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Low Absolute Risk of Thrombotic and Cardiovascular Events in Outpatient Pregnant Women with COVID-19

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ABSTRACT

Introduction: Pregnancy may contribute to an excess risk of thrombotic or cardiovascular events. COVID-19 increases the risk of these events, although the risk is relatively limited among outpatients. We sought to determine whether outpatient pregnant women with COVID-19 are at a high risk for cardiovascular or thrombotic events.
Materials & methods: We analyzed pregnant outpatients with COVID-19 from the multicenter CORONA-VTE-Network registry. The main study outcomes were a composite of adjudicated venous or arterial thrombotic events, and a composite of adjudicated cardiovascular events. Events were assessed 90 days after the COVID-19 diagnosis and reported for non-pregnant women ≤45 years, and for men ≤45 years, as points of reference.
Results: Among 6585 outpatients, 169 were pregnant at diagnosis. By 90-day follow-up, two pregnant women during the third trimester had lower extremity venous thrombosis, one deep and one superficial vein thrombosis. The cumulative incidence of thrombotic events was 1.20 % (95 % confidence interval [CI]: 0.0 to 2.84 %). Respective rates were 0.47 % (95 % CI: 0.14 % to 0.79 %) among non-pregnant women, and 0.49 % (95 % CI: 0.06 % to 0.91 %) among men ≤45 years. No non-thrombotic cardiovascular events occurred in pregnant

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; HELLP, hemolysis, elevated liver enzymes, and low platelets; MI, myocardial infarction; PE, pulmonary embolism; RT-PCR, reverse transcriptase polymerase chain reaction; VTE, venous thromboembolism.

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women. The rates of cardiovascular events were 0.53 % (95 % CI: 0.18 to 0.87) among non-pregnant women, and 0.68 % (95 % CI: 0.18 to 1.18) in men aged ≤45 years.
Conclusions: Thrombotic and cardiovascular events are rare among outpatients with COVID-19. Although a higher event rate among outpatient pregnant women cannot be excluded, the absolute event rates are low and do not warrant population-wide cardiovascular interventions to optimize outcomes.

1. Introduction

Hormonal surges, including elevated estrogen and stasis during pregnancy, increase the risk of thrombotic events [1]. Pregnancy is also associated with physiological changes that may increase cardiovascular demand or promote endothelial dysfunction [2–4]. For example, pregnancy has been associated with conditions such as peripartum cardiomyopathy [5], hypertension, and pre-eclampsia [6].

Coronavirus disease 2019 (COVID-19) can also be a prothrombotic condition [7], as a result of COVID-19-associated endotheliopathy [8], a hypercoagulable state, and stasis induced by limited mobility, and COVID-19 may also increase the risk of thrombotic events [9,10]. Furthermore, COVID-19, through illness severity and a pro-inflammatory profile, can expose patients to excess risk of other cardiovascular events, such as myocarditis and heart failure, and arrhythmias [11,12]. Although much of the world phased out from the *pandemic* state, COVID-19 continues to persist in an endemic form with variable peaks in incidence [13,14].

Recent studies have shown that the thrombotic and cardiovascular event rates are relatively low in the general population of outpatients with COVID-19 [15–17]. However, it remains uncertain whether coexistence of pregnancy and COVID-19 presents a higher risk for cardiovascular or thrombotic events among outpatients compared to non-pregnant females and males of similar age range. Accordingly, we used data from the multicenter CORONA-VTE-Network registry to report the 90-day cardiovascular and thrombotic events.

2. Methods

2.1. Data source

The CORONA-VTE-Network is a multicenter registry that includes >10,000 patients with COVID-19 confirmed with reverse transcriptase polymerase chain reaction (RT-PCR) from March 2020 to June 2022. These patients were included from the Mass General Brigham Health system (that includes Brigham and Women's Hospital, Massachusetts General Hospital, and several community hospitals), Beth Israel Deaconess Medical Center, Anne Arundel Medical Center, University of Virginia Medical Center, University of Colorado Health System, and Thomas Jefferson University Hospital. The study received institutional review board approval at each of the participating sites. Data were collected by trained medical abstractors and transferred to the registry coordinating center at Brigham and Women's Hospital. Additional details about the design of the CORONA-VTE-Network registry have been described previously [16,18].

