study is the possibility of a biased perception of COVID-19 severity, as it was conducted within the community setting. This may lead to an overestimation or underestimation of certain risk factors or outcomes related to DVT in the context of the pandemic.

The use of a retrospective diagnosis through coding is also a limitation. To mitigate this, patients' records were reviewed individually, however, it is possible that a patient with TVS or TVP might have been assigned the wrong code and, therefore could have been lost. In addition, the current study might have underestimated the incidence of VTEs as we assessed only symptomatic VTE events, as there was no Doppler screening in non-symptomatic patients.

CONCLUSION

In the present study, an association between COVID-19 and the development of DVT or SVT could not be established, however the preponderance of the risk factors for these conditions seem to have changed. Further studies are necessary to shed some light on this issue since robust evidence enables clinicians to minimize a possible venous thromboembolism risk in patients with SARS-CoV-2 infection.

Conflicts of interest:

Nothing to declare.

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