

ΠΑΝΕΠΙΣΤΗΜΙΟ
ΘΕΣΣΑΛΙΑΣ

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ΕΠΙΣΤΗΜΩΝ
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ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

Διδακτορική διατριβή

«Καρδιαγγειακοί παράγοντες κινδύνου, θρομβοεμβολικά συμβάντα και θνητότητα σε νοσηλευθέντες ασθενείς με COVID-19 κατά την διάρκεια των πρώτων 90 ημερών μετά την έξοδο τους από το νοσοκομείο»

υπό

Δημητρίου Γιαννή, MD, MSc

Ιατρού

Λάρισα,
Σεπτέμβριος 2024



UNIVERSITY OF THESSALY

SCHOOL OF HEALTH SCIENCES

FACULTY OF MEDICINE

PhD Thesis

"Cardiovascular risk factors, thromboembolic outcomes and mortality of hospitalized COVID-19 patients in the 90-day post-discharge period"

by

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Larissa,
September 2024

Διδακτορική διατριβή υποβληθείσα στο Τμήμα Ιατρικής του Πανεπιστημίου Θεσσαλίας
ως μέρος των απαιτήσεων για την απόκτηση του Διδακτορικού Διπλώματος

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PhD Thesis submitted to the Faculty of Medicine of the University of Thessaly in fulfillment of the requirements for the Ph.D. degree

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Η έγκριση της διδακτορικής διατριβής από το Τμήμα Ιατρικής της Σχολής Επιστημών Υγείας του Πανεπιστημίου Θεσσαλίας δεν υποδηλώνει αποδοχή των απόψεων του συγγραφέα (σύμφωνα με τις διατάξεις του άρθρου 202, παράγραφος 2 του Ν.5343/1932).

The approval of the PhD thesis by the Faculty of Medicine of the School of Health Sciences at the University of Thessaly does not imply acceptance of the author's views (according to the provisions of article 202, paragraph 2 of Law 5343/1932).

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Nov 2019 – June 2021	**Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY** Postdoctoral Research Scholar
Oct 2014 – Sep 2018	**2nd Propedeutical Department of Surgery, Hippokration General Hospital, Thessaloniki, Greece** General Surgery Resident
Sep 2013 – Sep 2014	**Greek Army, Mytilini, Lesvos, Greece** Medical Doctor/Second Lieutenant

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LICENSES & CERTIFICATIONS

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Feb, 2016	**German Medical License** Upper Bavaria (Regierung Von Oberbayern)
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PUBLICATIONS

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35. Ziogas IA, Evangeliou AP, **Giannis D**, Hayat MH, Mylonas KS, Tohme S, Geller DA, Elias N, Goyal L, Tsoulfas G. The Role of Immunotherapy in Hepatocellular Carcinoma: A Systematic Review and Pooled Analysis of 2,402 patients.. Oncologist. 2021 Jun;26(6):e1036-e1049. doi: 10.1002/onco.13638. Epub 2021 Jan 2. PMID: 33314549; PMCID: PMC8176986. Show publication

36. Boutiou E, Ziogas IA, **Giannis D**, Doufexi AE. Hereditary gingival fibromatosis in children: a systematic review of the literature. Clin Oral Investig. 2021 Jun;25(6):3599-3607. doi: 10.1007/s00784-020-03682-x. Epub 2020 Nov 13. PMID: 33188467. Show publication

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HONORS & AWARDS

Dec, 2022	**Research award** Issued by the Hellenic Medical Society Of New York
Sep, 2022	**Trainee Travel Scholarship** Issued by the Eastern Vascular Society
Jan, 2022	**Research award** Issued by the Hellenic Medical Society Of New York
Dec, 2020	**ASH Abstract Achievement Award** 62nd ASH Annual Meeting and Exposition Issued by the American Society of Hematology
Nov 2019 – Jun 2021	**Broxmeyer Fellowship in Clinical Thrombosis** Issued by the Broxmeyer Foundation
Sep, 2018	**Student recognition award** Award given to valedictorians of University of Thessaly, School of Medicine during the 28-years anniversary since the Medical School establishment
Nov, 2017	**Best oral presentation award** Title: "Hyponatremia as a marker of the severity of acute appendicitis'' 13th Conference of the Surgical Society of Northern Greece, November 3-5 2017, Thessaloniki, Greece
Jul, 2013	**Class Valedictorian** Faculty of Medicine, School of Health Sciences, University of Thessaly
Sep, 2010	**Academic Excellence Award & Scholarship** National Institute of Scholarships
Sep, 2010	**Academic Excellence Award & Scholarship** University of Thessaly
Sep, 2007	**Eurobank EFG Scholarship** Awarded for achieving highest grade among high school graduates of General Lyceum of Kalampaka

JOURNAL INVITED PEER REVIEWER

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1. Cochrane Database of Systematic Reviews
2. Transplant Infectious Disease (Wiley)
3. BMJ Open (BMJ)
4. BMC Infectious Diseases
5. BMC Cardiovascular Diseases
6. Expert Systems with Applications
7. Thrombosis Research

8. Intensive Care Medicine
9. Research and Practice in Thrombosis and Haemostasis
10. Journal of Thrombosis and Thrombosis and Thrombolysis
11. Aging (Impact Journals LLC)
12. Journal of Pediatric Infectious Diseases (Thieme Publishing Group)
13. Epidemiology and Infection (Cambridge University Press)
14. Journal of Medicine and Life (Carol Davila University Press
15. World Academy of Sciences Journal (Spandidos Publications)
16. Frontiers in Transplantation

ABSTRACT

Objectives: Thromboembolic events, including venous thromboembolism (VTE) and arterial thromboembolism (ATE), and mortality from subclinical thrombotic events occur frequently in coronavirus disease 2019 (COVID-19) inpatients. The risk and associated risk factors of post-discharge thromboembolism and death in hospitalized COVID-19 patients remain unclear. The aim of this study was to fill the current knowledge gap in post-discharge rates of VTE, ATE, all-cause mortality (ACM), and major complications in hospitalized patients with COVID-19. To this aim, we created a multicenter, prospective registry named CORE-19. Our second aim was to assess clinical and laboratory risk factors, as well as relevant medications, including anticoagulants, to predict risk of thromboembolic disease or death in the post-discharge period.

Methods: Our prospective registry included consecutive patients with COVID-19 hospitalized within our multihospital system from 1 March to 31 May 2020. We captured demographics, comorbidities, laboratory parameters, medications, post-discharge thromboprophylaxis, and 90-day outcomes. Data from electronic health records, health informatics exchange, radiology database, and telephonic follow-up were merged. Primary outcome was a composite of adjudicated VTE, ATE, and all-cause mortality (ACM). Principal safety outcome was major bleeding (MB). Further, we investigated the post-discharge rates and associated risk factors of ATE, VTE, and ACM in a high-risk subpopulation of hospitalized COVID-19 patients with coronary artery disease (CAD), carotid artery stenosis (CAS), peripheral arterial disease (PAD), or ischemic stroke.

Results: Among 4906 patients (53.7% male), mean age was 61.7 years. Comorbidities included hypertension (38.6%), diabetes (25.1%), obesity (18.9%), and cancer history (13.1%). Post-discharge thromboprophylaxis was prescribed in 13.2%. VTE rate was 1.55%; ATE, 1.71%; ACM, 4.83%; and major bleeding, 1.73%. Composite primary outcome rate was 7.13% and was significantly associated with advanced age (odds ratio [OR], 3.66; 95% confidence interval [CI]: 2.84–4.71), prior VTE (OR: 2.99; 95% CI: 2.00–4.47), intensive care unit (ICU) stay (OR: 2.22; 95% CI: 1.78–2.93), chronic kidney disease (CKD; OR: 2.10; 95% CI: 1.47–3.00), peripheral arterial disease (OR: 2.04; 95% CI: 1.10–3.80), carotid occlusive disease (OR: 2.02; 95% CI: 1.30–3.14), IMPROVE-DD VTE score ≥4 (OR: 1.51; 95% CI: 1.06–2.14), and coronary artery disease (OR: 1.50; 95% CI: 1.04–2.17). Post-discharge anticoagulation was significantly associated with reduction of the primary outcome (OR: 0.54; 95% CI: 0.47–0.81). In the high-risk subpopulation of 608 patients ATE rate was 27.3% (10.2% myocardial infarction, 10.1% ischemic stroke, 13.2% systemic embolism, 12.7% major adverse limb event); VTE rate was 6.9% (4.1% deep vein thrombosis, 3.6% pulmonary embolism); ACM rate was 9.5%; and the composite of ATE, VTE, or ACM 35.2% (214/608). Multivariate analysis showed significant association between this composite endpoint and age > 75 years (OR: 1.90, 95% CI: 1.22–2.94), PAD (OR: 3.23, 95% CI: 1.80–5.81), CAS (OR: 1.74, 95% CI: 1.11–2.75), congestive heart failure (CHF) (OR: 1.84, 95% CI:

1.02–3.35), previous VTE (OR: 3.08, 95% CI: 1.75–5.42), and ICU stay (OR: 2.93, 95% CI: 1.81–4.75).

Conclusions: COVID-19 inpatients remain at high risk of VTE, ATE, and ACM through 90 days after discharge. Independent predictors of post-discharge major thromboembolic events and death include advanced age >75 years, cardiovascular risk factors (personal history of VTE, coronary artery disease, carotid occlusive disease, and peripheral arterial disease), CKD, IMPROVE-DD VTE score ≥4, and ICU stay. Discharge anticoagulants, mostly prophylactic doses, were associated with 46% decrease in the composite endpoint of major thromboembolism or ACM. High-risk COVID-19 inpatients with cardiovascular disease experience even higher rates of ATE, VTE, or ACM through 90 days post-discharge and associated independent risk factors include age > 75 years, PAD, CAS, CHF, previous VTE, and ICU admission. The identification of high-risk hospitalized COVID-19 patients, including those with established cardiovascular disease, may provide additional targets and prognostic indicators for the prevention of major thromboembolism and mortality after hospital discharge. Randomized controlled trials are needed to explore the role of antithrombotic agents, especially anticoagulant and add-on antiplatelet therapy, in the immediate post-discharge period.

ΠΕΡΙΛΗΨΗ

Σκοπός: Τα θρομβοεμβολικά συμβάντα, συμπεριλαμβανομένης της φλεβικής θρομβοεμβολής και της αρτηριακής θρομβοεμβολής, καθώς και ο θάνατος από υποκλινικά θρομβωτικά συμβάντα εμφανίζονται συχνά σε νοσηλευόμενους ασθενείς με τη νόσο του κορωνοϊού 2019 (COVID-19). Ο κίνδυνος και οι σχετιζόμενοι παράγοντες κινδύνου θρομβοεμβολής και θνητότητας σε νοσηλευθέντες ασθενείς με COVID-19 μετά την έξοδο από το νοσοκομείο παραμένουν αδιευκρίνιστοι. Σκοπός της παρούσας μελέτης ήταν να καλύφθεί το κενό γνώσης σχετικά με τη συχνότητα φλεβικής θρομβοεμβολής, αρτηριακής θρομβοεμβολής, θνητότητας και μείζονων επιπλοκών μετά την έξοδο από το νοσοκομείο σε νοσηλευόμενους ασθενείς με COVID-19. Για το σκοπό αυτό δημιουργήσαμε μια πολυκεντρική, προοπτική βάση δεδομένων καταγραφής (CORE-19). Δευτερεύοντες στόχοι ήταν η εκτίμηση κλινικών και εργαστηριακών παραγόντων κινδύνου, καθώς και σχετικών φαρμάκων, περιλαμβανομένων των αντιπηκτικών, για την πρόβλεψη του κινδύνου θρομβοεμβολικής νόσου ή θανάτου μετά την έξοδο από το νοσοκομείο.

Μεθοδολογία: Η προοπτική βάση καταγραφής δεδομένων περιέλαβε διαδοχικούς ασθενείς με COVID-19 που νοσηλεύτηκαν στο πολυνοσοκομειακό σύστημα υγείας από την 1η Μαρτίου έως τις 31 Μαΐου 2020. Καταγράψαμε τα δημογραφικά στοιχεία, τις συννοσυρότητες, τις εργαστηριακές παραμέτρους, τους φαρμακευτικούς παράγοντες, τη θρομβοπροφύλαξη και τα συμβάντα στις 90 ημέρες μετά την έξοδο από το νοσοκομείο. Στη βάση καταγραφής συνδυάστηκαν τα δεδομένα από τους ηλεκτρονικούς φακέλους, τα συστήματα ανταλλαγής υγειονομικών πληροφοριών, βάσεις δεδομένων ακτινολογίας και δεδομένα που συλλέχθηκαν κατόπιν τηλεφωνικής επικοινωνίας. Το κύριο αποτέλεσμα

έκβασης περιλάμβανε το συνδυασμό φλεβικής θρομβοεμβολής, αρτηριακής θρομβοεμβολής, και θνητότητας από οποιαδήποτε αιτία. Κύρια έκβαση-δείκτης ασφάλειας της θεραπείας ήταν η μείζων αιμορραγία. Επιπλέον, διερευνήθηκε η συχνότητα και οι σχετιζόμενοι παράγοντες κινδύνου αρτηριακής θρομβοεμβολής, φλεβικής θρομβοεμβολής, και θνητότητας από οποιαδήποτε αιτία σε έναν υψηλού κινδύνου υποπληθυσμό νοσηλευμένων ασθενών με COVID-19 και στεφανιαία νόσο, στένωση καρωτίδων, περιφερειακή αρτηριακή νόσο, ή ιστορικό ισχαιμικού αγγειακού εγκεφαλικού επεισοδίου.

Αποτελέσματα: Από τους 4.906 ασθενείς (53,7% άνδρες), η μέση ηλικία ήταν 61,7 έτη. Οι συννοσυρότητες περιλάμβαναν υπέρταση (38,6%), σακχαρώδη διαβήτη (25,1%), παχυσαρκία (18,9%) και ιστορικό καρκίνου (13,1%). Θρομβοπροφύλαξη μετά την έξοδο από το νοσοκομείο χορηγήθηκε στο 13,2% του πληθυσμού. Η συχνότητα φλεβικής θρομβοεμβολής ήταν 1,55%, αρτηριακής θρομβοεμβολής 1,71%, θνητότητας από οποιαδήποτε αιτία 4,83%, και μείζονος αιμορραγίας 1,73%. Η συχνότητα του κύριου αποτελέσματος έκβασης ήταν 7,13% και σχετιζόταν σημαντικά με την προχωρημένη ηλικία (Λόγος πιθανοτήτων [OR]: 3,66; 95% διάστημα εμπιστοσύνης [CI]: 2,84-4,71), προηγούμενη φλεβική θρομβοεμβολή (OR: 2,99; 95% CI: 2,00-4,47), εισαγωγή στη μονάδα εντατικής θεραπείας (OR: 2,22; 95% CI: 1,78-2,93), χρόνια νεφρική νόσο (OR: 2,10; 95% CI: 1,47-3,00), περιφερειακή αρτηριακή νόσο (OR: 2,04; 95% CI: 1,10-3,80), καρωτιδική στένωση (OR: 2,02; 95% CI: 1,30-3,14), βαθμολογία στην κλίμακα IMPROVE-DD VTE ίση ή μεγαλύτερη του 4 (OR: 1,51; 95% CI: 1,06-2,14) και στεφανιαία νόσο (OR: 1,50; 95% CI: 1,04-2,17). Η αντιπηκτική αγωγή μετά την έξοδο από το νοσοκομείο σχετιζόταν σημαντικά με μείωση του κύριου αποτελέσματος έκβασης (OR: 0,54; 95% CI: 0,47-0,81). Στην υποομάδα υψηλού κινδύνου των 608 ασθενών, η συχνότητα

αρτηριακής θρομβοεμβολής ήταν 27,3% (10,2% έμφραγμα μυοκαρδίου, 10,1% ισχαιμικό εγκεφαλικό επεισόδιο, 13,2% συστηματική (περιφερική) εμβολή, 12,7% μείζον ισχαιμικό επεισόδιο του άκρου), η συχνότητα φλεβικής θρομβοεμβολής ήταν 6,9% (4,1% εν τω βάθει φλεβοθρόμβωση, 3,6% πνευμονική εμβολή), η θνητότητα από οποιαδήποτε αιτία ήταν 9,5%, και η συχνότητα του συνδυαστικού αποτελέσματος αρτηριακής θρομβοεμβολής, φλεβικής θρομβοεμβολής, και θνητότητας από οποιαδήποτε αιτία ήταν 35,2% (214/608). Η πολυπαραγοντική ανάλυση έδειξε σημαντική συσχέτιση μεταξύ του κύριου συνδυαστικού αποτελέσματος έκβασης και ηλικίας άνω των 75 ετών (OR: 1,90, 95% CI: 1,22-2,94), περιφερειακής αρτηριακής νόσου (OR: 3,23, 95% CI: 1,80-5,81), καρωτιδικής στένωσης (OR: 1,74, 95% CI: 1,11-2,75), καρδιακής ανεπάρκειας (OR: 1,84, 95% CI: 1,02-3,35), προηγούμενης φλεβικής θρομβοεμβολής (OR: 3,08, 95% CI: 1,75-5,42) και εισαγωγής στη μονάδα εντατικής θεραπείας (OR: 2,93, 95% CI: 1,81-4,75).