2.2. Patients

For this pre-specified study, we included adult (aged ≥18 years) pregnant patients, who were in the outpatient setting at the time of COVID-19 diagnosis (until the end of the subsequent day). Pregnancy was ascertained through clinical notes, wherein all included pregnant patients had either a documented positive human chorionic gonadotropin test or a prior ultrasound confirming their pregnancy, or both.

It was decided, a priori, to also include outcomes data for non-pregnant outpatient women ≤45 years, and for outpatient men ≤45 years for descriptive purposes in reference to pregnant women.

2.3. Outcomes

The two main outcomes of interest were incident thrombotic events and incident major cardiovascular events. Thrombotic events were defined as a composite of venous thromboembolism, or arterial thrombosis including type I myocardial infarction (MI), ischemic stroke, or systemic arterial thrombosis/embolism. Cardiovascular events were defined as a composite of thrombotic events, myocarditis or heart failure requiring inpatient treatment, new atrial fibrillation/flutter, or cardiovascular death. All cardiovascular outcomes were adjudicated by independent clinicians using predefined criteria [18].

As ancillary outcomes, we also ascertained, among pregnant patients, 90-day rates of non-cardiovascular adverse pregnancy outcomes including preeclampsia, eclampsia, and pregnancy loss, as well as fetal outcomes in patients in whom such data were available within 90 days from COVID-19 diagnosis. Such data existed only in the subset of included patients from the Mass General Brigham Health system.

2.4. Statistical analysis

In addition to outcomes data, demographics and co-morbidity profile were ascertained in all patients. For baseline characteristics, categorical variables were reported using frequency counts and percentages. Mean and standard deviation were used for reporting continuous variables.

Cumulative incidence rates of thrombotic and cardiovascular events were reported using percentages, along with 95 % confidence intervals (CIs) that were obtained using the Kaplan–Meier approach. The corresponding cumulative incidence curve were visualized for comparison of the three group. The Log-rank test was used to report if the survival distributions were different between groups. The statistical analysis was conducted using R software (R for Linux; version 4.2.0; R Core Team 2022).

3. Results

As of August 8, 2023, we identified 169 pregnant women in the CORONA-VTE Network registry, of whom 43 were in the first, 47 were in the second, and 79 were in the third trimester of pregnancy at the time of diagnosis. As descriptive comparators, there were also 1729 outpatient non-pregnant women ≤45 years, and 1080 outpatient men ≤45 years. Table 1 summarizes the baseline characteristics in these patients and the relevant clinical therapies.

During the 90-day follow-up period, two pregnant women developed a thrombotic event, both within the first 30 days of COVID-19 and both during the third trimester of pregnancy (Table 2). The cumulative incidence of thrombotic events was 1.20 % (95 % CI: 0.0 to 2.84 %). In contrast, the 90-day cumulative incidences of thrombotic events were 0.47 % (95 % CI: 0.14 % to 0.79 %) among outpatient women ≤45 years, and 0.49 % (95 % CI: 0.06 % to 0.91 %) among men ≤45 years.

By 90-day follow-up, there were no additional non-thrombotic cardiovascular events in pregnant women. Therefore, the 90-day cumulative incidence of cardiovascular events among pregnant women was 1.20 % (95 % CI: 0.0 to 2.84 %). Among nonpregnant outpatient women ≤45 years, there were 9 cardiovascular events (cumulative incidence 0.53 %, 95 % CI: 0.18 % to 0.87 %). Three of the events were deep vein thrombosis (DVT), four were pulmonary embolisms (PE), one was a superficial vein thrombosis, and one was an ischemic stroke. One patient who experienced a PE also was diagnosed with a superficial vein

Table 1
Baseline characteristics and COVID-19-related therapies.

