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The prevalence of vascular complications in SARS-CoV-2 infected outpatients

Yvonne Goßlau · Tobias Dominik Warm · Edgar Franklin Hernandez Cancino · Inge Kirchberger · Christine Meisinger · Jakob Linseisen · Alexander Hyhlik-Duerr

Summary
Background The risk of thromboembolic events is increased for coronavirus disease (COVID)-19 inpatients. For severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected outpatients, only few data are available so far.
Methods In our prospective single-center study, 461 SARS-CoV-2-infected outpatients were screened for the presence of deep vein thrombosis.
Results Two outpatients had suffered a deep vein thrombosis. An association with previously known risk factors, such as preexisting thrombosis in the medical history or cardiovascular risk factors, could not be proven.
Conclusion General thromboprophylaxis in SARS-CoV-2-infected outpatients is still not recommended.

Keywords Thrombosis prophylaxis · COVID-19 · Outpatient treatment · Mild illness · SARS-CoV-2

Prävalenz vaskulärer Komplikationen bei ambulanten Patienten mit SARS-CoV-2-Infektion

Zusammenfassung
Grundlagen Das Risiko für thrombembolische Ereignisse ist für stationäre COVID-19-Patienten erhöht. Für ambulant behandelte SARS-CoV-2-Infizierte liegen bisher nur wenige Daten vor.
Methodik In der prospektiven Single-Center-Studie der Autoren wurden 461 SARS-CoV-2-Infizierte mit ambulantem Behandlungsverlauf auf das Vorliegen einer tiefen Beinvenenthrombose untersucht.
Ergebnisse Bei 2 ambulanten Patienten war eine Beinvenenthrombose aufgetreten. Ein Zusammenhang mit bisher bekannten Risikofaktoren, wie vorbestehender Thrombose in der Anamnese oder kardiovaskulären Risikofaktoren, konnte nicht nachgewiesen werden.
Schlussfolgerung Eine generalisierte Thromboseprophylaxe bei ambulanten SARS-CoV-2-Infizierten wird weiterhin nicht empfohlen.

Dr. Y. Goßlau (✉) · T. D. Warm · E. F. Hernandez Cancino · Prof. Dr. A. Hyhlik-Duerr
Vascular Surgery, Faculty of Medicine, University of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany
yvonne.gosslau@uk-augsburg.de

Dr. I. Kirchberger · Prof. Dr. C. Meisinger · Prof. Dr. J. Linseisen
Epidemiology, Faculty of Medicine, University of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany

Introduction

An increased risk of thromboembolic events has been described several times for patients with COVID-19 disease [1, 2]. A recent meta-analysis estimates the risk for hospitalized patients at 14.1%, and for intensive care patients as high as 22.7% [3]. Little is known about the risk of outpatients. As the recently updated guidelines of various medical professional societies confirm, the evidence on thrombosis prophylaxis for outpatient infected patients is to be rated as very low [4, 5].

The primary endpoint of the present study was to survey the prevalence of thrombosis in SARS-CoV-2-infected outpatients and correlate it with the risk factors described in previous studies.

Materials and methods

The present study is a prospective single-center study. Patient acquisition was carried out via the local health offices of the city and district of Augsburg. All residents reported there with a positive SARS-CoV-2 smear by November 2020 ($n = 1600$) were invited in

writing to voluntarily participate in the study. At the time of examination, the positive smear had to be at least 14 days old, and the quarantine had to have been lifted.

A positive vote of the ethics committee of the Ludwig Maximilian University of Munich has been obtained (no. 20-735), and the study has also been registered with Clinical Trials (no. NCT04615026).

In the period from 11.2020 to 05.2021, a total of 525 subjects were examined at the University Hospital Augsburg after having had a SARS-CoV-2 infection, with a focus on vascular complications such as deep vein thrombosis (DVT) or intermittent claudication. Of these subjects, 461 study participants had been treated exclusively as outpatients; the hospitalized patients were excluded for this data collection because the focus of the study was on the outpatient cohort (Fig. 1).

In addition to the course of the disease, demographic data, comorbidities, previous medication, and risk factors for severe courses and the occurrence of thromboembolic events (TE) were recorded. Clinical examinations included compression ultrasonography of the leg veins and determination of the ankle-brachial index in case of a history of intermittent claudication. The course of the disease was recorded using a standardized questionnaire. The documentation, quality assurance, and storage of the study data were pseudonymized in a database.

The descriptive statistics were compiled with the analysis program SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). The metric data were tested for normal distribution; if nonnormal, the median and interquartile range were reported.