Συμπεράσματα: Οι νοσηλευθέντες ασθενείς με COVID-19 βρίσκονται σε υψηλό κίνδυνο για φλεβική θρομβοεμβολή, αρτηριακή θρομβοεμβολή, και θνητότητα έως και 90 ημέρες μετά την έξοδο από το νοσοκομείο. Ανεξάρτητοι προγνωστικοί παράγοντες των μείζονων θρομβοεμβολικών συμβάντων και της θνητότητας μετά την έξοδο από το νοσοκομείο περιλαμβάνουν την προχωρημένη ηλικία, καρδιαγγειακούς παράγοντες κινδύνου (ιστορικό φλεβικής θρομβοεμβολής, στεφανιαία νόσος, καρωτιδική στένωση και περιφερειακή αρτηριακή νόσος), χρόνια νεφρική νόσο, βαθμολογία στην κλίμακα IMPROVE-DD VTE ≥4 και εισαγωγή στη μονάδα εντατικής θεραπείας. Τα αντιπηκτικά φάρμακα που χορηγούνται μετά την έξοδο από το νοσοκομείο, κυρίως σε προφυλακτικές δόσεις, συσχετίστηκαν με μείωση του συνδυασμού μείζονος θρομβοεμβολής και θανάτου. Οι νοσηλευθέντες ασθενείς με COVID-19 και συνυπάρχουσα καρδιαγγειακή νόσο παρουσιάζουν ακόμη υψηλότερη συχνότητα αρτηριακής θρομβοεμβολής, φλεβικής

θρομβοεμβολής και θανάτου έως και 90 ημέρες μετά την έξοδο από το νοσοκομείο και οι σχετιζόμενοι ανεξάρτητοι παράγοντες κινδύνου περιλαμβάνουν την προχωρημένη ηλικία (άνω των 75 ετών), περιφερειακή αρτηριακή νόσο, στεφανιαία νόσο, αποφρακτική νόσο καρωτίδων, καρδιακή ανεπάρκεια, ιστορικό φλεβικής θρομβοεμβολής και εισαγωγή στη μονάδα εντατικής θεραπείας. Η αναγνώριση ασθενών COVID-19 υψηλού κινδύνου, συμπεριλαμβανομένων αυτών με συνυπάρχουσα καρδιαγγειακή νόσο, μπορεί να υποδείξει επιπλέον στόχους και προγνωστικούς δείκτες για την πρόληψη της μείζονος θρομβοεμβολής και θνητότητας μετά την έξοδο από το νοσοκομείο. Τυχαιοποιημένες μελέτες χρειάζονται για να εξεταστεί ο ρόλος των αντιθρομβωτικών παραγόντων, ειδικά των αντιπηκτικών και της προσθήκης αντιαιμοπεταλιακής αγωγής στην άμεση περίοδο μετά την έξοδο από το νοσοκομείο.

"In the fields of observation chance favors only the prepared mind"

Louis Pasteur

Contents

Chapter 1. Foreword

In the wake of the unprecedented global health crisis precipitated by the COVID-19 pandemic, the pursuit of knowledge has become an imperative in understanding the profound and far-reaching consequences.

As the virus invaded communities worldwide, New York City found itself at the epicenter of the storm, dealing with an unparalleled surge in cases, overwhelmed healthcare infrastructure, and an acute need for comprehensive research to inform evidence-based interventions.

Thrombotic complications emerged as an important issue in patients infected with COVID-19. When the COVID-19 pandemic hit New York, we were among the first researchers to recognize that this was an unprecedented situation caused by a highly thrombogenic virus.

The actual incidence of arterial and venous thromboembolic events in hospitalized patients with COVID-19 has not been fully elucidated. Further, there is a lack of data regarding post-discharge thromboembolic events in the COVID-19 hospitalized population. Against this backdrop, we undertook an investigator-initiated, multicenter, prospective registry named CORE-19 with data derived from a multihospital health system in New York to study the risk of up to 90-day post-discharge thromboembolic complications in hospitalized patients with COVID-19. Further, we investigated post-discharge outcomes in a subpopulation with common cardiovascular comorbidities.

Lastly, in this opening section of the PhD thesis, I have to express my gratitude to all those who helped me achieve this accomplishment. If I have seen further, it is by standing on the shoulders of giants.

First, I would like to thank my supervisors Professor Miltiadis Matsagkas and Professor Eleni Arnaoutoglou for their tremendous support and guidance. Without any doubts, Prof. Matsagkas and Prof. Arnaoutoglou believed in my potential to complete the thesis from the first day I proposed the idea. Undoubtedly, without the support and trust of these two aforementioned professors, the completion of this thesis would have not been possible.

I would also like to express my eternal gratitude to Professor Alex Spyropoulos who without knowing me offered a position in his lab and believed that I would be able to perform in a fast-paced and competitive environment in a place such as New York city. Citing the words of Frank Sinatra's song "Theme from New York, New York" he told me "If you can make it here, you'll make it anywhere; it's up to you". Prof. Spyropoulos served as a unique mentor, teaching me to face obstacles and challenges as opportunities to evolve and over the years this relationship made me stronger and put me on a trajectory to achieve things that seemed impossible.

Most importantly, I would like to thank my parents, Ioanna and Athanasios, for the unwavering support and sacrifices they have made to ensure my education. Their selfless dedication to providing me with the opportunities and resources needed for academic growth has been the cornerstone of my journey. The act of parents making sacrifices for you and foregoing pleasures is a privilege that should not be taken for granted. I would also like to thank my wife Maria and my sister Panagiota for their support, through their understanding, patient listening, thoughtful advice, and words of encouragement when the

workload seemed overwhelming. Thank you all from the bottom of my heart for being my pillars of strength during this academic pursuit.

Larissa,

September 2024

Dimitrios Giannis

Chapter 2. General Information

2.1 COVID-19

2.1.1 Definition and pathogenesis

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family of Coronaviridae, which are large, enveloped, single-stranded RNA viruses that mainly cause respiratory and gastrointestinal disease. (1) The virus is spherical in shape (2), has a diameter of approximately 60-140 nm (3–5) and the viral genome is a single-stranded RNA molecule of approximately 29.9 kb in size, which encodes for structural proteins, including the spike (S), envelope (E), membrane (M), and nucleoprotein (N) proteins, and nonstructural proteins, including the 3-chymothrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase. The virus is enveloped by a lipid bilayer that contains copies of the viral spike (S) protein, consisting of the S1 subunit (binds to the cell entry receptor) and S2 subunit (mediates membrane fusion). (3,6–8) Sars-CoV-2 enters the host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely distributed in various organs such as the lungs and upper respiratory tract, small intestine, and arterial and venous endothelium. (9,10) Subsequently, the virus initiates the transcription and translation of viral proteins in the endoplasmic reticulum**.** (8,11) The viral replication activates the production of interferons and chemokines that act in an autocrine and paracrine fashion to promote an antiviral effect and to activate the innate and adaptive immunity that facilitate the defense against the virus. (8) The overt inflammation results in lung injury, known as diffuse alveolar damage, consisting of pneumocyte death, type II pneumocyte hyperplasia, exudates, interstitial and alveolar edema, and platelet-fibrin thrombi. (12)

2.1.2 Epidemiology and risk factors

SARS-CoV-2 emerged in December 2019 in Wuhan, China, rapidly spread around the world, and has currently affected more than 700 million patients and over 7 million patients have died globally. COVID-19 has had a significant impact on healthcare systems, economies, and social norms. (13,14)

SARS-CoV-2 is primarily transmitted through respiratory droplets generated when an infected person talks, coughs, or sneezes in poorly ventilated or crowded settings or by touching surfaces contaminated with the virus. (15–17) Various factors can affect an individual's risk of developing severe disease or dying from COVID-19. Age is an important factor, with older adults being at a higher risk of severe disease and death. (18–22) Males are at higher risk of worse outcomes and mortality from COVID-19 compared to females. (22,23) Underlying comorbidities, such as cardiovascular disease, diabetes mellitus, and obesity, have been associated with an increased risk of severe disease and mortality. (24,25) Socioeconomic and minority status can also play a role, with individuals in lower socioeconomic groups being at a higher risk of contracting the virus and experiencing severe disease due to a variety of factors such as lack of access to healthcare. (26–28)

2.1.3 Clinical manifestations and diagnosis

The clinical manifestations of COVID-19 can vary significantly, with the most common symptoms at presentation including fever (>85%), cough (>65%) and myalgia or fatigue (>40%). (3,7,29) The severity of COVID-19 ranges from no symptoms or mild symptoms (in the majority of cases) to severe illness, intensive care unit (ICU) level of care (up to 20-25% of hospitalized patients), sepsis and death. (29–31) Respiratory symptoms are commonly mild, including sore throat and cough, but complications may develop such as

pneumonia and acute respiratory distress syndrome (ARDS), characterized by acute hypoxemic respiratory failure requiring mechanical ventilation along with multiorgan failure associated with acute renal, cardiac, and hepatic injury. (32–34) Cardiovascular manifestations include acute myocardial infarction (MI), arrhythmias, myocarditis, congestive heart failure (CHF) exacerbation, and thrombotic events. (35–37) The incidence of gastrointestinal symptoms ranges between 15%-27% based on pooled data analyses, and include lack of appetite, nausea or vomiting (12%), and diarrhea (17%). (38–41) The complete spectrum of presentations and complications associated with COVID-19 during hospitalization and in the post-discharge period has been partially elucidated but is not fully known.

Diagnosis of COVID-19 involves a combination of clinical evaluation and laboratory testing. Laboratory tests, such as antigen detection rapid diagnostic tests or polymerase chain reaction (PCR)/nucleic acid amplification (NAAT) tests are used to detect the presence of the SARS-CoV-2 virus in respiratory samples. Antigen detection tests have acceptable sensitivity (76.0%-78.2%) and excellent specificity (99.5%-100.0%) based on recent pooled analyses. (42,43)

2.1.4 Treatment and prevention

Treatment for COVID-19 encompasses a range of strategies aimed at alleviating symptoms, maintaining vital organ function, and addressing potential complications. In mild cases, self-isolation, rest, and symptom management with over-the-counter medications such as acetaminophen or NSAIDs are typically recommended.(44) Severe cases may necessitate hospitalization, where oxygen therapy, antiviral medications, and immunomodulatory drugs may be administered. Further, targeted COVID-19 treatment approaches have evolved over

time based on emerging evidence and clinical trials. The antiviral drug remdesivir demonstrated promising results in reducing the recovery time in hospitalized patients (10 days with remdesivir vs 15 days in the placebo group). (45) Dexamethasone administered at low dose (6 mg once daily) was found to reduce mortality rates among patients requiring supplemental oxygen (RR = 0.82) or mechanical ventilation (RR = 0.64), but was not effective in those not receiving respiratory support and increased mortality at higher dose (10-20mg daily) in patients not on oxygen or patients on simple oxygen only (RR = 1.59). (46–48) Monoclonal antibodies against the spike protein, such as sotrovimab and casivirimab/imdevimab (REGEN-CoV), have been authorized for emergency use in high-risk individuals to reduce the viral load, prevent disease progression, decrease the incidence of hospitalization and death, and protect against the emergence of new variants.(49–52) Lastly, therapeutic anticoagulation (UFH or LMWH) administered for up to 14 days has shown benefits in terms of mortality and major thromboembolism in non-ICU hospitalized patients with increased D-dimer levels (CIIa evidence), while in ICU patients prophylactic dose heparin is recommended (AI evidence).(53)

Prevention plays a crucial role in controlling the spread of COVID-19. Public health measures, such as vaccination campaigns, mask-wearing, contact tracing and testing, and social distancing, are essential in mitigating transmission. (54,55) The development of COVID-19 vaccines has played a crucial role in preventing the spread, preventing severe illness, reducing hospitalizations, and mitigating the impact of the virus with an efficacy ranging between 70%-100% and mildly attenuated efficacy (>90%) at 6 months after administration. (54,56–58) Continued adherence to preventive measures, along with regular testing, contact tracing, and quarantine measures have further limited the spread of the virus. (55,59–61)

2.2 Major thromboembolism and mortality in COVID-19

2.2.1 Pathogenetic mechanisms of coagulopathy in COVID-19

COVID-19 is strongly associated with macrovascular thromboembolic events, including venous thromboembolism (VTE), such as deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as arterial thromboembolism (ATE), such as ischemic stroke and MI, particularly in hospitalized patients with severe or critical illness. (62–65). The pathophysiology underlying the formation of clots has not been fully elucidated yet, but current data suggest that a complex pathway of interacting inflammatory cytokines (interleukins, interferons, tumor necrosis factors), platelet and neutrophil activation and interaction, and endothelial cell dysfunction, trigger a cascade of coagulation abnormalities**.** The effect is more pronounced in patients with severe COVID-19 affected by a prothrombotic state that leads to a multifold increased risk of in-hospital major thromboembolism**.** (65,66) Coagulation parameters (PT, aPTT) and markers of coagulopathy, including thrombocytopenia, elevated levels of D-dimer, fibrin degradation products, have been associated with both thromboembolic events and mortality in individuals with COVID-19. (30,67) The current data suggests upregulation of procoagulant pathways and inhibition of antithrombotic mechanisms along with decreased fibrinolysis. (68) The prospective observational HemoCoV study that investigated thromboelastometry parameters in ICU COVID-19 patients demonstrated hypercoagulability (increased amplitude at 5 and 10 min after clotting time) and hypofibrinolysis (increased clot stability) in patients with severe COVID-19 and non-survivors despite anticoagulation with prophylactic or intermediated dose LMWH. (69) Similarly, Aires and colleagues showed that patients with COVID-19 have a prothrombotic state as demonstrated by reduced

clotting time and time to clot formation in thromboelastometry. (70) Further, thromboelastometry profiles may be used to distinguish severe from non-severe COVID-19 patients, and thromboelastometry may identify phenotypes predisposing to increased thrombotic risk that can be used for individualized therapeutic interventions.(71,72)

At the molecular level, it has been proposed that the SARS-CoV-2 virus infects endothelial cells by binding to the angiotensin-converting enzyme 2 receptor, causes endotheliopathy/endotheliitis and promotes the formation of microthrombi in the lungs, changes in cardiac biomarkers and platelet dysfunction. (66,73,74) The direct and indirect endothelial cell damage results in decreased antithrombotic activity inherent to the normal endothelium, manifested as increased platelet activation and increased von Willebrand factor (vWF) levels. (75,76) Platelet-neutrophil interaction has been suggested as a key mechanism of COVID-19 coagulopathy. (77) Platelets in COVID-19 are hyperreactive and express high levels of P-selectin and release increased amounts of platelet factor 4(PF4), a factor that promotes the adhesion of neutrophils on endothelial cells and formation of neutrophil extracellular traps (NETs). (78,79) Previous work suggests that elevated D-dimers in hospitalized medically ill patients, including those with pneumonia and sepsis, either as a stand-alone tool or implemented in VTE risk assessment models is an independent prognostic biomarker to predict VTE and may have special significance and implications in COVID-19 populations. (30,80,81) Very elevated D-dimers, in the context of severe or critical COVID-19 disease, has been associated with an increased risk of thromboembolic events and poor prognosis. (65) Thromboinflammation and immunothrombosis have been proposed as major mechanisms of COVID-19 pathogenesis and involve overt inflammation, cytokine release, activation of coagulation pathways resulting in microvascular thrombosis, thrombotic microangiopathy and multi-organ

damage**.** (82,83) Increased levels of proinflammatory cytokines that disrupt the endothelial integrity and function have been reported in COVID-19, including IL-6, IL-1β, IFN-γ, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP). (76,84,85) Specifically, the positive association between IL-6 and fibrinogen levels in patients with COVID-19 ARDS, the increased release of NETs, the activation and deposition of complement components, and the platelet-leukocyte interaction and aggregate formation support the theory of thromboinflammation. (33,77,86–89) Thrombotic microangiopathy is associated with thrombocytopenia, microangiopathic hemolytic anemia, end organ damage, and pulmonary capillary stasis/microthrombi that form despite prophylactic anticoagulation. In summary, high rates of undiagnosed pulmonary microthrombi at time of death suggest an association between microvascular thrombosis, tissue ischemia, organ failure, and mortality. (90,91)