	Pregnant women ($n = 169$)	Non-pregnant women ≤ 45 years ($n = 1729$)	Men ≤ 45 years ($n = 1080$)
Pregnancy trimester at the time of diagnosis	–	–	–
First (%)	25	0	0
Second (%)	28	0	0
Third (%)	46	0	0
Age (years, SD)	31 (5.7)	32 (7.6)	31 (7.9)
BMI (kg/m^2)	31 (7.3)	30 (7.7)	30 (7.2)
Prior Venous Thromboembolism (%)	0.59	1.9	1.1
Family history of Venous Thromboembolism (%)	2.4	0.93	0.19
Current smoker (%)	2.4	4.1	7.4
Diabetes	7.1	5.7	5.5
Hypertension	11	7.8	12
History of coronary disease (%)	0	0.12	0.56
History of peripheral artery disease (%)	0.59	0.17	0.093
History of stroke or transient ischemic attack (%)	0.59	0.23	0.83
History of heart failure (%)	0.59	0.23	0.46
Active cancer (%)	1.8	1.3	0.56
Hemodialysis (%)	0	0.12	0.37
Baseline dual antiplatelet therapy[a] (%)	0	0	0.19
Baseline use of anticoagulation (%)	0.59	0.69	0.56
Therapies (new use after COVID-19)			
Corticosteroids (%)	1.8	2.6	2.0
Antiviral agents (%)	2.4	1.7	1.9
Anticoagulants (%)	0.59	0.46	0.83
Antiplatelet agents (%)	6.5	0.75	0.93
Vaccinated[b] (%)	45	55	50

BMI = Body Mass Index.
[a] Only applicable for Mass General Brigham health system patients.
[b] Only includes patients with COVID-19 diagnosis after vaccines were made available 12/14/2020 (pregnant women $n = 29$; non-pregnant women ≤45 years $n = 305$; men ≤45 years $n = 128$).

Table 2
Detailed description of cardiovascular events in outpatient pregnant patients.

	Type of event	Narrative summary
Patient A	Deep vein thrombosis	A 26-year-old woman with a history of asthma and morbid obesity at 31 weeks of gestation was diagnosed with COVID-19 in an outpatient facility after displaying symptoms. Within 72 h, she presented to the emergency department with dyspnea and was subsequently hospitalized. During her inpatient stay, a symptomatic deep vein thrombosis in the left calf was identified.
Patient B	Superficial vein thrombosis	A 41-year-old woman at 32 weeks of gestation, with history of varicose veins presented to an outpatient clinic with clinical features suggestive of COVID-19 and subsequently tested positive. Twenty-three days post-diagnosis, she returned to the outpatient facility with complaints of pain and swelling in her left leg and was diagnosed with superficial vein thrombosis.

thrombosis. In outpatient men with COVID-19 who were ≤45 years, there were 7 cardiovascular events (cumulative incidence: 0.68 %, 95 % CI: 0.18 % to 1.18 %) (Fig. 1). Out of these events, there were three DVTs, one PE, one new diagnosis of atrial fibrillation, one diagnosis of MI and one diagnosis of myocarditis. One patient diagnosed with MI also was diagnosed with a DVT and superficial vein thrombosis by the 90-day follow-up. One patient who experienced a DVT also had a subsequent diagnosis of PE, and heart failure and a diagnosis of stroke by the 90-day follow-up.

There were seven unique non-thrombotic maternal outcomes. Four patients were diagnosed with preeclampsia (cumulative incidence: 5.19 %, 95 % CI: 2.04 % to 12.61 %), three of which occurred during the third trimester and one during the post-partum period. There were three pregnancy losses (cumulative incidence: 3.9 %, 95 % CI: 1.33 % to 10.84 %) diagnosed at 6, 8, and 15 weeks of gestation. No major fetal adverse outcomes were identified.

4. Discussion

This multicenter study of younger outpatient individuals with COVID-19 has some key observations. First, similar to some prior studies [15–17,19], we note that the absolute event rate is relatively low and that most outpatients with COVID-19, including the vulnerable population of pregnant women, remain free from thrombotic or cardiovascular events (**Graphical Abstract**, Fig. 2). Second, cardiovascular events that did occur were in the form of thrombotic events. Although limited by small number of events, the point estimates may also suggest a heightened risk of thrombotic events in the early period of infection among pregnant women, compared with non-pregnant women or men aged ≤45 years. However, this latter observation needs confirmatory data in future.