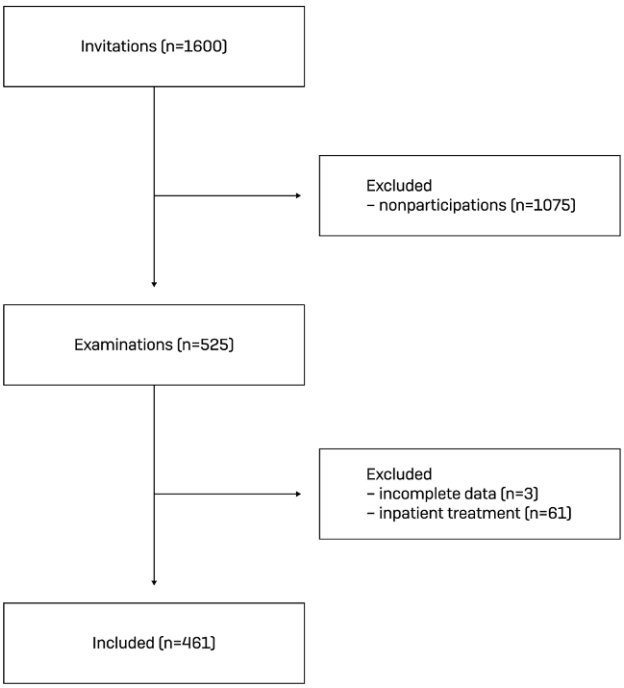

Fig. 1 Graphic presentation of participant enrollment

Results

The response rate after study invitation was 32.8%. Median age of the study participants was 49 years, 209 men and 252 women were included. The mean time interval between the first positive PCR test for the SARS-CoV-2 virus and examination in the study was 238 days.

The demographic data, cardiovascular risk factors, and comorbidities are shown in Table 1.

Regarding severity, there were various clinical courses of SARS-CoV-2 infection. In 2.8%, the infection remained asymptomatic. The frequencies

Table 1 Demographics of SARS-CoV-2-infected individuals treated in an outpatient-only setting

	N
	461 (100.0%)
Age	
Median (IQR)	49 (24)
Age ≥ 60 years	94 (20.4%)
Sex	
Male	209 (45.3%)
Female	252 (54.7%)
Diverse	0
BMI	
Median (IQR)	25.0 (6.0)
≤ 30 kg/m^2	377 (82.3%)
> 30 kg/m^2	81 (17.7%)
Time between first positive SARS-CoV-2 smear and follow-up examination in days	
Median (IQR)	238.0 (194.0)
CVRF	
Hypertension	85 (18.6%)
Dyslipidemia	28 (6.1%)
Diabetes	16 (3.5%)
Current smoker	44 (9.5%)
Former smoker	174 (37.7%)
Pregnancy:	3 (1.2%)
Comorbidities	
Coronary heart disease	18 (3.9%)
Heart attack	9 (2.0%)
Thrombosis	11 (2.4%)
Pulmonary embolism	5 (1.1%)
Apoplexy	8 (1.8%)
Other cardiovascular event	41 (8.9%)
Chronic venous insufficiency	57 (12.4%)
Medication before SARS-CoV-2 infection	
Anticoagulant medication[a]	29 (6.3%)
Steroid therapy	0
Statin therapy	24 (5.2%)
Anticoagulant medication administered during SARS-CoV-2 infection	16 (3.5%)

IQR interquartile range, *BMI* body mass index (m/kg^2), *CVRF* cardiovascular risk factors
[a]Antiplatelet therapy/anticoagulants

Table 2 Presence of symptoms associated with SARS-CoV-2 infection during infection

	N
	461 (100.0%)
SARS-CoV-2 symptoms	
Headache	302 (66.1%)
Pain in the joints or muscles	302 (66.1%)
Disturbance of sense of taste	288 (63.0%)
Disturbance of smell	286 (62.6%)
Coughing	270 (59.0%)
Sore throat/pharyngeal pain	244 (53.4%)
Cold or runny nose	216 (47.4%)
Fever (from 38.1 °C)	198 (43.4%)
Chills	193 (42.2%)
Shortness of breath at rest	146 (32.0%)
Red eye or conjunctivitis	36 (7.9%)
Asymptomatic[a]	13 (2.8%)

[a]Asymptomatic = no symptoms associated with SARS-CoV-2 infection with respect to the symptoms selected in this table

of different SARS-CoV-2-associated symptoms are shown in Table 2.

The prevalence of deep vein thrombosis (DVT) was determined for the 461 outpatients treated in the study. A total of two DVT were found (0.4%). In 3.5% of the patients, a coagulation medication was administered during the infection.

There were no differences in the classic cardiovascular risk factors between the group with DVT compared to the group without DVT.

Symptoms of leg swelling and calf pain were reported by 22 and 75 study participants, respectively. These were present in only one of the two participants with DVT.

The classic risk factors for DVT are shown in Table 3.

None of the subjects with DVT were on long-term anticoagulant medication. One of the DVT patients had a body mass index (BMI) above 30. Bleeding events were not reported. The detailed clinical characteristics of the two patients with DVT are shown in Table 4.

Arterial events did not occur. One subject complained of a new walking distance restriction since the SARS-CoV-2 infection. In this case, the ABI was recorded and within the normal range (1.2).