2.2.2 Venous thromboembolism in COVID-19

COVID-19 patients are at a significantly increased risk of thromboembolic events at any stage of the disease, including the preadmission phase, hospitalization, and the post-discharge period. (92) The risk of VTE in hospitalized patients with COVID-19 has been assessed extensively, with more than 80 such studies identified (93)**.** Studies reporting pooled inpatient rates of COVID-19 associated VTE are subject to high heterogeneity, (94) though pooled rates for the early pandemic are 10-15% for VTE and early reports from large cohorts placed the incidence of inpatient VTE between 1.7%-2.9%. (30,63,93,95,96). The incidence of VTE was significantly higher in studies implementing screening Doppler US (40.3%; 95% CI, 27.0–54.3) compared to those without screening US (9.5%; 95% CI, 7.5–11.7), and higher in patients requiring ICU level of care. (93,95)

The risk of major thromboembolism and death remains elevated in the immediate and late post-discharge period. (37,97–99) Rates of post-discharge VTE may be at least four-fold greater in COVID-19 patients compared with pre-pandemic populations and range between 0.2%-14.7%, with a recent meta-analysis showing a pooled incidence of 1.8% (DVT and PE incidence 0.9% and 1.5%, respectively) at a mean follow-up of 61.7 days and VTE occurring at an average of two weeks post-discharge.(98) Recent large cohort US data including 40,524 COVID-19 hospitalized patients reported a 13.4% rate of thromboembolic events during hospitalization, a 4.3% of thromboembolic events after discharge, and a mortality rate of 15.0% at a mean follow-up of 80.3 days, including a 1.44% rate for DVT and 1.24% rate for PE at a mean time of 8.5 and 6.4 weeks after discharge, respectively. (37) Another large US study derived data from the US Department of Veteran Affairs database and included 153,760 COVID-19 patients (of which 131,612 were non-hospitalized), 5,637,647 contemporary controls, and 5,859,411 historical controls followed at 12 months after the acute infection, and showed increased risk of stroke (HR=1.52, 95% CI: 1.43-1.62), MI (HR=1.63, 95% CI: 1.51-1.75), PE (HR=2.93, 95% CI: 2.73-3.15), DVT (HR=2.09, 95% CI: 1.94-2.24), superficial vein thrombosis (HR=1.95, 95% CI:1.80-2.12). (100) Previously published data from a network cohort study including 909,473 COVID-19 patients (32,329 hospitalized) showed a cumulative 90-day post-diagnosis VTE rate of 0.2–0.8%, with increased rates among hospitalized patients (4.5%). (101) Nationwide level-analysis in Europe has previously confirmed that COVID-19 is associated with an increased DVT and PE risk, especially in patients with comorbidities, for at least three and six months, respectively. (102) The meta-analysis by Zuin et al. revealed a VTE, DVT, and PE pooled incidence of 1.8%, 0.9%, and 1.5%, respectively at two months after discharge with the majority of events occurring within two weeks post-discharge. However, heterogeneity

between current literature complicates the generalizability to other high-risk subgroups, including patients with arterial disease. (98)

2.2.3 Arterial thromboembolism in COVID-19

Viral infections have been associated with myocardial and systemic vascular injury and with exacerbation of pre-existing arterial disease. (103,104) Patients with preexisting cardiovascular disease have high ACE2 expression and are more susceptible to severe COVID-19, based on a recently published genomic meta-analysis that associated increased ACE2 levels with both COVID-19 severity and cardiovascular disease and may explain the increased rate of endothelial injury/arterial complications, through the facilitation of viral cell-entry**.** (105–108) Further, the risk of arterial thrombosis in hospitalized COVID-19 patients may reflect the modified effect of COVID-19 induced inflammation on a chronically damaged endothelium. Atherosclerosis is associated with low-grade inflammation contributing to endothelial damage, accumulation, and disruption of atherosclerotic plaques, and acute arterial thromboembolic complications.(109–111) In COVID-19 inpatients ATE rates have been placed at 3-5%. (93,112)

Multiple previous studies and clinical trials of hospitalized COVID-19 patients reveal an increase of ATE during the post-discharge period, with implications up to one year after diagnosis. (98,113,114) Previous observational study data shows that the risk for ATE remains high up to 49 weeks after discharge, with a 14-fold increased risk for first arterial thrombosis during the first week after COVID-19 hospitalization and a 1.46-fold increased risk during weeks 27 to 49. (115) Rates of post-discharge ATE have been estimated up to 39.8/1000 person-years in a large population-level study of 118,879 hospitalized patients with COVID-19 in the United Kingdom. (115) Data from a network

cohort study conducted in four European countries (909,473 COVID-19 patients) revealed a 90-day post-diagnosis cumulative ATE rate 0.1–0.8% with a 3.1% rate among those hospitalized. (101) In the US, prospective data derived from the early phase of the pandemic placed the ATE rate at 1.71% in the 90-day post-discharge period.(113) Subsequently, a recently published retrospective observational study of 40,524 hospitalized patients with COVID-19 reported post-discharge rates of ischemic stroke, MI, and acute limb ischemia of 1.18%, 1.53%, and 0.10%, respectively at a mean follow-up of 70.7 days and time to first-event 71.6, 52.6, and 83.5 days, respectively. (37) Data from a recent meta-analysis of 7,816 discharged patients with COVID-19 showed an ATE rate of 1.46% for a post-discharge follow-up period of up to 6 months among the included studies, while another large meta-analysis of 20,875,843 patients in the post-acute phase of COVID-19 showed a cumulative post-discharge rate of incident MI between 0.1 to 1.1% with a mean follow-up of 8.5 months. (116,117)

Patients with COVID-19 and pre-enrollment indication for dual antiplatelet therapy were not included in the randomized trials and the current evidence and expert recommendations/guidelines recommend continuation of prior antiplatelet therapy and according to guidelines for non-COVID-19 patients. (118) However, despite the potential benefits of antiplatelets (anti-inflammatory, antithrombotic, and analgesic), currently available high-quality data from randomized trials does not support (conflicting data) the initiation of acetylsalicylic acid (ASA) or P2Y12 (such as clopidogrel or ticagrelor) as single agent or combined with ASA. (119–121) Interestingly, the REMAP-CAP trial in hospitalized severe COVID-19 patients showed a benefit on 90-day mortality, at the cost of a significantly increased risk of major bleeding in patients receiving antiplatelets (OR = 2.97; 95% CI, 1.23–8.28). (122) The observed benefit of antiplatelet therapy at 90 days and

the persistently increased risk of arterial thromboses for several months after the diagnosis of COVID-19 indicate the need for well-designed trials investigating the risks and benefits of antiplatelets in the post-discharge period.

2.2.4 Mortality associated with major thromboembolism in COVID-19

Thromboembolism is a major risk factor for mortality in COVID-19 based on clinical and in vitro data. Early autopsy data in hospitalized patients with COVID-19 suggested that ~60% and up to 100% of thrombotic events including PE and pulmonary vasculature thrombosis may not be suspected before death, indicating that thrombotic mechanisms play a major role in mortality. (90,91) Comparative post-mortem autopsy studies between patients with COVID-19 as the primary/contributing cause of death and patients with a cause of death unrelated to COVID-19 revealed an up to 81% versus 46% rate of lung vasculature microangiopathy, pulmonary artery branch thromboses, or PE, respectively. (123) The association between microvascular thrombosis and COVID-19 mortality was further supported by Haberecker et al. in their autopsy study of 15 patients showing a significant association between COVID-19 related death and the presence of pulmonary endotheliitis or pulmonary fibrin thrombi. (124) Pooled analysis of studies reporting post-mortem data showed a 59.2% rate of microthrombi, 21% rate of small vessel endotheliitis/capillaritis, and 8.3% rate of PE. (125) Clots on pathology reports consist of fibrin and/or platelets and mostly involve small and occasionally medium sized vessels, occupying more than 25% of the lung parenchyma bilaterally in one study by Carsana et al. (12,125)

Early in the pandemic it was recognized that COVID-19 non-survivors had significantly elevated levels of D-dimer and fibrin degradation products. (126) Later,

mortality was associated with increased levels of vWF and soluble thrombomodulin. (127) Larger cohorts further validated D-dimer and the IMPROVE-DD (International Medical Prevention Registry on Venous Thromboembolism plus D-Dimer) risk assessment model as predictors of poor prognosis in COVID-19. (29,80,128–130)

2.2.5 Anticoagulation strategies

In an effort to decrease morbidity and mortality in COVID-19 and based on reports showing COVID-19 associated hypercoagulability and postmortem studies showing macrothrombi and in-situ pulmonary thrombosis, several studies investigated the role of anticoagulation in inpatient (therapeutic or intermediate dose versus standard dose thromboprophylaxis), outpatient and post-discharge settings. (131–139) A recent meta-analysis including 47 studies revealed a significantly decreased risk of thromboembolism (OR: 0.21 95%CI: 0.06-0.74) and a mortality benefit in patients under non-ICU care receiving therapeutic or intermediate anticoagulation. Therapeutic anticoagulation was associated with a significantly increased risk of bleeding in the non-randomized studies (OR 3.45, 95% CI, 2.32 - 5.13), an effect that was non-significant in the RCTs.(140) Pooled data from a meta-analysis of seven randomized controlled trials with a sample size of 5154 and a mean follow-up of 33 days showed a 45% decreased VTE rate in patients treated with escalated dose thromboprophylaxis, with comparable mortality and an associated 73% increased risk of major bleeding in the escalated dose group. (141) Results derived from the randomized controlled trials are conflicting, but the multiplatform trial (REMAP-CAP, ATTACC, ACTIV-4-a) and the HEP-COVID trial reported a similar benefit with therapeutic dose anticoagulation in non-ICU patients, and well-established findings include a benefit in terms of 21-day organ free support or decreased major thromboembolism in

inpatients requiring non-ICU level of care, with the greatest benefit occurring within 14-days of treatment with therapeutic dose anticoagulation and in patients with elevated D-dimer. (141,142) The open-label, randomized multiplatform trial (REMAP-CAP, ATTACC, ACTIV-4-a) studied the efficacy and safety of therapeutic dose anticoagulation with heparin compared to standard of care thromboprophylaxis in hospitalized patients with COVID-19. The trial found increased probability of survival to hospital discharge with reduced need for organ support (numbers of days free of organ support) in non-critically ill patients (N=2219 patients), but the benefit was not observed in critically ill patients (N=1098 patients). (131,132) Further analysis of the data derived from the multiplatform trial in 72 patients, who became critically ill while on therapeutic-dose heparin when they were non-critically ill, showed that continuation of therapeutic-dose compared to reduced-dose heparin was non-beneficial and potentially harmful. (143) The HEP-COVID multicenter randomized trial (N=253) studied the efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19 with D-dimer levels more than 4 times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater. The primary efficacy outcome (composite of VTE, ATE, or death from any cause) incidence was 32% lower (RR = 0.68, p = 0.03) in the therapeutic (28.7%) vs the standard of care group (41.9%) and without significant increase (p = 0.17) in major bleeding at 30 days after enrollment (4.7% vs 1.6%, respectively), but the treatment effect was not seen in ICU patients (RR = 0.92, p=0.71). (133) The multicenter randomized controlled INSPIRATION trial (N=562 patients) performed in 10 centers in Iran investigated the effect of enoxaparin thromboprophylaxis at an intermediate weight based (1mg/kg daily) versus standard-dose (40 mg daily) in ICU-admitted COVID-19 patients and reported comparable results in the

primary outcome consisting of VTE, ATE, need for ECMO, or mortality at 30 after enrollment (45.7% and 44.1%, respectively, p = 0.7). (137) More recently, the COVI-DOSE multicenter, randomized open-label, phase 4 trial (N = 1000 patients) conducted in 20 French centers investigated the role of a weight adjusted intermediate dose LMWH compared to a fixed standard of care dose LMWH administered for up to 28 days to non-critically ill (80.1%) or critically ill (19.9%) and showed no difference in both populations in terms of symptomatic VTE (DVT or PE) between the two regimens (1.2% vs 2.1%, p = 0.31) and an increased risk of clinically relevant non-major bleeding in the adjusted dose group (4.9% vs 1.9%, HR:2.69, p = 0.011). (144) Based on these findings, a meta-analysis that included 6 studies and 2130 critically ill patients from the HEP-COVID, the multiplatform (REMAP-CAP, ATTACC, ACTIV-4-a), and the INSPIRATION trial among others, reported no difference in all-cause mortality (RR = 1.01, p = 0.93), ATE (RR = 1.07, p = 0.79) and decreased VTE between an escalated (intermediate or therapeutic) compared to standard thromboprophylaxis (RR = 0.57, p = 0.02) at the cost of increased risk of minor bleeding (RR = 1.65, p = 0.02) and increased clinically but marginally statistically non-significant risk of major bleeding (RR = 1.65, p = 0.07.(145) In moderately ill patients with COVID-19, therapeutic-dose versus standard-dose thrombopropylaxis with LMWH or UFH, showed no benefit in the incidence of a composite endpoint of mortality, need for invasive and non-invasive mechanical ventilation, or need for admission to the ICU (16.2% versus 21.9%, respectively, p = 0.12) at up to 28 days after enrollment in the RAPID trial, but mortality was lower in the group allocated to therapeutic compared to prophylactic heparins (1.8% versus 7.6%, respectively, p = 0.006).(135) Therapeutic anticoagulation with DOAC in the inpatient setting was found nonbeneficial in the multicenter, randomized, controlled ACTION trial (N=615 patients, 94% non-critically ill patients), which compared

rivaroxaban versus standard thromboprophylaxis with LMWH or UFH through a hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen to day 30 (win ratio 0.86, p = 0.4). Of note, therapeutic anticoagulation with rivaroxaban was associated with a 3-fold increased risk of major or clinically-relevant non-major bleeding (RR = 3.64, p = 0.001). (136) Similarly, the open-label, multicenter, randomized COVID-PREVENT trial (N = 111 patients with moderate/severe COVID-19) compared therapeutic anticoagulation with rivaroxaban 20mg daily for 7 days followed by rivaroxaban 10mg for 28 days versus thromboprophylaxis with heparin for 7 days followed by no thromboprophylaxis and showed no difference in D-dimer levels at 7 days (p = 0.78), clinical outcomes as defined by the 7-category ordinal COVID-19 scale by WHO (p = 0.085), and the composite secondary endpoint of major thromboembolism, all-cause mortality or progression to intubation or invasive ventilation at 35 days after randomization (10.9% vs 21.4%, p = 0.264, respectively). Of note, an exploratory analysis of the COVID-PREVENT data showed improved clinical outcomes in patients on rivaroxaban with a baseline D-dimer greater than 2 times the ULN (Relative effect: 0.632, p = 0.026). (146) The benefit of treatment dose heparins early in the course of COVID-19 may reflect their activity against both macrovascular and microvascular thrombosis, prior to the development of an irreversible vicious cycle of hyperinflammatory state/cytokine storm (thromboinflammation). (133,147,148) Indeed, a recent secondary analysis of the ATTACC/ACTIV-4a trial non-critically ill patient data showed different benefits from therapeutic-dose heparin based on the severity of inflammation reflected in levels of C-reactive protein (CRP). Elevated CRP (CRP 40-100 mg/L or ≥100 mg/L compared to patients with CRP <40 mg/L at baseline) was associated with increased need for organ support, length of hospital stay, risk of 28-day mortality, and major thromboembolism or

mortality. Non-critically ill patients with COVID-19 and CRP 40-100 mg/L benefited the most from treatment dose UFH or LMWH compared to thromboprophylaxis, as shown by the increased organ support-free days (OR: 1.63, 97.9% posterior probability of benefit). There was no benefit in patients with more severe inflammation (CRP ≥100 mg/L) (149) Further, another prespecified secondary analysis of the same trials in non-critically ill hospitalized patients with COVID-19 showed that therapeutic dose heparin was associated with a decreased incidence of severe AKI (KDIGO stage 2 or 3) or death in patients receiving therapeutic dose heparin compared to thromboprophylaxis (4.4% vs 5.5%) with a 97.7% probability of superiority in patients with stage 3 AKI or death (3.1 vs 4.6%, adjusted RR: 0.64, 95%CI: 0.40-0.99). (150) These results indicate that therapeutic dose heparin no only decreases the risk of thrombosis but also acts as an anti-inflammatory agent that protects against multiorgan failure when administered early in the course of COVID-19 before irreversible overt inflammation develops.