Very few prior studies have reported the thrombotic and cardiovascular outcomes among pregnant patients with recent COVID-19 infection (Table 3) [20–22]. Collectively, these studies have shown a greater risk of cardiovascular events, particularly venous thromboembolism in pregnant patients who are afflicted with COVID-19. However, several of these studies used administrative claims data, and none reported dedicated and adjudicated results among outpatient pregnant women with COVID-19.

The findings of this analysis may have relevant clinical implications. Most importantly, these data provide reassurance that the vast majority of outpatients with COVID-19 have a very low risk of thrombotic and cardiovascular events. This study extends the reassurance to the majority of pregnant women, as well. In fact, there were only two thrombotic cardiovascular events, no cardiovascular deaths, and no non-thrombotic cardiovascular events among pregnant women. Although the absolute number of thrombotic events in this study is small, we noted that both of the thrombotic events were diagnosed during the third trimester of pregnancy, in the lower extremities, and within the first 30 days of COVID-19. This is consistent with prior observations that have suggested the third trimester to be a period of greatest incidence of DVT [23,24]. It can be hypothesized that such findings, in addition to hormonal hypercoagulability, might be related to the gravid uterus, and resultant diminished venous return contributing to venous stasis. Such findings can be more relevant during the acute phase of COVID-19, when most of the thrombotic events accrue. While awaiting more data, it may be that additional follow-up or prophylactic therapies may be considered in a case-by-case basis for a small minority of higher risk individuals who are not already on prophylactic anticoagulation [25]. We should also acknowledge that although we did not observe thrombotic events in the post-partum period, the follow-up duration for CORONA-VTE Network was only 90 days, not allowing for capturing of post-partum data in the majority of pregnancies.

Our study collected the occurrence of non-thrombotic maternal outcomes including HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, eclampsia, preeclampsia, and pregnancy loss in this study. We identified preeclampsia among 5.2 % of participants. This event rate is not higher, and is potentially lower than the national average in the United States [26,27]. The reported rate of early pregnancy loss in our study is similarly reassuring and not higher than that of the expected rate (up to 10 %) by the American College of Obstetrics and Gynecology [28]. Additionally, our study reported no major adverse fetal outcomes, compared with a rate of 5.73 stillbirths per 1000