Table 3 Presence of classic DVT risk factors in SARS-CoV-2-infected patients treated as outpatients only

	N
	461 (100.0%)
Significantly limited physical activity	379 (83.1%)
Pregnancy	3 (1.2%)
Current smoking	44 (9.5%)
Hormone therapy	27 (5.9%)
Anamnestic DVT	11 (2.4%)

DVT deep vein thrombosis

Table 4 Case profiles for SARS-CoV-2-infected outpatients only with deep vein thrombosis at the time of follow-up

	DVT case 1	DVT case 2
Age in years	71	49
Sex	Female	Male
BMI (kg/m^2)	22.23	32.74
Time between first positive SARS-CoV-2 smear and follow-up examination in days	248	129
CVRF		
Hypertension	No	No
Dyslipidemia	Yes	No
Diabetes	No	No
DVT risk factors		
Significantly limited physical activity	No	No
Current smoker	Yes	Yes
Hormone therapy	No	No
Anamnestic DVT	No	No
Comorbidities		
Coronary heart disease	No	No
Heart attack	No	No
Thrombosis	No	No
Pulmonary embolism	No	No
Apoplexy	No	No
Other cardiovascular event	No	No
Chronic venous insufficiency	No	No
Anticoagulant medication[a]	No	No
Steroid therapy	No	No
Statin therapy	Yes	No
Anticoagulant medication administered during SARS-CoV-2 infection	No	No
SARS-CoV-2 symptoms		
Headache	No	No
Pain in the joints or muscles	No	No
Disturbance of sense of taste	Yes	No
Disturbance of smell	No	No
Coughing	Yes	Yes
Sore throat/pharyngeal pain	Yes	Yes
Cold or runny nose	Yes	Yes
Fever (from 38.1 °C)	Yes	No
Chills	No	No
Shortness of breath at rest	No	No
Red eye or conjunctivitis	No	No

DVT deep vein thrombosis, *BMI* body mass index (m/kg^2), *CVRF* cardiovascular risk factors
[a]Antiplatelet therapy/anticoagulants

Discussion

In the present study, two DVTs were detected among the 461 SARS-CoV-2-infected outpatients, which corresponds to 0.4% of the collective.

The prevalence of DVT in the overall population is age dependent and ranges from 0.9 to 10.7% [6].

Thus, there are no indications of an increased DVT prevalence in outpatients with SARS-CoV-2 infection.

An increased incidence of TE in COVID-19 disease was observed in hospitalized patients [7]; these findings cannot be generalized to outpatients.

The course of the disease in hospitalized patients is generally more severe and complicated, especially due to the triggered immune reactions [8–11].

A total of 16 study participants reported that they had received anticoagulation medication (antiplatelet or anticoagulation) during the infection. The reasons for this were not recorded. At the time the study was conducted, there were no scientific findings on the risk of DVT in outpatients, which is why this was presumably an empirical medication based on the known increased risk for inpatients at this time.

Several risk factors for the clustered occurrence of TE in COVID inpatients have been described. These include age over 60 years, arterial hypertension, and diabetes mellitus [12]. In our data collection, however, there was no significantly increased risk of DVT for the outpatients with corresponding risk factors. The classic risk factors in the sense of the Virchow triad also did not lead to an increased incidence of thrombosis.

No DVT occurred under a pre-existing anticoagulant medication.

In a national Scottish registry study that included both inpatients and outpatients, an increased risk of TE was demonstrated, particularly in the first 7 days after a positive test result [13].

The prospective study by Connors et al. on antithrombotic therapy in outpatients was stopped because the occurrence of thromboembolic events was too rare [14]. This is confirmed by the data we collected; generalized implementation of thromboprophylaxis in SARS-CoV-2-infected outpatients can still not be recommended. In symptomatic patients with a high-risk profile, pharmacological thromboprophylaxis can be considered if there are no contraindications. The individual risk of bleeding should always be considered [5, 15].

Strengths and limitations

The strengths of the present study are the large number of patients and the high response rate after invitation, which represents a good cross section of the normal population. Limitations are the lack of a control group and the relatively young age of the patients. In addition, the data collection was carried out in during fixed period of time, thus representing different intervals to the infection and not according to a standardized interval. Therefore, it is a survey of prevalence and not incidence. The thromboses diagnosed in color-coded doppler sonography (CCDS) cannot be reliably correlated with the time of SARS-CoV-2 infection if the clinical course is asymptomatic.

The transferability of our results to newer virus variants is limited due to the different disease courses.

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Author Contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yvonne Goßlau, Tobias Dominik Warm, Inge Kirchberger, and Christine Meisinger. The first draft of the manuscript was written by Yvonne Goßlau and Tobias Dominik Warm, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest Y. Goßlau, T. D. Warm, E.F. Hernandez Cancino, I. Kirchberger, C. Meisinger, J. Linseisen, and A. Hyhlik-Duerr declare that they have no competing interests.

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