Similar to inpatient settings, extended thromboprophylaxis has been considered to reduce the risk of VTE in COVID-19 patients after discharge. The MICHELLE trial investigated a high-risk group of COVID-19 patients using the IMPROVE VTE score ≥4 or elevated (≥2 times the ULN) D-dimer and found a 67% relative risk reduction for the composite primary endpoint of major thromboembolism and cardiovascular death in patients receiving rivaroxaban 10 mg daily for 30 days after discharge compared to no anticoagulation (3.14% vs 9.43%, respectively). Extended thromboprophylaxis with rivaroxaban was shown to be a cost-effective option to prevent major thromboembolism and cardiovascular death in high-risk COVID-19 patients after discharge. (139,151) Based on these findings, the ISTH guidelines support the treatment with prophylactic dose rivaroxaban for 30 days in highly-selected COVID-19 patients who were previously

hospitalized to reduce the risk of VTE in the post-discharge period. (152) However, recent data from a multicenter UK study including 1,944 (971 per group) matched patients with and without thromboprophylaxis (either DOAC or LMWH) for a median duration over 4 weeks found no difference in VTE up to 90 days after hospital discharge (1.3% vs 0.92%, p = 0.52, respectively). (153) Extended post-discharge thromboprophylaxis may be considered for high-risk patients with International Medical Prevention Registry on Venous Thromboembolism plus D-Dimer (IMPROVE-DD) VTE score ≥4 or elevated (≥2 times the ULN) D-dimer, as supported by the ISTH guidelines (139,152).

In the outpatient setting randomized controlled trials of prophylactic anticoagulation have not showed any benefits in terms of prevention of thromboembolism, clinical status deterioration or decreased mortality. (138,154–157) The PREVENT-HD was a multicenter (US), double blinded, randomized controlled trial comparing rivaroxaban 10 mg vs placebo daily for up to 35 days in outpatient symptomatic COVID-19 (N=1284 patients) that found no benefit in reducing VTE, ATE, hospitalization rates and mortality. (138) Similarly, another randomized study by Ananworanich et al. enrolled 497 patients with mild COVID-19 and showed no difference in disease progression rates between patients treated with rivaroxaban and patient receiving placebo (20.7% vs 19.8%, respectively, p = 0.78).(154) A meta-analysis that combined the results of these two trials showed no benefit in the composite endpoint of major thromboembolism, all cause hospitalization, and all-cause mortality or the secondary endpoint of all-cause hospitalization, despite decreased arterial and thrombotic events. Based on these results, rivaroxaban is not indicated as a broad prehospital treatment in patients with acute COVID-19. (158) The randomized, multicenter (Europe) OVID trial that compared enoxaparin 40mg daily versus no thromboprophylaxis for 14 days in symptomatic COVID-19 outpatients older than 50 years (N=473 patients)

showed no difference in the composite endpoint of hospitalization or all-cause mortality within 30 days after enrollment. (155) The ACTIV-4B multicenter (US) randomized, double, blinded trial (N=657 patients) showed no difference in VTE, ATE, hospitalization, and all-cause mortality between symptomatic COVID-19 outpatients receiving therapeutic apixaban (5mg), prophylactic apixaban (2.5mg) or placebo for 45 days. (156) Lastly, the multicenter CARE-COALITION VIII randomized clinical trial (N=660 patients) compared rivaroxaban 10mg daily for 2 weeks versus local standard of care showing no difference in the primary efficacy endpoint (VTE, ATE, need for mechanical ventilation, and mortality). (159) Of note, these randomized trials have terminated early due to low enrollment or low event rates and this may affect the generalizability of their findings.

2.2.6 Antiplatelet strategies

Early in the pandemic it was proposed that antiplatelet therapy may mitigate risk in the hospitalized COVID-19 population. An association between antiplatelet drug use and improved prognosis in COVID-19 patients was reported in early observational studies, but later was not confirmed by randomized trials. (160–163) In the early phases of the pandemic most observational studies included patients receiving antiplatelets prior to confirmed COVID-19 diagnosis in contrast to during hospitalization in randomized trials. (119,120,122,160,164) These findings may be partially explained by the effects of chronic antiplatelet therapy that prevented platelet activation prior to disease onset and progression to severe COVID-19; there was greater benefit with increased duration of treatment or antiplatelet administration in the early stages of COVID-19, prior to onset of overt inflammation. (119,160) In addition, the effect of antiplatelets may have been skewed by concomitant use of treatment dose anticoagulants. Patients with COVID-19 and pre-

enrollment indication for dual antiplatelet therapy were not included in the randomized trials and the recently published guideline by the American College of Chest Physicians (CHEST) suggests continuation of prior antiplatelet therapy and according to guidelines for non-COVID-19 patients. (118)

High-quality randomized trial data in hospitalized COVID-19 patients reveal that antiplatelet medications have yet to show benefit in prevention of major thromboembolism and death, and in fact may cause harm in non-critically ill hospitalized COVID-19 patients. (119,164) The ACTIV-4a randomized clinical trial explored the effects of combined P2Y12 inhibitors (ticagrelor or clopidogrel) and treatment dose heparin versus treatment dose heparin only in non-critically ill COVID-19 patients (n=562) for 14 days or until hospital discharge, and showed no benefit in the antiplatelet group in terms of major thromboembolism, including ATE (ischemic stroke, MI, and systemic embolism), or death at 28 days.(119) The REMAP-CAP trial investigated the effect of aspirin and P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in hospitalized critically ill COVID-19 patients, and despite showing a benefit on 90-day mortality (HR: 1.22; 95% CI, 1.06–1.40), demonstrated comparable rates of ATE in patients receiving antiplatelets compared to control (3.7% vs 2.3%, respectively). (122) The RECOVERY trial was a randomized, open-label, multicenter trial that included more than 14,000 hospitalized COVID-19 patients receiving either aspirin 150 mg daily or standard of care until discharge and evaluated 28-day mortality. Despite a reduction in length of stay until discharge and a slightly greater chance of being discharged alive within 28 days, there was no benefit from aspirin in terms of mortality, need for mechanical ventilation, or ATE events, including ischemic stroke, MI, and systemic embolism, while major bleeding risk was increased by 55%.(164) The recently published COVID-PACT trial, a multicenter, open-label, randomized controlled trial,

included COVID-19 patients receiving ICU-level care that were assigned to either antiplatelet therapy with clopidogrel 300 mg at randomization, followed by 75 mg daily, versus no antiplatelet therapy for the prevention of ATE and VTE. Reported ATE events were low in both groups and there was no benefit from clopidogrel use, with consistently nonsignificant results in prespecified subgroup analyses, including patients with atherosclerotic cardiovascular disease, diabetes, or age > 65 years, with comparable moderate and severe bleeding rates (4.0% vs 6.4%).(120) Lastly, the ACT trial was a multicenter, randomized, controlled trial that assigned hospitalized patients with COVID-19 to rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily for 28 days versus neither therapy and found no difference in terms of mortality, major thromboembolism including ATE (stroke, MI, acute limb ischemia) and PE at 45 days, and revealed a statistically significant increased risk of bleeding in the anticoagulant/antiplatelet arm (1.6% vs 0.66%, respectively). (165) The recently published ISTH guidelines consider the use of antiplatelets to reduce mortality in select critically ill hospitalized COVID-19 patients as an adjunct to prophylactic dose heparins, (122,152,164) and recommend against the use of antiplatelets in non-critically ill patients due to potential harm. (152)

2.3 Post-acute COVID-19 syndrome and longterm coagulopathy in COVID-19 survivors

2.3.1 Post-acute COVID-19 syndrome ("Long COVID")

Patients with COVID-19 may experience prolonged post-infection symptoms affecting multiple organs several weeks to months after resolution of the acute illness, including but not limited to fatigue, headache, cognitive dysfunction, palpitations, chest pain, shortness of breath, hair loss, and loss of taste or smell that affect daily functioning

(166–169) Symptoms might be persistent from the acute illness or develop later as new-onset symptoms following an initial recovery period. (167) This recently recognized post-acute COVID-19 syndrome (PACS), also known as "Long COVID", usually occurs within 3 months from the initial infection, with symptoms lasting for at least 2 months and cannot be explained by alternative diagnosis i.e. diagnosis of exclusion. (167) The incidence of PACS varies based on the time point set by each study and the follow up (Incidence range 9%-81%), but pooled analysis estimated it to be 43% (95% CI: 39%-46%) overall, with a higher rate of 54% (95% CI: 44%-63%) in previously hospitalized and 49% (95% CI: 35%-63%) in female COVID-19 patients. (170) Risk factors for PACS include advanced age, female sex, white race, poor physical and mental health, obesity/overweight status, and asthma. (171)

2.3.2 Coagulopathy as a mechanism of post-acute COVID-19 syndrome

The multiorgan involvement in the post-discharge period indicates that PACS may be caused by dysregulation of prothrombotic, antithrombotic and inflammatory mechanisms**.** (87,172) Persistent thromboinflammation with endotheliopathy, abnormal fibrin generation, and platelet hyperreactivity of arterial and venous vascular beds have been suggested as mechanisms contributing to PACS. (173) Increased levels of markers of endothelial dysfunction/activation (vWF, thrombomodulin, factor VIII), decreased levels of the metalloprotease ADAMTS-13, along with elevated regenerating endothelial cells post-COVID-19 indicate endothelial injury and a prothrombotic state extending beyond the acute phase. (174–177) Other prothrombotic changes include persistently increased thrombin generating potential and a hypofibrinolytic state at 4 months after hospital discharge. (178) Platelet hyperreactivity, increased platelet-neutrophil aggregate formation, thrombocytosis,

and increased NET formation from neutrophils similar to the acute phase have been observed in patients with PACS, thus supporting thromboinflammation as one of the core mechanisms in PACS. (179–181) In support of these mechanisms, the study by Fan et al. found elevated D-dimer and IL-6, markers of ongoing thromboinflammation, at up to 16 months after the acute infection. (182) Elevated D-dimer levels were also reported by Townsend et al. at 3 months post-infection in a cohort of 150 patients, including 54% outpatients. Hospitalization and age>50 years old were significantly associated with elevated D-dimer. (183)

Mechanisms that have been suggested as the main drivers of thromboinflammation in PACS include persistent endothelial and organ structural changes, residual viral reservoir, and immune system dysfunction. (87) Sars-CoV-2 nucleic acids have been detected in the bowel at 4-7 months after acute COVID-19 (184,185), and frequency was higher in patients with PACS compared to patients without PACS symptoms in the study by Zollner et al. (185) Based on autopsy data from patients that died in the setting of severe COVID-19, Sars-CoV-2 is widely distributed in non-respiratory tissues including the heart, lymph nodes, adrenal gland, eye, and the central nervous system as late as 8 months following the onset of infection. (186)

Findings supporting the theory of immune system dysregulation include the upregulation of mediators of the innate immune response (S100A8, HGMB1), neutrophil activation (Lipocalin-2), fibrosis signaling (Matrix metalloproteinase 7), alveolar repair (Hepatocyte growth factor), inflammation (IL-1β,IL-6, tumor necrosis factor), antigen persistence (proliferative-exhausted T cells), and the expansion of specific and non-specific cytotoxic CD8+ T cells, CD4+ T cells, and myeloid-derived suppressor cells. (187–190)

Chapter 3. Specific part

3.1 Purpose of the analysis

There are limited and conflicting data on the rates of thromboembolic events and death in the post-discharge period for hospitalized patients with COVID-19, with most previous studies limited by small sample sizes, retrospective designs, and non-standardized follow-up. The risk and associated risk factors of post-discharge thromboembolism and death in hospitalized COVID-19 patients remain poorly defined. To overcome the current knowledge gap in post-discharge rates of VTE, ATE, death, and secondary complications in hospitalized patients with COVID-19, we undertook an investigator-initiated, multicenter, prospective registry named CORE-19. Our second aim was to assess clinical and laboratory risk factors, as well as relevant medications, including anticoagulants, to predict the risk of thromboembolic disease or death in the post-discharge period. Further, we investigated post-discharge outcomes in a subpopulation with common comorbidities, such as coronary artery disease (CAD), carotid artery stenosis (CAS), peripheral arterial disease (PAD), or ischemic stroke.

3.2 Cardiovascular risk factors, thromboembolic outcomes and mortality of hospitalized COVID-19 patients in the 90-day post-discharge period

3.2.1 Introduction

Previous data from randomized trials suggest an elevated rate of major and fatal thromboembolic events in high-risk medically ill patients (including those with pneumonia and sepsis) within 6 weeks of hospital discharge, with a significant 28% to 38% risk reduction using extended thromboprophylaxis. (191,192) There have been few previous efforts to assess predictors of thrombosis or death in the post-discharge period for

hospitalized patients with COVID-19, which represent a subpopulation of the acutely medically ill population. However, the data on the rates of thromboembolic events and death in the post-discharge period for hospitalized patients with COVID-19 are conflicting, with previous studies limited by retrospective designs, poorly defined outcomes and non-standardized follow-up. The aim of this study was to investigate the rates of VTE, ATE, death, and secondary complications in hospitalized patients with COVID-19 at 3 months after discharge.

3.2.2 Methods

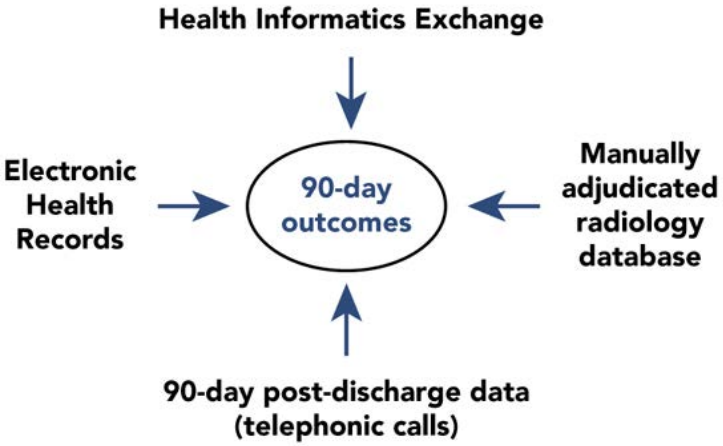
3.2.2.1 Study cohort

This study was a prospective registry of consecutive patients diagnosed with COVID-19 within a large US based health system. The Institutional Review Board approved the study (#20-0363) and, as described in the International Conference on Harmonisation guidelines for Good Clinical Practice, provided regulatory oversight. The study was performed with a waiver of informed consent and a de-identified dataset. The patient population consisted of discharged adults (age >18 years) with a polymerase chain reaction–confirmed COVID-19 diagnosis admitted to 1 of the 12 hospitals within the health system due to nonobstetric/nongynecologic reasons from March 1st to May 31st 2020 and responding to follow-up phone calls. Transfers between in-system hospitals were considered as a single visit. For patients with multiple hospitalizations for COVID-19, only the first hospitalization was considered. The health system policy, which went into effect on April 7th, 2020, at the height of the pandemic, recommended extended thromboprophylaxis with the direct oral anticoagulant (DOAC) rivaroxaban (10 mg orally) or low molecular weight heparin (LMWH) enoxaparin (40 mg subcutaneously daily; if creatinine clearance ≥15 mL/min) for

30 days in patients with COVID-19 with an IMPROVE VTE score of ≥4 or D-dimer twice the upper limit of normal (ULN) or higher. The IMPROVE-DD VTE score is a previously validated VTE risk assessment model for patients without COVID-19, and further validated for patients with COVID-19 during the pandemic. (81,193)

Data of interest were assessed by electronic medical record and health informatics exchange (HIE) review, a filtered radiology informatics database, and manual REDCap data entry with a comprehensive data collection form (including data derived from telephonic patient calls) through 90 days post-discharge (**Figure 1**). Our data set included demographic characteristics, all available diagnoses, comorbidities, VTE risk factors, laboratory values (highest values during index hospitalization), and medications, including in-hospital and post-discharge thromboprophylaxis, and image results assessed up to 90 days after hospital discharge.