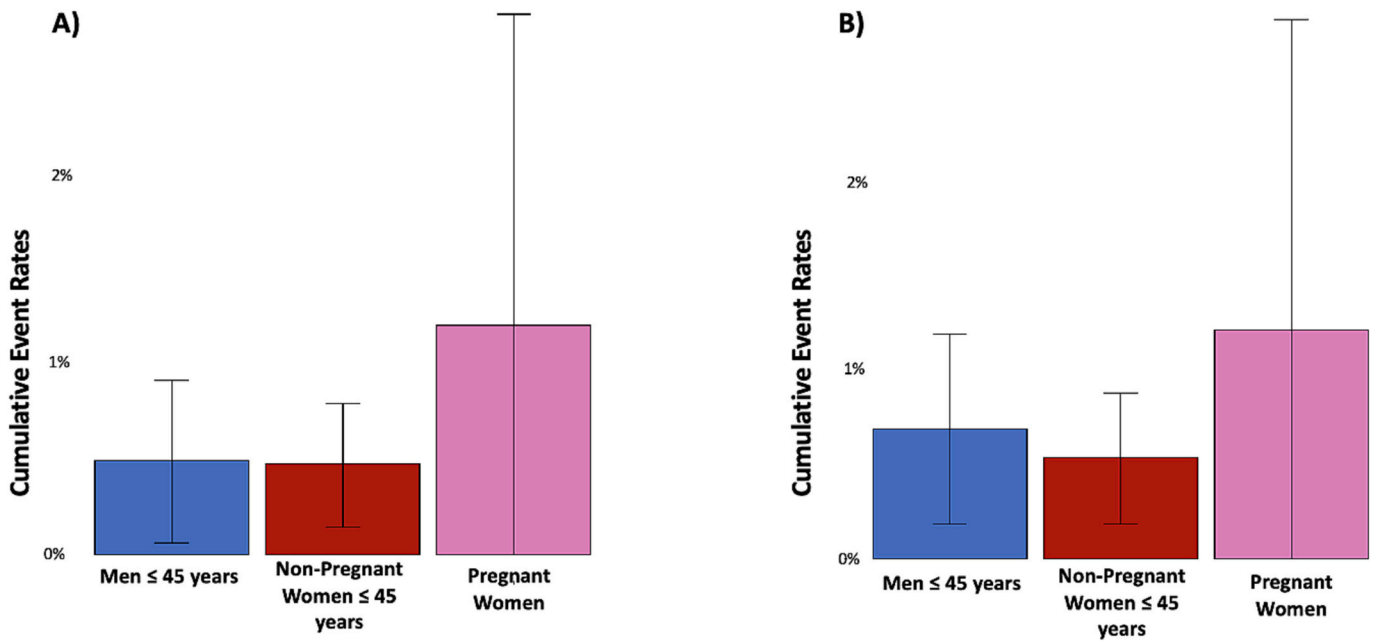

Fig. 1. Thrombotic Events (A) and Cardiovascular Events (B). The height of the boxes indicates the point estimate for cumulative incidence, and the vertical error bars indicate the 95 % confidence interval.

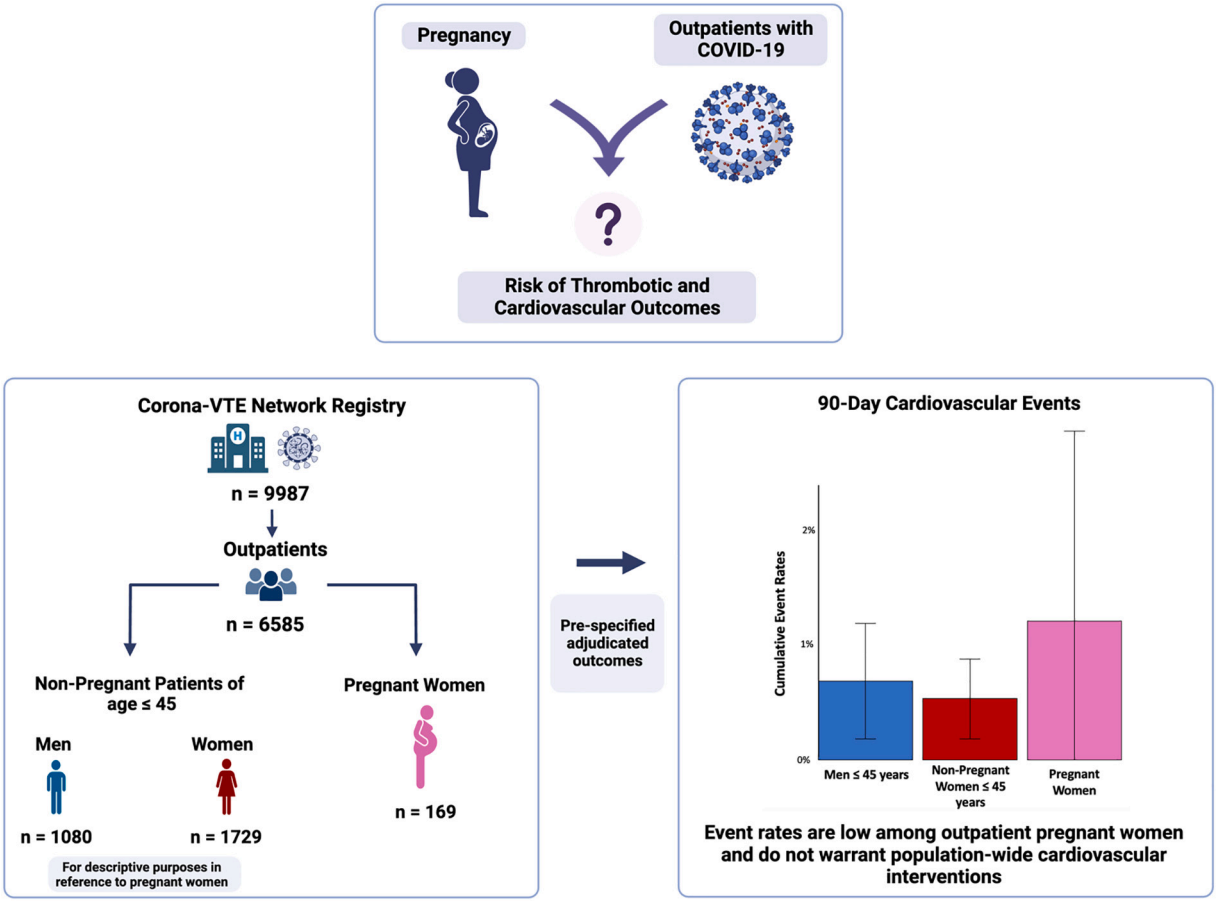

Fig. 2. Risk of thrombotic and cardiovascular outcomes in pregnant outpatients with Covid-19.

deliveries reported in the United States (U.S.) [29].

This study should be considered in the context of its strengths and limitations. Clinical multicenter U.S. data, with independent adjudication of outcomes using validated definitions are the main strengths of this study. However, because of the resource-intensive nature of data collection and ascertainment at the individual patient level,

Table 3
Prior Studies Assessing the Incident Thrombotic or Cardiovascular Events in Patients with COVID-19 During Pregnancy.

Study	Population	Sample size	Outcome(s)	Setting	Case/ outcome Ascertainment	Summary of findings
Jering, K. et al. 2021 [20]	Women hospitalized for childbirth	*N* = 406, 466 Pregnant patients with COVID-19 vs. pregnant patients without COVID-19	MI, VTE	Multicenter Inpatient	ICD-10 Codes within national claims database	MI and VTE rates were higher among pregnant patients with COVID-19 than in pregnant patients without COVID-19 (MI: 0.1 % vs 0.004 %, VTE: 0.2 % vs 0.1 %; $P < 0.0001$). No outpatient specific outcomes were reported.
Zahid, S. et al. 2023 [21]	Women hospitalized for childbirth	N = 3,412,316 Pregnant patients with covid vs. pregnant patients without covid	Cardiovascular, VTE, and in-hospital mortality	Multicenter Inpatient	ICD-10 codes within a national claims database	Patients with COVID-19 had an increased risk of in-hospital mortality (aOR: 14.86 [95 % CI: 10.85–20.34]; P < 0.01), VTE (aOR: 2.94 [95 % CI: 2.31–3.74]; $P < 0.01$), and stroke (aOR: 1.72 [95 % CI: 1.19–2.48]; P < 0.01). The odds of heart failure among COVID-19 patients were not significantly different compared to those without COVID-19 (aOR: 2.44 [95 % CI: 0.91–6.54]). No outpatient specific outcomes were reported.
Metz, T. et al. 2021 [22]	Women with a positive COVID-test during pregnancy	*N* = 1219 with COVID-19 during pregnancy, delivery or postpartum across 5 different COVID-19 illness severity	VTE, ICU admission, maternal death	Multicenter, inpatient & outpatient	Electronic medical records data abstraction by trained research team	The incidence of VTE among those with severe-critical illness (8/141, 6 %) was higher than those with mild-moderate (1/499, 0.2 %) or asymptomatic illness (0/579, 0 %). Inpatients and outpatients were included in the study cohort; however, outpatient specific outcomes were not separately reported.

We searched PubMed (Medline) for articles using the following search strategy (7/21/2023): (("COVID-19"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR COVID-19[TIAB] OR SARS-CoV-2[TIAB] OR "coronavirus 19"[all Fields]) AND ("venous thromboembolism"[MeSH Terms] OR "venous thrombosis"[MeSH Terms] OR "pulmonary embolism"[MeSH Terms] OR "myocardial infarction"[MeSH Terms] OR "ischemic stroke"[MeSH Terms] OR "arterial thrombosis"[TIAB] OR "venous thromboembolism"[TIAB] OR "venous thrombosis"[TIAB] OR "pulmonary embolism"[TIAB] OR "myocardial infarction"[TIAB] OR "ischemic stroke"[TIAB] OR "arterial thrombosis"[TIAB] OR "myocarditis"[MeSH Terms] OR "myocarditis"[TIAB] OR "Takotsubo Cardiomyopathy"[MeSH Terms] OR "Takotsubo Cardiomyopathy"[TIAB] OR "atrial fibrillation"[MeSH Terms] OR "atrial fibrillation"[TIAB] OR "heart failure"[MeSH Terms] OR "heart failure"[TIAB]) AND ("pregnancy"[MeSH Terms] OR "pregnant"[all Fields] OR "pregnancy"[TIAB]))
aOR = adjusted odds ratio; CI = Confidence Interval; ICD = international classification of diseases; MI = myocardial infarction; VTE = venous thromboembolism.