Figure 1. Data sources for post-discharge thromboembolic outcomes and mortality of hospitalized patients with COVID-19



A dedicated team of 35 abstractors (including medical residents, fellows, and medical students supervised by the doctoral candidate Dimitrios Giannis, MD) attempted to contact discharged patients through at least three phone calls on different days and at different times to obtain one set of data elements during the study period using the standardized and structured REDCap questionnaire. The abstractors initially attempted a total of 100-150 total calls per day, while this rate gradually increased in parallel to the learning curve and experience that abstractors acquired after the completion of approximately 100 calls per abstractor. The rate eventually increased to 250-300 call attempts daily. The team of abstractors was guided through educational material (live remote guide-through sessions, recorded video guidance with instructions, electronic copies of the REDCap DCF, a phone script/checklist that included all important questions to be asked during a phone call, and a frequently asked questions file), daily support through a secure communication chat/portal, and weekly meetings between the study leadership and the team of abstractors to review the team progress and set next goals. Calls were assigned as batches of 100 calls per abstractor and at least three attempts on different days and times were made to contact non-responding patients. An excel datasheet, stored in a secure online portal was used to assign the calls, highlight data of interest, follow-up non-respondents, and grade the abstractor contribution. Weekly statistics, feedback regarding the abstractors' participation and any issues impairing the expected progress were discussed during the weekly meetings. A daily support, including weekends and out of office hours, was offered by the doctoral candidate, to ensure the resolution of any issues or concerns that abstractors were having during the data capture, data entry, and phone calls.

All study data were aggregated and systematically stored in an online unified repository/datamart (in parallel to offline securely stored back-ups). Our database includes

data extracted through automatic extract-transform-load (ETL) processes that query and transfer data from radiology databases, electronic health records (through identification of International Classification of Diseases 9th or 10th Revision codes), and the HIE and REDCap sources. The online unified repository resides in an instance of Microsoft SQL Server database and uses a common data model that ensures semantic interoperability between data originating from disparate sources and accurate interpretation of statistical analyses.

The team of abstractors called the patients and entered any post-discharge outcomes in the standardized REDCap questionnaire. Subsequently, in the population of respondents, demographic characteristics, all available diagnoses, comorbidities, VTE risk factors, laboratory values (highest values during index hospitalization), medications including in-hospital and post-discharge thromboprophylaxis, and post-discharge events were captured through automatic ETL processes that extracted data from radiology images, electronic health records, and HIE. All post-discharge outcomes that were captured manually through phone calls (in REDCap) or automatically through ETL processes were pooled in a common file that was then used by the abstractors to manually screen the patients' records and confirm or reject the presence of an outcome. The post-discharge outcomes were adjudicated by 2 senior abstractors, and any disagreements were resolved by a third experienced abstractor (doctoral candidate/member of the advisory committee).

3.2.2.2 Definitions

The primary efficacy outcome was a composite of VTE (DVT and PE), ATE (stroke, MI, non-MI coronary revascularization, major adverse limb event, and systemic embolism), and all-cause mortality (ACM) within 90 days after hospital discharge. DVT was defined as a

non-compressible venous segment on compression ultrasonography or presence of an intraluminal filling defect on venogram. PE was defined as an intraluminal filling defect on computed tomography (CT) angiography or spiral CT. The health system policy did not include any systematic screening for VTE during this study. Stroke was defined by a new focal neurologic defect lasting ≥24 hours, as confirmed by a neurologist with imaging studies. MI was defined by detection of a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: 1) symptoms of acute myocardial ischemia, 2) new or presumed new significant ST segment–T wave changes or new left bundle branch block development of pathologic Q waves in the electrocardiogram, 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology, or 4) identification of an intracoronary thrombus by angiography or autopsy. Major adverse limb event was defined by confirmation of arterial obstruction by imaging (including ultrasound, CT, magnetic resonance imaging, or conventional angiography), surgical findings, or pathology. Systemic embolism was defined as abrupt vascular insufficiency associated with radiologic evidence of arterial occlusion in the absence of other likely mechanisms. Death was determined by telephonic patient calls. The principal safety outcome was major bleeding (MB) using International Society on Thrombosis and Haemostasis criteria. (194) Secondary outcomes included rehospitalization (with or without ICU admission), congestive heart failure (CHF) exacerbation, atrial fibrillation/flutter, interstitial lung disease, myocarditis, and ARDS using standardized definitions.

3.2.2.3 Statistical analysis

Data were summarized using descriptive statistics. Categorical variables were summarized using frequencies and percentages; continuous variables were summarized using means and standard deviations. Logistic regression analyses were performed to assess the association between independent variables and the composite outcome consisting of VTE or ATE or ACM (yes or no). Univariate analyses were performed first, followed by multivariate analyses. In the final logistic regression model, the following variables were included regardless of their univariate *p* values: age, body mass index, IMPROVE-DD VTE score, use of anticoagulants or antiplatelet agents, D-dimer >4 to 6 times the ULN or >6 times the ULN, history of VTE, CAD, history of PAD, history of carotid occlusive disease, CHF, chronic renal disease, race, and ICU admission. Variables with univariate *P* values <.2 were also included in the final model if selected through backward selection process. Results are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were conducted using SAS software (version 9.4; Cary, NC). A 2- tailed *P* value <.05 was considered statistically significant.

3.2.3 Results

3.2.3.1 Baseline characteristics, comorbidities, laboratory parameters, and inpatient treatment

Of a total of 11,249 adult nonobstetric/nongynecologic hospitalized patients with COVID-19 (March 1st to May 31st, 2020), 3,081 died in hospital **(Figure 2)**. We thus identified 8,168 eligible patients, of whom we attempted to contact 8,034 through phone calls. Our abstractors were able to capture the outcomes of 4,906 unique patients (61% response rate) at a mean follow-up of 92.0 ± 13.8 days **(Table 1).** The cohort had a mean age of 61.7 ±

17.5 years, was predominantly male (53.7%), and consisted of 36.6% White, 21.4% Black, and 8.1% Asian patients; an additional 29.6% of patients who did not self-identify their race were grouped in the "other" category.

Figure 2. Study population selection flowchart

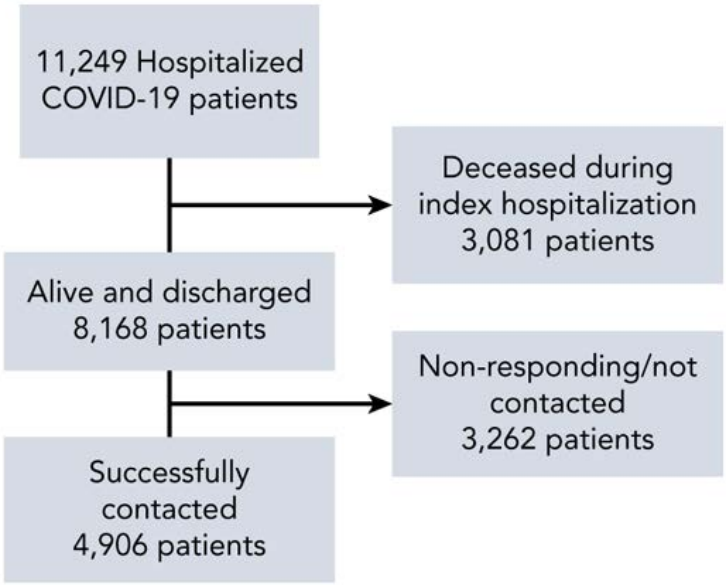


Table 1. Demographic characteristics, comorbidities and venous thromboembolism risk factors

Population characteristics (N = 4906)	
Age (Mean (SD)); (Median (IQR))	61.7 (17.5); 63.0 (25.0)
Gender (N (%))	
Male	2633 (53.7)
Female	2273 (46.3)
Race (N (%))	
African American/Black	1051 (21.4)
Asian	396 (8.1)
Caucasian/White	1797 (36.6)

Other or Unspecified	1451 (29.6)
Unknown	211 (4.3)
Ethnicity	
Hispanic or Latino	1051 (21.4)
Not Hispanic or Latino	3373 (68.8)
Unknown	166 (3.4)
Declined	316 (6.4)
Comorbidities N (%)	
Hypertension	1895 (38.6)
Diabetes mellitus	1234 (25.1)
Coronary artery disease	340 (6.9)
Heart failure	219 (4.5)
Atrial fibrillation	321 (6.5)
Valvular heart disease	12 (0.2)
Chronic renal disease	334 (6.8)
Chronic lung disease	359 (7.3)
Chronic liver disease	48 (1.0)
Thyroid disease	354 (7.2)
BMI>35kg/m^{2} *	752 (18.9)
ICU stay	578 (11.8)
Bleeding (Hx)	438 (8.9)
Ischemic stroke (Hx)	174 (3.6)
Carotid occlusive disease (Hx)	181 (3.7)
Peripheral arterial disease (Hx)	83 (1.7)
VTE Risk factors N (%)	
Personal Hx of VTE	531 (10.8)
Family Hx of VTE	69 (1.4)
Thrombophilia	69 (1.4)
Cancer Hx	644 (13.1)
Autoimmune disease	102 (2.1)
Paraplegia/Hemiplegia	18 (0.4)

SD: Standard Deviation
Hx: History
ICU: Intensive Care Unit
VTE: Venous Thromboembolism
BMI: Body mass index

Main comorbidities included hypertension in 38.6%, diabetes mellitus in 25.1%, body mass index >35 kg/m^2 in 18.9%, ICU admission at index hospitalization in 11.8%, CAD in 6.9%, CHF in 4.5%, atrial fibrillation in 6.5%, history of ischemic stroke in 3.6%, history of CAS in 3.7%, PAD in 1.7%, history of bleeding in 8.9%, chronic renal disease in 6.8%, chronic lung disease in 7.3%, chronic liver disease in 1.0%, and thyroid disease in 7.2%.

Main VTE risk factors at baseline included a personal history of VTE in 10.8%, known thrombophilia in 1.4%, cancer in 13.1%, autoimmune disease in 2.1%, family history of VTE in 1.4%, and paraplegia or hemiplegia in 0.4%.

The population characteristics and main comorbidities of 3262 patients who were eligible and did not respond to follow-up phone calls or were not contacted are summarized in **Table 2**. There did not seem to be major differences in demographic characteristics and comorbidities between the group of patients for whom follow-up was available and this group.

Table 2. Demographic characteristics and comorbidities of alive and discharged patients that were not contacted

Population characteristics (N = 3262)	
Age (Mean (SD))	62.2 (17.5)
Gender (N (%))	
Male	1812 (55.5)
Female	1450 (44.5)
Race (N (%))	
African American/Black	675 (20.7)
Asian	268 (8.2)
Caucasian/White	1178 (36.1)
Other	893 (27.4)
Unknown	248 (7.6)
Ethnicity	
Hispanic or Latino	728 (22.3)
Not Hispanic or Latino	2165 (66.4)
Unknown	183 (5.6)
Declined	186 (5.7)
Comorbidities N (%)	
Hypertension	1335 (40.9)
Diabetes mellitus	905 (27.7)
Coronary artery disease	234 (7.1)
Heart failure	142 (4.5)
Atrial fibrillation	198 (6.1)
Valvular heart disease	6 (0.2)
Chronic renal disease	185 (5.7)

Chronic lung disease	234 (7.2)
Chronic liver disease	35 (1.1)
Thyroid disease	237 (7.3)
Bleeding (Hx)	372 (11.4)
Ischemic stroke (Hx)	124 (3.8)
Carotid occlusive disease (Hx)	129 (4.0)
Peripheral arterial disease (Hx)	45 (1.4)
Paraplegia/Hemiplegia	10 (0.3)

In-hospital laboratory parameters included mild leukocytosis (white blood cell count, $11.0 \pm 6.7 \times 10^3/\mu L$), mildly increased serum creatinine (1.8 ± 2.5 mg/dL), elevated troponin I (1.0 ± 3.9 ng/mL), markedly increased D-dimer (3373.6 ± 7113.2 ng/mL), increased IL-6 (63.3 ± 112.6 pg/mL), C-reactive protein (138.7 ± 99.1 mg/L), lactic acid (2.2 ± 1.7 mmol/L), and lactate dehydrogenase (469.1 ± 541.7 μ/L) **(Table 3)**.

Table 3. Key laboratory parameters during index hospitalization

Laboratory parameters*	**N**	**Mean ± SD**	**Median ±IQR**
WBC (K/uL)	4187	11.0±6.7	9.5±6.8
Hb (g/dL)	4186	12.9±2.1	12.9±2.7
Hct (%)	4186	39.7±6.1	39.6±7.7
PLT (K/uL)	4187	341.8±153.1	318.0±206.0
Serum creatinine (mg/dL)	4041	1.8±2.5	1.0±0.7
TnI (ng/mL)	261	1.0±3.9	0.1±0.2

TnT (ng/mL)	206	0.3±0.8	0.1±0.1
D-Dimer (ng/mL)	508	3373.6±7113.2	779.0±2500.0
IL-6 (pg/mL)	92	63.3±112.6	22.0±36.0
CRP (mg/L)	626	138.7±99.1	122.1±137.5
Lactic acid (mmol/L)	1269	2.2±1.7	1.8±1.3
LDH (u/L)	2339	469.1±541.7	401.0±250.0
Antiphospholipid antibodies			
Anticardiolipin IgG (GPL)	30	17.3±17.0	11.5±10.8
Anticardiolipin IgM (MPL)	32	19.6±20.6	16.9±14.3
β2GPI IgA (SAU)	4	11.5±2.4	11.7±3.5
β2GPI IgM (SMU)	5	39.5±58.5	14.3±1.2
LA dRVVT (sec)	21	41.5±10.3	39.9±12.8
LA SCT (ratio)	14	0.89±0.19	0.91±0.24

*Normal lab values:

TnI (ng/mL): 0.00-0.03

TnT (ng/mL): 0.0-0.06

D-Dimer (ng/mL): 0.0-229.0

IL-6 (pg/mL): 0.0-13.0

CRP (mg/L): 0.0-0.4

Lactic acid (mmol/L): 0.5-2.0

LDH (u/L): 50.0-242.0

Anticardiolipin IgG (GPL): 0.0-12.5

Anticardiolipin IgM (MPL): 0.0-12.5

β2GPI IgA (SAU): 0.0-20.0

β2GPI IgM (SMU): 0.0-.20.0

*Highest value during initial hospitalization

SD: Standard Deviation

N: Number of patients with available laboratory parameter value

WBC: White Blood Cell count

Hb: Hemoglobin

Hct: Hematocrit

PLT: Platelet count

TnI: Troponin I

TnT: Troponin T

IL-6: Interleukin 6

CRP: C-reactive protein

LDH: Lactate dehydrogenase

MPL: M phospholipids

GPL: G phospholipids

β2GP1: Beta-2-Glycoprotein 1

LA dRVVT: Lupus Anticoagulant Dilute Russell's viper venom time

LA SCT: Lupus Anticoagulant Silica Clotting Time

In-hospital medications included IL-6 antagonists (tocilizumab or sarilumab) in 56.3%, hydroxychloroquine in 55.6%, statins in 30.6%, glucocorticoids in 27.1%, aspirin in 21.9%, other antiplatelet agents in 5.7%, famotidine in 14.3%, antibiotics in 10.5%, IL-1 antagonist (anakinra) in 6.0%, and antivirals in 2.0% **(Table 4).**

Table 4. Key in-hospital and discharge medications

Medications N (%)	Inhospital	Discharge
IL-6 antagonists*	2762 (56.3)	262 (5.3)
Hydroxychloroquine	2728 (55.6)	262 (5.3)
Statins	1500 (30.6)	135 (2.8)

Aspirin	1073 (21.9)		91 (1.9)	
Other antiplatelets**	279 (5.7)		29 (0.6)	
Famotidine	699 (14.3)		65 (1.3)	
Antibiotics	517 (10.5)		31 (0.6)	
Anakinra	295 (6.0)		0 (0.0)	
Antivirals	98 (2.0)		1 (0.02)	
IVIG	26 (0.5)		0 (0.0)	
Glucocorticoids	1329 (27.1)		118 (2.4)	
Inhospital Glucocorticoids (N = 1329) * **				
Medication	**N (%)**		**Dose (mg)**	**Days**
Hydrocortisone	36 (27.1)		51.1 (29.6)	7.2 (14.7)
Prednisone	290 (21.8)		31.8 (17.6)	15.5 (33.2)
Prednisolone	1 (<0.01)		60.0 (0.0)	3.6 (0.0
Methylprednisolone	1301 (97.9)		55.4 (70.4)	6.4 (12.6)
Dexamethasone	70 (5.3)		7.9 (7.2)	12.4 (21.0)
Bethamethasone	5 (<0.01)		13.2 (2.7)	1.0 (0.0)
Anticoagulants N (%)	**Prophylactic**	**Treatment**	**Prophylactic**	**Treatment**
Enoxaparin	2630 (53.6)	272 (5.5)	62 (1.3)	13 (0.3)
UFH (SQ)	984 (20.1)	-	3 (0.06)	-
UFH (IV)	-	230 (4.7)	-	-
Fondaparinux	1 (0.02)	5 (0.1)	-	-
Apixaban	309 (6.3)	52 (1.1)	180 (3.7)	-
Dabigatran	-	-	-	-
Rivaroxaban	112 (2.3)	51 (1.0)	336 (6.9)	1(0.02)
Argatroban (IV)	-	-	-	-
Warfarin	-	77 (1.6)	-	17 (0.4)

Anticoagulants at discharge and IMPROVE-DD score, N (%)			
	Anticoagulant at discharge		
	Yes	*No*	*p*
IMPROVE-DD <4	380 (9.7)	3537 (90.3)	**<.0001**
IMPROVE-DD ≥ 4	213 (21.5)	776 (78.5)	

*Tocilizumab or Sarilumab

**Clopidogrel, Prasugrel, Ticagrelor, Cangrelor

*** Inhospital corticosteroids frequency:

Betamethasone (QD), Dexamethasone (QD, BID, TID, QID), Hydrocortisone (QD, BID, TID, QID), Methylprednisolone (QD, BID, TID, QID, q4h), Prednisolone (QD), Prednisone (QD, BID)

IL-6: Interleukin 6

IVIG: Intravenous immunoglobulin

UFH: Unfractionated heparin

DOACS: Direct oral anticoagulants

At index hospitalization, thromboprophylaxis consisted of prophylactic enoxaparin in 53.6%, treatment dose enoxaparin in 5.5%, subcutaneous prophylactic unfractionated heparin in 20.1%, IV treatment-dose unfractionated heparin in 4.7%, prophylactic apixaban in 6.3%, treatment-dose apixaban in 1.1%, prophylactic rivaroxaban in 2.3%, treatment-dose rivaroxaban in 1.0%, and treatment-dose warfarin in 1.6% **(Table 4, Table 5).**

Post-discharge thromboprophylaxis was prescribed in 12.7% of the population and consisted of prophylactic-dose rivaroxaban in 6.9%, prophylactic-dose apixaban in 3.7%, and prophylactic-dose enoxaparin in 1.3%. The rate of post-discharge thromboprophylaxis in patients with an IMPROVE-DD VTE score ≥4 was 21.5% compared with patients with

an IMPROVE-DD VTE score <4 who had a post-discharge thromboprophylaxis rate of 9.7% (P < .0001).

Table 5. Anticoagulant Medications

Anticoagulation	Prophylactic	Treatment
Unfractionated heparin SQ, any dose	X	
Fondaparinux any dose < 7.5 mg daily	X	
Fondaparinux any dose ≥ 7.5 mg daily		X
Unfractionated heparin IV		X
Argatroban IV		X
Apixaban any dose < 10 mg daily	X	
Apixaban any dose ≥ 10 mg daily		X
Dabigatran 150 mg twice a day		X
Coumadin/warfarin any dose		X
Rivaroxaban any dose < 20 mg daily	X	
Rivaroxaban any dose ≥ 20 mg daily		X
Enoxaparin any dose < 80mg daily	X	
Enoxaparin any dose ≥ 80mg daily		X

Abbreviations: IV, intravenous.

3.2.3.2 Venous thromboembolism at 90 days post-discharge

VTE was diagnosed in 76 patients (1.55%) after discharge and included 44 DVTs (0.90%), 42 PEs (0.85%), 2 splanchnic vein thrombosis (0.04%), and 3 other vein thromboses (0.06%; right cephalic vein, n = 1; brachiobasilic arteriovenous fistula, n = 1; and superior vena cava, n = 1) (**Table 6**; **Figure 3**).

Figure 3. Post-discharge thromboembolic outcomes and risk factors of hospitalized patients with COVID-19

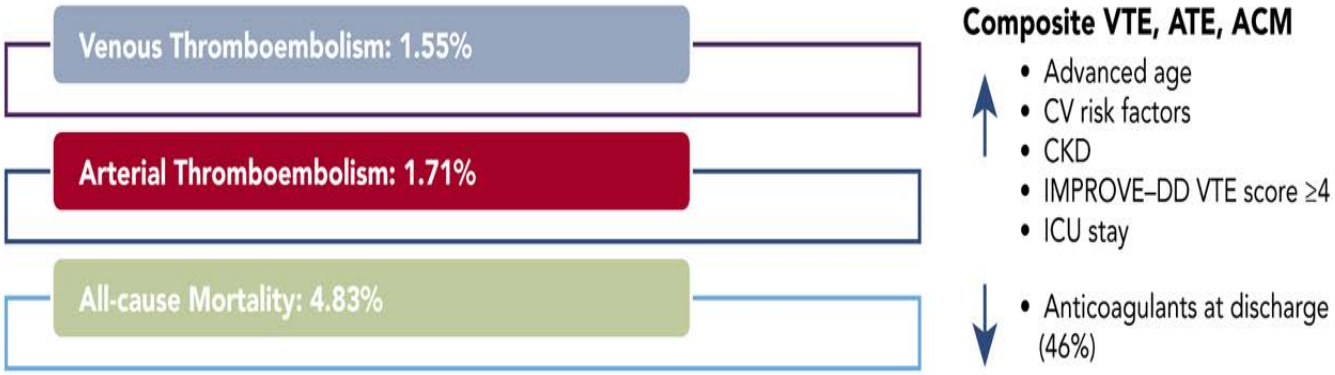


Table 6. VTE, ATE, Mortality, Major bleeding and other post-discharge outcomes

***Venous thromboembolism* N (%)**	**76* (1.55)**
Deep vein thrombosis	44 (0.90)
Pulmonary embolism	42 (0.85)
Splanchnic vein thrombosis	2 (0.04)
Other vein thrombosis	3 (0.06)
Arterial thromboembolism N (%)	84* (1.71)
Stroke	22 (0.45)
Myocardial Infarction	24 (0.49)
Non-MI coronary revascularization	6 (0.12)
Major adverse limb event	26 (0.53)
Systemic Embolism	16 (0.33)
All-Cause Mortality	237 (4.83)
Major Bleeding	85 (1.73)
Other outcomes N (%)	
Re-hospitalization	759 (15.5)

ICU admission	230 (4.69)
Heart failure exacerbation	63 (1.28)
Atrial fibrillation/flutter	22 (0.45)
Interstitial lung disease	26 (0.53)
Myocarditis	1 (0.02)
ARDS	113 (2.3)

3.2.3.3 Arterial thromboembolism at 90 days post-discharge

ATE was diagnosed after discharge in 84 patients (1.71%) and included stroke in 22 (0.45%), MI in 24 (0.49%), non-MI coronary revascularization in 6 (0.12%), major adverse limb event in 26 (0.53%), and systemic embolism in 16 (0.33%).

3.2.3.4 Composite outcome of major thromboembolism and death

The composite outcome of VTE, ATE, or ACM rate was 7.13% (350 of 4906 patients). Post-discharge ACM was 4.83% **(Figure 3)**.

Univariate analysis showed that the composite outcome was associated with age >75 years (OR, 4.33; 95% CI, 3.47-5.40), race (other; OR, 0.47; 95% CI, 0.36-0.62), CAD (OR: 2.45; 95% CI, 1.78-3.39), CHF (OR: 1.99; 95% CI, 1.31-3.00), atrial fibrillation (OR: 2.50; 95% CI, 1.80-3.46), chronic renal disease (OR: 2.86; 95% CI, 2.10-3.91), thyroid disease (OR: 1.58; 95% CI, 1.10-2.26), admission to the ICU (OR: 2.66; 95% CI, 2.10-3.38), history of bleeding (OR: 2.39; 95% CI, 1.78-3.21), history of ischemic stroke (OR: 3.13; 95% CI, 2.10-4.67), CAS (OR: 3.23; 95% CI, 2.19-4.77), and PAD (OR: 2.96; 95% CI, 1.67-5.23; (**Table 7**). VTE risk factors that were associated with the composite outcome included personal history of VTE (OR, 4.29; 95% CI, 3.35-5.50), family history of VTE

(OR, 4.07; 95% CI, 2.30-7.20), known thrombophilia (OR, 4.07; 95% CI, 2.30-7.20), history of cancer (OR, 1.57; 95% CI, 1.18-2.08), and IMPROVE-DD VTE score ≥4 (OR, 3.64; 95% CI, 2.91-4.55). Lastly, the composite end point was associated with a D-dimer level >6 times the ULN (OR, 1.81; 95% CI, 1.43-2.31) and a neutrophil/lymphocyte ratio ≥3 (OR, 1.39; 95% CI, 1.07-1.81).

Table 7. VTE, ATE or Mortality: Univariate analysis

Predictor	**Odds Ratio**	**95% CI**	**p**
Age (>75y)	4.33	3.47-5.40	**<.0001**
Female sex	0.97	0.78-1.21	.810
Race			
Caucasian/White	1.00	1.00-1.00	
African American/Black	0.73	0.55-0.96	.811
Asian	0.73	0.48-1.10	.843
Other	0.47	0.36-0.62	**.0001**
Comorbidities			
Hypertension	1.37	1.10-1.70	.005
Diabetes mellitus	1.30	1.03-1.65	.030
Coronary artery disease	2.45	1.78-3.39	**<.0001**
Congestive heart failure	1.99	1.31-3.00	**.001**
Atrial fibrillation	2.50	1.80-3.46	**<.0001**
Valvular heart disease	1.18	0.15-9.20	.872
Chronic renal disease	2.86	2.10-3.91	**<.0001**
Chronic lung disease	0.97	0.64-1.48	.897
Chronic liver disease	1.52	0.60-3.87	.378
Thyroid disease	1.58	1.10-2.26	**.013**
BMI>35kg/m^2	0.85	0.67-1.08	.186

ICU admission	2.66	2.10-3.38	**<.0001**
Bleeding (Hx)	2.39	1.78-3.21	**<.0001**
Ischemic stroke (Hx)	3.13	2.10-4.67	**<.0001**
Carotid occlusive disease (Hx)	3.23	2.19-4.77	**<.0001**
Peripheral arterial disease (Hx)	2.96	1.67-5.23	**.0002**
VTE Risk factors N (%)			
Personal Hx of VTE	4.29	3.35-5.50	**<.0001**
Family Hx of VTE	4.07	2.30-7.20	**<.0001**
Thrombophilia	4.07	2.30-7.20	**<.0001**
Cancer Hx	1.57	1.18-2.08	**.0019**
Autoimmune disease	0.53	0.19-1.44	.211
Paraplegia/Hemiplegia	1.63	0.37-7.12	.520
IMPROVE-DD (≥4)	3.64	2.91-4.55	**<.0001**
D-Dimer			
0-920 (<4x ULN)	1.00	1.00-1.00	
921-1380 (4-6x ULN)	1.51	0.99-2.30	.054
>1380 (>6x ULN)	1.81	1.43-2.31	**<.0001**
NLR≥3	1.39	1.07-1.81	**.013**
Medications at discharge			
Anticoagulants	0.85	0.60-1.21	.367
Antiplatelets	1.56	0.87-2.80	.137

Hx: History

ICU: Intensive Care Unit

VTE: Venous Thromboembolism

BMI: Body mass index

NLR: Neutrophil/Lymphocyte ratio

Multivariate analysis showed significant association between VTE, ATE, or ACM with advanced age (>75 years; OR: 3.66; 95% CI, 2.84-4.71; *P* < .0001), race (other; OR: 0.68; 95% CI, 0.50-0.93; P = .015), IMPROVE-DD VTE score ≥4 (OR: 1.51; 95% CI, 1.06-2.14; *P* = .023), personal history of VTE (OR: 2.99; 95% CI, 2.00-4.47; *P* < .0001), CAD (OR: 1.50; 95% CI, 1.04-2.17; *P* = .032), PAD (OR: 2.04; 95% CI, 1.10-3.80; *P* = .024), CAS (OR: 2.02; 95% CI, 1.30-3.14; *P* = .0002), chronic renal disease (OR: 2.10; 95% CI, 1.47-3.0; *P* < .0001), and admission to the ICU (OR: 2.22; 95% CI, 1.78-2.93; *P* < .0001) **(Table 8**). The use of anticoagulant medications prescribed at discharge was significantly associated with a 46% reduction in the composite primary outcome, with ACM comprising the majority of this outcome (OR: 0.54; 95% CI, 0.47-0.81; *P* = .003). Sensitivity analysis was also performed in the subgroup of patients receiving prophylactic-dose anticoagulant medications at discharge, and the anticoagulant medication effect was consistent with a reduction in this composite primary outcome (OR: 0.55; 95% CI, 0.37-0.83; *P* = .0046). The results of a multivariate analysis that was not part of the prespecified analysis and included only VTE and ATE without mortality as a sensitivity analysis are shown in **table 9**.

Table 8. VTE, ATE or Mortality: Multivariate analysis

Comorbidities			
Predictor	**Odds Ratio**	**95% CI**	**p**
Age (>75y)	3.66	2.84-4.71	**<.0001**
BMI>35kg/m^2	0.95	0.73-1.24	.691
Race: African American/Black*	0.79	0.57-1.09	.149
Race: Asian*	1.18	0.75-1.84	.476

Race: Other*	0.68	0.50-0.93	**.015**
IMPROVE-DD (≥4)	1.51	1.06-2.14	**.023**
Anticoagulants (discharge)	0.54	0.47-0.81	**.003**
Antiplatelets (discharge)	1.50	0.77-2.90	.231
D-Dimer: 4-6x ULN**	1.17	0.74-1.85	.507
D-Dimer: >6x ULN**	1.09	0.81-1.45	.577
Personal Hx of VTE	2.99	2.00-4.47	**<.0001**
Coronary artery disease	1.50	1.04-2.17	**.032**
Peripheral arterial disease (Hx)	2.04	1.10-3.80	**.024**
Carotid occlusive disease (Hx)	2.02	1.30-3.14	**.0002**
Heart failure	0.93	0.58-1.51	.787
Chronic renal disease	2.10	1.47-3.0	**<.0001**
ICU admission	2.22	1.78-2.93	**<.0001**
Lymphocyte	0.97	0.96-0.99	<.0001

Hx: History

ICU: Intensive Care Unit

VTE: Venous Thromboembolism

BMI: Body mass index

*Compared to Caucasian/White

** Compared to 4x ULN

Table 9. VTE or ATE (sensitivity analysis): Multivariate analysis

Comorbidities			
Predictor	**Odds Ratio**	**95% CI**	**p**
Age (>75y)	2.08	1.41-3.06	**<.0001**
BMI>35kg/m^2	0.79	0.53-1.18	.442
IMPROVE-DD (≥4)	0.90	0.43-1.85	.767

Anticoagulants (discharge)	0.79	0.47-1.33	.368
Antiplatelets (discharge)	2.80	1.33-5.90	**.007**
D-Dimer: 4-6x ULN**	1.48	0.96-2.29	.075
D-Dimer: >6x ULN**	1.39	0.65-2.98	.396
Personal Hx of VTE	12.72	6.22-26.03	**<.0001**
Coronary artery disease	1.26	0.70-2.24	.442
Peripheral arterial disease (Hx)	2.93	1.41-6.12	**.004**
Carotid occlusive disease (Hx)	1.49	0.78-2.85	.225
Heart failure	0.68	0.33-1.42	.306
Chronic renal disease	3.07	1.89-4.98	**<.0001**
Family History of VTE	4.31	1.94-9.55	**0.0003**
ICU admission	2.22	1.78-2.93	**<.0001**

3.2.3.5 Major bleeding and secondary outcomes

MB was diagnosed in 85 patients (1.73%). Of these 85 patients with MB, 15 (17.6%) were prescribed post-discharge anticoagulants. The MB rate in patients discharged with anticoagulants was 2.45% (15/612) compared to 1.63% (70/4294) in patients without post-discharge anticoagulants.

Secondary post-discharge events included a rate of rehospitalization of 15.5%, with 4.69% admitted to the ICU, ARDS in 113 (2.3%), CHF exacerbation in 63 (1.28%); new-onset atrial fibrillation/flutter in 22 (0.45%), and interstitial lung disease in 26 (0.53%).