we were unable to sufficiently power this pre-specified analysis of the CORONA-VTE-Network registry [18]. In addition, non-cardiovascular maternal and fetal outcomes were not among the pre-specified objectives of the registry and were able to obtain such data only for the subset of patients from the Mass General Brigham Health System. Further, data elements in CORONA-VTE Network did not capture whether or not pregnancies were singleton. Lastly, despite inclusion of a diverse population from several centers within 5 States in the USA, the data in CORONA-VTE Network are restricted to those States, not others, or data from other countries. While we are unaware of large effect modification by race in this subgroup, confirmatory findings for patients from other ethno-racial backgrounds in future will be welcome.

In conclusion, this study confirms that the vast majority of younger outpatients with COVID-19, including pregnant women, have a 90-day course free from thrombotic or cardiovascular events, thereby not warranting population-wide screening or intervention for cardiovascular complications including thrombosis. Additional investigations may be needed to better define the potential risk in higher-risk pregnant individuals during the third trimester who are not otherwise on prophylactic antithrombotic therapy.

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CRediT authorship contribution statement

Behnood Bikdeli: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Darsiya Krishnathasan:** Writing – review & editing, Data curation. **Candrika D. Khairani:** Writing – review & editing, Data curation. **Antoine Bejjani:** Writing – original draft, Data curation. **Julia Davies:** Writing – review & editing, Data curation. **Nicole Porio:** Writing – review & editing, Data curation. **Anthony Tristani:** Writing – review & editing, Data curation. **Andre Armero:** Writing – review & editing, Data curation. **Ali A. Assi:** Writing – review & editing, Methodology, Data curation. **Victor Nauffal:** Writing – review & editing, Data curation. **Umberto Campia:** Writing – review & editing, Methodology, Data curation. **Zaid Almarzooq:** Writing – review & editing, Methodology, Data curation. **Eric Wei:** Writing – review & editing, Methodology, Data curation. **Marcos D. Ortiz-Rios:** Writing – review & editing, Methodology, Data curation. **Valeria Zuluaga-Sánchez:** Data curation. **Aditya Achanta:** Writing – review & editing, Data curation. **Sirus J. Jesudasen:** Writing – review & editing, Methodology. **Bruce Tiu:** Writing – review & editing, Data curation. **Geno J. Merli:** Writing – review & editing, Investigation. **Orly Leiva:** Writing – review & editing, Data curation. **John Fanikos:** Writing – review & editing, Investigation. **Elvira Grandone:** Writing – review & editing. **Aditya Sharma:** Writing – review & editing, Methodology, Investigation. **Samantha Rizzo:** Writing – review & editing, Data curation. **Mariana B. Pfeferman:** Writing – review & editing, Data curation. **Ruth B. Morrison:** Writing – review & editing, Data curation. **Alec Vishnevsky:** Writing – review & editing, Methodology, Investigation. **Judith Hsia:** Writing – review & editing, Methodology, Investigation. **Mark R. Nehler:** Writing – review & editing, Methodology, Investigation. **James Welker:** Writing – review & editing, Methodology, Investigation, Data curation. **Marc P. Bonaca:** Writing – review & editing, Methodology, Investigation. **Brett Carroll:** Writing – review & editing, Methodology, Investigation. **Samuel Z. Goldhaber:** Writing – review & editing, Methodology, Investigation. **Zhou Lan:** Writing – review & editing,

Formal analysis. **Gregory Piazza:** Writing – review & editing, Supervision, Methodology, Investigation.

Declaration of competing interest

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