3.3 Cardiovascular risk factors, thromboembolic outcomes and mortality of hospitalized COVID-19 patients with cardiovascular comorbidities (CAS, MI, PAD, stroke) in the 90-day post-discharge period

3.3.1 Introduction

There is a need for high-quality data on post-discharge outcomes in high-risk subpopulations of hospitalized COVID-19 patients with cardiovascular disease, such as CAD, CAS, PAD, and ischemic stroke. The identification of high risk hospitalized COVID-19 patients with established cardiovascular disease may provide additional targets and prognostic indicators for the prevention of major thromboembolism and mortality after hospital discharge. To this end, the current analysis investigated the rates of major thromboembolism and death and associated risk factors in a high-risk subgroup of the CORE-19 population with baseline cardiovascular disease.

3.3.2 Methods

3.3.2.1 Study cohort

The focus of this analysis was a subgroup of hospitalized patients with COVID-19 and pre-existing cardiovascular comorbidities including a history of CAD, CAS, PAD, or ischemic stroke derived from a prospective registry of consecutive patients diagnosed with COVID-19 within a multi-hospital US based health system from March 1st, 2020, through May 31st, 2020 during the early phases of the COVID-19 pandemic. The health system Institutional Review Board approved our study (#20-0363) and provided regulatory oversight. The methods of data extraction have been described previously (Section 3.2.2.1)

including electronic medical record and health informatics exchange review, use of a filtered radiology informatics database, and manual REDCap data entry with a comprehensive data collection form (including data derived from telephonic patient calls) from hospital admission through 90 days after discharge with pooling of variables of interest in a common file and manual adjudication by abstractors to confirm or reject the presence of an outcome.

Variables of interest included demographics, comorbidities, thrombotic risk factors, laboratory values (highest values during index hospitalization), medications of interest including in-hospital and post-discharge antiplatelet and anticoagulant medications, and post-discharge events (as described in section 3.2.2.1).

3.3.2.2 Definitions

The thromboembolic outcome of the analysis was a composite of ATE (stroke, MI, non-MI coronary revascularization, major adverse limb event, and systemic embolism), VTE (DVT and PE), and ACM within 90 days after hospital discharge. Definitions and methods of confirmation of ATE and VTE have been previously described (Section 3.2.2.2). The safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). (194) Secondary outcomes included rehospitalization, ICU admission, CHF exacerbation, and new onset atrial fibrillation/flutter, using standardized definitions.

3.3.2.3 Statistical analysis

Data were summarized using descriptive statistics. Categorical variables were summarized using frequency and percentage; continuous variables were summarized using mean and

standard deviation and median with interquartile range. Logistic regression analyses were performed to assess the association between independent variables and the composite outcome consisting of ATE or VTE or ACM (yes or no). Univariable analyses were performed first, followed by multivariate analyses.

The following factors were included in the initial model regardless of p value from univariable analysis: age, race, body mass index, history of CAD, history of PAD, history of CAS, CHF, use of antithrombotics (anticoagulants or antiplatelet agents), IMPROVE-DD VTE score, D-dimer category (< 4 times the ULN, 4 to 6 times the ULN, or > 6 times the ULN), history of VTE, chronic renal disease, and ICU admission.

Variables with p value < 0.2 in the univariable analysis were also included in the initial model and were further selected through a backward elimination procedure. Factors were selected for the model if the corresponding p-value was < 0.05. Variables included in the final model based on these criteria were age, history of PAD, history of CAS, CHF, history of VTE, and ICU admission. Of note, a higher p value threshold (p > 0.2) was tested as a backward selection criterion, but there was no improvement in terms of area under the curve. Results are reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were conducted using SAS software (version 9.4; Cary, NC). A 2-tailed p-value < 0.05 was considered statistically significant.

3.3.3 Results

3.3.3.1 Baseline characteristics, comorbidities, laboratory parameters, and inpatient treatment

From a total of 11,249 adult non-obstetric/non-gynecologic hospitalized patients with COVID-19 from March 1st, 2020, through May 31st, 2020, 3,081 died in-hospital. We thus identified 8,168 eligible patients, of whom we attempted to contact 8,034. Full outcomes were captured for 4,906 unique patients (61% response rate), including a cohort of 608 patients with CAD, CAS, PAD, or prior history of ischemic stroke **(Figure 4)**. For patients alive at 90 days after discharge (N = 535), mean follow-up was 93.3 ± 15.7 days, and for patients that died within 90 days after discharge (N = 56), mean follow-up was 23.7 ± 19.8 days; 90-day post-discharge vital status was missing in 17 patients. The cohort had a mean age of 71.0 ± 12.6 years and was male predominant (65.1%), with a race breakdown of 40.6% White, 20.4% African American/Black, 11.4% Asian, and 23.5% "Other" (patients who did not self-identify race) (**Table 10**).

Figure 4. Subgroup-analysis population selection process

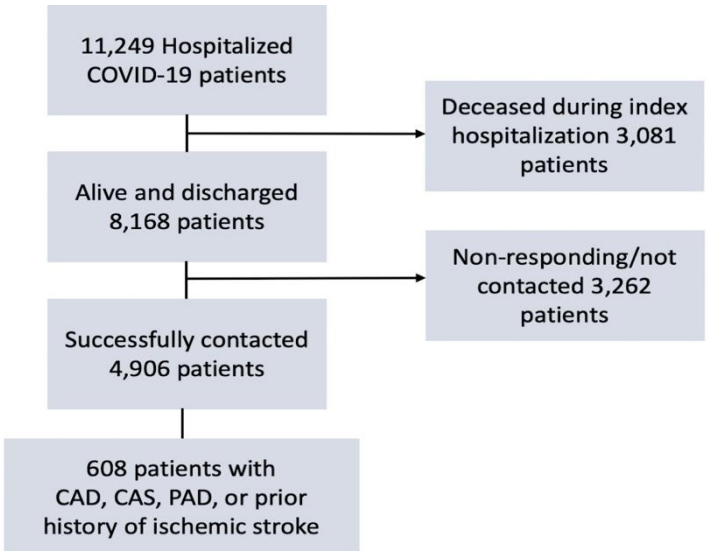


Table 10. Demographic characteristics, comorbidities and thromboembolic risk factors

Population characteristics (N = 608)	
Age (Mean (SD)); (Median (IQR))	71.0 (12.6); 73.0 (17.5)
Gender (N (%))	
Male	396 (65.1)
Female	212 (34.9)
Race (N (%))	
African American/Black	124 (20.4)
Asian	69 (11.4)
Caucasian/White	247 (40.6)
Other or Unspecified	143 (23.5)
Unknown	25 (4.1)
Ethnicity	
Hispanic or Latino	75 (12.3)
Not Hispanic or Latino	456 (75.0)
Unknown	24 (4.0)
Declined	53 (8.7)
Comorbidities N (%)	
Hypertension	421 (69.2)
Diabetes mellitus	274 (45.1)
Coronary artery disease	375 (61.7)
Heart failure	86 (14.1)
Atrial fibrillation	104 (17.1)
Valvular Heart disease	6 (1.0)
Chronic Renal disease	95 (15.6)

Chronic lung disease	59 (9.7)
Chronic liver disease	8 (1.3)
Thyroid disease	68 (11.2)
ICU stay	137 (22.5)
Bleeding (Hx)	136 (22.4)
Ischemic stroke (Hx)	185 (30.4)
Carotid occlusive disease (Hx)	193 (31.7)
Peripheral arterial disease (Hx)	90 (14.8)
Thrombotic Risk factors N (%)	
Personal Hx of VTE	87 (14.3)
Family Hx of VTE	12 (2.0)
Thrombophilia	12 (2.0)
Cancer Hx	90 (14.8)
Autoimmune disease	12 (2.0)
Paraplegia/Hemiplegia	1 (0.2)

SD: Standard Deviation

Hx: History

ICU: Intensive Care Unit

VTE: Venous Thromboembolism

Main comorbidities/risk factors included hypertension (69.2%), diabetes mellitus (45.1%), ICU admission at index hospitalization (22.5%), CAD (61.7%), CHF (14.1%), atrial fibrillation (17.1%), history of ischemic stroke (30.4%), CAS (31.7%), PAD (14.8%), history of bleeding (22.4%), chronic renal disease (15.6%), chronic lung disease (9.7%), chronic liver disease (1.3%), and thyroid disease (11.2%).

Main comorbidities associated with increased risk for major thromboembolism included a personal history of VTE (14.3%), known thrombophilia (2.0%), family history of VTE (2.0%), cancer (14.8%), autoimmune disease (2.0%), and paraplegia or hemiplegia (0.2%).

Mean in-hospital laboratory parameters included mild leukocytosis (11.5 ± 6.7 K/uL), elevated serum creatinine (2.2 ± 2.6 mg/dL), elevated Troponin I (1.1 ± 4.5 ng/ml), markedly increased D-Dimer (3478.5 ± 8020.8 ng/mL), and increased IL-6 (46.1 ± 63.5 pg/ml), C-reactive protein (24.3 ± 65.3 mg/L), lactic acid (2.0 ± 1.6 mmol/L) and lactate dehydrogenase (445.4 ± 233.6 u/L) **(Table 11)**.

Table 11. Key laboratory parameters during index hospitalization

Laboratory parameters*	**N**	**Mean ± SD**	**Median ±IQR**
WBC (K/uL)	608	11.5±6.7	9.8±6.6
Hb (g/dL)	608	13.1±2.1	13.2±3.1
Hct (%)	608	41.1±6.6	41.1±8.7
PLT (K/uL)	608	334.3±158.5	302.5±205.0
Serum creatinine (mg/dL)	608	2.2±2.6	1.3±1.0
TnI (ng/mL)	84	1.1±4.5	0.1±0.1
TnT (ng/mL)	75	190.1±480.9	31±131.0
D-Dimer (ng/mL)	460	3478.5±8020.8	778.0-±2258.0
IL-6 (pg/mL)	20	46.1±63.5	22.5±33.0
CRP (mg/L)	516	24.3±65.3	1.3±2.3
Lactic acid (mmol/L)	251	2.0±1.6	1.7±1.2
LDH (u/L)	397	445.4±233.6	398.0±246.0

Antiphospholipid antibodies			
Anticardiolipin IgG (GPL)	10	12.1±5.6	9.9±4.7
Anticardiolipin IgM (MPL)	9	16.2±12.0	15.9±17.5
LA dRVVT (sec)	8	40.3±10.0	39.6±14.1
LA SCT (ratio)	12	1.07±0.26	1.08±0.26

*Normal lab values:

TnI (ng/mL): 0.00-0.03

TnT (ng/mL): 0.0-0.06

D-Dimer (ng/mL): 0.0-229.0

IL-6 (pg/mL): 0.0-13.0

CRP (mg/L): 0.0-0.4

Lactic acid (mmol/L): 0.5-2.0

LDH (u/L): 50.0-242.0

Anticardiolipin IgG (GPL): 0.0-12.5

Anticardiolipin IgM (MPL): 0.0-12.5

*Highest value during initial hospitalization

SD: Standard Deviation

N: Number of patients with available laboratory parameter value

WBC: White Blood Cell count

Hb: Hemoglobin

Hct: Hematocrit

PLT: Platelet count

TnI: Troponin I

TnT: Troponin T

IL-6: Interleukin 6

CRP: C-reactive protein

LDH: Lactate dehydrogenase

MPL: M phospholipids

GPL: G phospholipids

LA dRVVT: Lupus Anticoagulant Dilute Russell's viper venom time

LA SCT: Lupus Anticoagulant Silica Clotting Time

Relevant in-hospital medications included IL-6 antagonists (tocilizumab or sarilumab) (56.1% of patients), hydroxychloroquine (56.1%), statins (71.2%), glucocorticoids (31.4%), famotidine (19.7%), antibiotics (15.8%), IL-1 antagonist (anakinra) (5.4%), and antivirals (2.6%) (**Table 12)**.

Table 12. Key in-hospital and discharge medications

Medications N (%)	**In-hospital**	**Discharge**
IL-6 antagonists*	341 (56.1)	34 (5.6)
Hydroxychloroquine	341 (56.1)	34 (5.6)
Statins	433 (71.2)	47 (7.7)
Famotidine	120 (19.7)	6 (1.0)
Antibiotics	96 (15.8)	5 (0.8)
Anakinra	33 (5.4)	0 (0.0)
Antivirals	16 (2.6)	1 (0.02)
IVIG	4 (0.7)	0 (0.0)
In-hospital corticosteroids* **		
Medication	**N (%)**	
Hydrocortisone	3 (0.5)	
Prednisone	41 (6.74)	

Prednisolone	1 (0.2)			
Methylprednisolone	140 (23.0)			
Dexamethasone	6 (1.0)			
Betamethasone	-			
Antithrombotics				
Antiplatelets N (%)	**In-hospital**		**Discharge**	
Aspirin	412 (67.8)		31 (5.1)	
Clopidogrel	187 (30.8)		25 (4.1)	
Prasugrel	5 (0.8)		-	
Ticagrelor	19 (3.1)		3 (0.5)	
Cangrelor	2 (0.3)		-	
Anticoagulants N (%)	**Prophylactic**	**Treatment**	**Prophylactic**	**Treatment**
Enoxaparin	283 (46.6)	75 (12.3)	6 (1.0)	3 (0.5)
UFH (SQ)	156 (25.7)	-	2 (0.3)	-
UFH (IV)	-	74 (12.2)	-	-
Fondaparinux	-	-	-	-
Apixaban	47 (7.7)	51 (8.4)	43 (7.1)	-
Dabigatran	-	-	-	-
Rivaroxaban	17 (2.8)	15 (2.5)	35 (5.8)	-
Argatroban (IV)	-	-	-	-
Warfarin	-	24 (4.0)	-	6 (1.0)

*Tocilizumab or Sarilumab

**Clopidogrel, Prasugrel, Ticagrelor, Cangrelor

*** In-hospital corticosteroids frequency:

Betamethasone (QD), Dexamethasone (QD, BID, TID, QID), Hydrocortisone (QD, BID, TID, QID), Methylprednisolone (QD, BID, TID, QID, q4h), Prednisolone (QD), Prednisone (QD, BID)

IL-6: Interleukin 6
IVIG: Intravenous immunoglobulin
UFH: Unfractionated heparin

At index hospitalization, antithrombotic use consisted of 77.5% antiplatelets, including aspirin (67.8%), clopidogrel (30.8%), ticagrelor (3.1%), prasugrel (0.8%), and cangrelor (0.3%) and 92.3% anticoagulant medications (70.4% prophylactic and 21.9% treatment dose) including prophylactic enoxaparin (46.6%), treatment dose enoxaparin (12.3%), subcutaneous prophylactic unfractionated heparin (25.7%), intravenous treatment dose unfractionated heparin (12.2%), prophylactic dose apixaban (7.7%), treatment dose apixaban (8.4%), prophylactic rivaroxaban (2.8%), treatment dose rivaroxaban (2.5%), and treatment dose warfarin (4.0%) **(Table 12)**.

Post-discharge antithrombotics consisted of 7.9% antiplatelets, including aspirin (5.1%), clopidogrel (4.1%), and ticagrelor (0.5%) and 15.3% anticoagulant medications (14.0% prophylactic and 1.3% treatment dose) including prophylactic dose enoxaparin (1.0%), treatment dose enoxaparin (0.5%), subcutaneous prophylactic unfractionated heparin (0.3%), prophylactic dose apixaban (7.1%), prophylactic dose rivaroxaban (5.8%), and treatment dose warfarin (1.0%).

3.3.3.2 Arterial thromboembolism at 90 days post-discharge

ATE was diagnosed after discharge in 166 patients (27.3%) and included 61 (10.1%) strokes, 62 (10.2%) MIs, 2 (0.3%) non-MI coronary revascularizations, 77 (12.7%) major adverse limb events, and 80 (13.2%) systemic embolisms **(Table 13, Figure 5).**

Figure 5. Post-discharge thromboembolic outcomes and risk factors of hospitalized patients with COVID-19

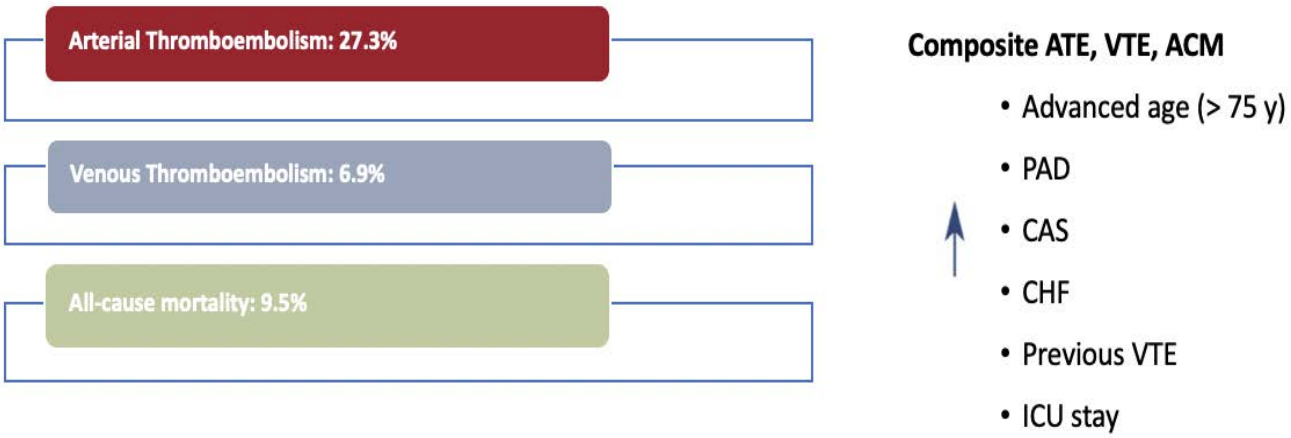


Table 13. Components of major thromboembolism (ATE and VTE), Mortality, Major bleeding and other post-discharge outcomes

Arterial thromboembolism N (%)	166* (27.3)
Stroke	61 (10.1)
Myocardial Infarction	62 (10.2)
Non-MI Coronary Revascularization	2 (0.3)
Major adverse limb event	77 (12.7)
Systemic Embolism	80 (13.2)
Venous thromboembolism N (%)	42* (6.9)
Deep vein thrombosis	25 (4.1)
Pulmonary embolism	22 (3.6)
All-Cause Mortality	56 (9.5)
Major Bleeding	43 (7.1)
Other outcomes N (%)	
Re-hospitalization	148 (24.7)
ICU admission	137 (22.5)

Heart failure exacerbation	82 (13.5)
Atrial fibrillation/flutter	19 (3.1)

ICU: Intensive Care Unit
ATE: Arterial Thromboembolism
VTE: Venous Thromboembolism
*Unique patients

3.3.3.3 Venous thromboembolism at 90 days post-discharge

VTE was diagnosed in 42 patients (6.9%) after discharge and included 25 (4.1%) DVTs and 22 (3.6%) PEs (**Table 13).**

3.3.3.4 Composite outcome of major thromboembolism and death

The composite outcome of ATE, VTE, or ACM occurred in 214 (35.2%) patients. Post-discharge ACM was 9.5%.

Univariate analysis showed that the composite endpoint was associated with age older than 75 years (OR: 1.43; 95% CI: 1.02-2.02), race (other) (OR: 0.63, 95% CI: 0.41-0.99), CAD (OR: 0.47, 95% CI: 0.34-0.67), hypertension (OR:0.67, 95% CI: 0.47-0.95), CHF (OR: 1.68, 95% CI: 1.05-2.68), admission to the ICU (OR: 3.22, 95% CI: 2.17-4.79), prior history of bleeding (OR: 1.66, 95% CI: 1.12-2.46), prior history of ischemic stroke (OR: 1.52, 95% CI: 1.07-2.18), CAS (OR: 1.62, 95% CI: 1.14-2.31), and PAD (OR: 2.42, 95% CI: 1.53-3.82) **(Table 14)**. Thrombotic risk factors that were associated with the composite outcome included a personal history of VTE (OR: 3.81, 95% CI: 2.37-6.11), known thrombophilia (OR: 5.58, 95% CI: 1.49-20.82), D-dimer greater than 6 times the

ULN (OR:1.51, 95% CI: 1.01-2.27), and IMPROVE-DD VTE score of 4 or more (OR: 1.81, 95% CI: 1.04-3.18).

Table 14. Major Thromboembolism or Mortality: Univariate analysis

Predictor	**Odds Ratio**	**95% CI**	**P**
Age (>75y)	1.43	1.02-2.02	**.038**
Female sex	1.13	0.80-1.61	.547
Race			
Caucasian/White	1.00	1.00-1.00	
African American/Black	1.03	0.66-1.60	.904
Asian	0.56	0.31-1.01	.051
Other	0.63	0.41-0.99	**.045**
Comorbidities			
Hypertension	0.67	0.47-0.95	**.025**
Diabetes mellitus	0.78	0.56-1.10	.157
Coronary artery disease	0.47	0.34-0.67	**<.0001**
Congestive heart failure	1.68	1.05-2.68	**.035**
Atrial fibrillation	1.17	0.76-1.81	.478
Valvular heart disease	1.81	0.36-9.03	.471
Chronic renal disease	1.32	0.84-2.01	.231
Chronic lung disease	0.66	0.36-1.20	.173
Chronic liver disease	1.08	0.26-4.56	.918
Thyroid disease	1.24	0.74-2.09	.409
BMI>35kg/m^2	1.35	0.30-6.09	.696
ICU admission	3.22	2.17-4.79	**<.0001**
Bleeding (Hx)	1.66	1.12-2.46	**.011**
Ischemic stroke (Hx)	1.52	1.07-2.18	**.021**
Carotid occlusive disease (Hx)	1.62	1.14-2.31	**.008**
Peripheral arterial disease (Hx)	2.42	1.53-3.82	**.0001**

Thrombosis Risk factors N (%)			
Personal Hx of VTE	3.81	2.37-6.11	**<.0001**
Thrombophilia	5.58	1.49-20.82	**0.011**
Cancer Hx	1.44	0.91-2.28	.118
Autoimmune disease	1.03	0.30-3.54	.968
IMPROVE-DD (≥4)	1.81	1.04-3.18	**0.037**
D-Dimer			
0-920 (<4x ULN)	1.00	1.00-1.00	
921-1380 (4-6x ULN)	1.81	0.87-3.79	.113
>1380 (>6x ULN)	1.51	1.01-2.27	**0.048**
Medications at discharge			
Antiplatelets	1.50	0.82-2.73	.187
Anticoagulants	1.20	0.76-1.89	.431

Hx: History

ICU: Intensive Care Unit

ATE: Arterial Thromboembolism

VTE: Venous Thromboembolism

BMI: Body mass index

ULN: Upper limit of normal

Multivariable analysis showed significant association between ATE, VTE, or ACM and advanced age (> 75 years) (OR: 1.90, 95% CI: 1.22-2.94, p = 0.004), PAD (OR: 3.23, 95% CI: 1.80-5.81, p = < 0.0001), CAS (OR: 1.74, 95% CI: 1.11-2.75, p = 0.017), CHF (OR: 1.84, 95% CI: 1.02-3.35, p = 0.044), a personal history of VTE (OR: 3.08, 95% CI: 1.75-5.42, p < 0.0001), and admission to the ICU (OR: 2.93, 95% CI: 1.81-4.75, p < 0.0001) **(Table 15).**

Table 15. Major Thromboembolism or Mortality: Multivariable analysis

Comorbidities			
Predictor	**Odds Ratio**	**95% CI**	**P**
Age (>75y)	1.90	1.22-2.94	**0.004**
Peripheral arterial disease (Hx)	3.23	1.80-5.81	**<.0001**
Carotid occlusive disease (Hx)	1.74	1.11-2.75	**.017**
Congestive heart failure	1.84	1.02-3.35	**0.044**
ICU admission	2.93	1.81-4.75	**<.0001**
Personal Hx of VTE	3.08	1.75-5.42	**<.0001**

Hx: History

ICU: Intensive Care Unit

VTE: Venous Thromboembolism

ATE: Arterial Thromboembolism

3.3.3.5 Major bleeding and secondary outcomes

MB was diagnosed in 43 (7.1%) patients. Secondary post-discharge events included re-hospitalization in 24.7% of patients (with 22.5% admitted to the ICU), CHF exacerbation in 82 (13.5%) patients, and new-onset atrial fibrillation/flutter in 19 (3.1%) patients.

Chapter 4. Discussion

Our prospective multihospital registry of 4,906 adult hospitalized patients with COVID-19 followed up at 92 days represents one of the largest original prospective studies to date that investigate the post-discharge major thromboembolic events and death in this population. Our study found that hospitalized patients with COVID-19 had a post-discharge ACM rate of nearly 5%; an ATE rate of 1.71% that

included stroke, MI, non-MI coronary revascularization, major adverse limb event, and systemic embolism; and a VTE rate of 1.55%, more than half of the events of which included PE, with a composite primary outcome rate of 7.13% in the 90-day period post-discharge. Our results reveal three important findings. First, VTE, ATE, and ACM occur with a higher frequency during this post-discharge period than previously thought. Second, key predictors of post-discharge major thromboembolic events and death include advanced age >75 years, cardiovascular risk factors (personal history of VTE, CAD, CAS, and PAD), CKD, IMPROVE-DD VTE score ≥4, and ICU stay. Third, post-discharge anticoagulants, mostly at prophylactic dosages, reduce the risk of major thromboembolic events and death by 46%.

Similar to our findings, previous data showed that the risk of major thromboembolism and death remains elevated in the immediate and late post-discharge period. (37,97,98,100,102) Rates of post-discharge VTE may be at least four-fold greater in COVID-19 patients compared with pre-pandemic populations and range between 0.2%-14.7%, with a meta-analysis showing a pooled incidence of 1.8% (DVT and PE incidence 0.9% and 1.5%, respectively) at a mean follow-up of 61.7 days and VTE occurring at an average of two weeks post-discharge. (98) Early data showed a rate of post-discharge VTE up to 14.7% in COVID-19 patients at two months after discharge. (99) In the US, a large retrospective observational study of 40,524 COVID-19 hospitalized patients reported a 13.4% rate of thromboembolic events during hospitalization and a mortality rate of 15.0% at a mean follow-up of 80.3 days. Thromboembolic events occurred in a 4.3% of the population after discharge, including rates of DVT and PE of 1.44% and 1.24%,

respectively at a mean follow-up of 70.7 days, with a time to first-event 59.7 and 44.5 days, respectively, while an overall 18.74% of the population received anticoagulants at discharge. (37) Another large US study utilized data from the US Department of Veteran Affairs database and included 153,760 COVID-19 patients (of which 131,612 were non-hospitalized), 5,637,647 contemporary controls, and 5,859,411 historical controls followed at 12 months after the acute infection, and showed increased risk of stroke (HR=1.52, 95% CI: 1.43-1.62), MI (HR=1.63, 95% CI: 1.51-1.75), PE (HR=2.93, 95% CI: 2.73-3.15), DVT (HR=2.09, 95% CI: 1.94-2.24), superficial vein thrombosis (HR=1.95, 95% CI:1.80-2.12). (100) Previously published data from a network cohort study including 909,473 COVID-19 patients (32,329 hospitalized) showed a cumulative 90-day post-diagnosis VTE rate of 0.2–0.8%, with increased rates among hospitalized patients (4.5%). (101) Nationwide level-analysis in Europe has previously confirmed that COVID-19 is associated with an increased risk of DVT and PE, especially in patients with comorbidities, for at least three and six months, respectively. (102) Pooled data analysis by Zuin et al. revealed a VTE, DVT, and PE pooled incidence of 1.8%, 0.9%, and 1.5%, respectively at two months after discharge with the majority of events occurring within two weeks post-discharge. However, heterogeneity between current literature complicates the generalizability to other high-risk subgroups, including patients with arterial disease.(98) Another more recent pooled analysis that focused on studies reporting thromboprophylaxis rates at discharge, identified a range of post-discharge VTE between 0-8.19% (median 0.7%) at a median follow-up of 49.5 days. (195)

The post-discharge MB rate of 1.73% shown in our study is within the range of 0-3.7% of eight studies included in a systematic review (total 18 included studies of 52,927

patients) that reported an overall post-discharge thromboprophylaxis rate of 19.25%. (195) In addition, our MB rate is multifold higher than previous rates of MB of ~0.2% seen in contemporary studies of extended post-discharge thromboprophylaxis of hospitalized medically ill patients before the COVID-19 era. Of the 85 patients with MB in our study, only 15 (17.6%) were prescribed post-discharge anticoagulants. The MB rate in the population discharged with anticoagulants was 2.45% compared to 1.63% in patients without post-discharge anticoagulants. These data suggest that although the majority of MB occurred in the patient population not prescribed post-discharge anticoagulants, a clinically important relationship between post-discharge anticoagulation and MB cannot be ruled out. An important bleeding diathesis in hospitalized patients with COVID-19 also cannot be excluded, although the rates of thrombotic events (and presumably unrecognized thrombotic events leading to death) are at least two-fold higher than MB events.

Our study found that advanced age >75 years, cardiovascular risk factors (personal history of VTE, CAD, CAS, PAD), CKD, IMPROVE-DD VTE score ≥4, and ICU stay were all significantly associated with post-discharge major thromboembolic events and death, with ORs of ~2.0 to 3.66, whereas "other" race in patients who did not self-identify race seemed protective, with an OR of 0.68. Advanced age, history of cardiovascular disease, and ICU level of care have been consistently associated with poor outcomes and increased thrombotic events and mortality in hospitalized patients with COVID-19. (64,196,197) CKD has also been associated with increased risk of thrombotic events and mortality in patients with COVID-19. (198,199) The IMPROVE VTE score has been extensively validated in medically ill patients (200), and addition of an elevated D-dimer >2 times the ULN to improve model discrimination has identified medically ill patients

(including those with pneumonia and sepsis) with a nearly threefold increased risk for VTE. (201) Consistent reports support that elevated D-dimer, which may reflect the hyperinflammatory state and cytokine storm that leads to thromboinflammation, especially >4 or 6 times the ULN, is a strong predictor of mortality and thrombosis in patients with COVID-19. (63,126) In our study, a D-dimer greater than six-fold the ULN was predictive of our primary outcome in univariate analysis, but it lost significance in the multivariate analysis. However, the IMPROVE-DD VTE score, which incorporates elevated D-dimer, was a significant predictor of post-discharge cardiovascular events and death, with an OR of 1.5 in the multivariate analysis. Notably, the IMPROVE-DD VTE score has been validated in hospitalized patients with COVID-19, with patients with a score ≥4 having a high risk of thrombosis. (81)

An important observation in our study is that anticoagulants (either LMWH or a DOAC), mainly at prophylactic doses prescribed at hospital discharge, were significantly associated with a reduction in the composite outcome of VTE, ATE, or ACM by 46% in hospitalized patients with COVID-19. ACM represented the key component of the composite outcome. Previous autopsy-based studies in hospitalized patients with COVID-19 revealed that unsuspected antemortem thrombotic events such as in situ PE and pulmonary arterial thrombi may play a key role in subsequent death. (90,91,123–125) The health system policy at the time of the current study advocated for extended anticoagulant thromboprophylaxis for 30 days after hospitalization in high-risk hospitalized patients with COVID-19. (202) Previous high-quality data from randomized trials in high-risk hospitalized medically ill patients (including those with sepsis/pneumonia, IMPROVE VTE score ≥4, and elevated D-dimer) revealed a 28% to 38% risk reduction for major and

fatal thromboembolic events (including ATE and VTE) using extended post–hospital discharge thromboprophylaxis with a DOAC. (191,192) Antithrombotic guidelines in hospitalized patients with COVID-19 diverge on this topic, with most societies suggesting extended thromboprophylaxis based on an individualized approach for patients at high thrombotic and low bleeding risk and no contraindications to anticoagulants, and recommending against routine VTE prophylaxis after hospital discharge. (53,203) Patient at high risk for VTE are defined by previously published guidance statements as those with persistent VTE risk factors, including an IMPROVE VTE score ≥ 4 or 2-3 with a D-dimer 2 times the ULN, and without high risk for bleeding. (152,204) The MICHELLE trial investigated a high-risk group of COVID-19 patients using the IMPROVE VTE score ≥ 4 or elevated (≥ 2 times the ULN) D-dimer and found a 67% relative risk reduction for the composite primary endpoint of major thromboembolism and cardiovascular death in patients receiving rivaroxaban 10 mg daily for 30 days after discharge compared to no anticoagulation (3.14% versus 9.43%, respectively). The randomized controlled trial ACTIV-4C compared apixaban at a dose of 2.5mg administered twice daily versus placebo for 30 days after discharge, and reported comparable rates (2.13% vs 2.31%, respectively) for the primary efficacy endpoint of arterial and venous thromboembolism and death with infrequent major bleeding events (0.4% vs 0.2%, respectively). Notably, the trial was terminated early due to decreasing enrollment and composite efficacy endpoint event rates lower than expected. (205) Based on these findings, ISTH guidelines support prophylactic dose rivaroxaban for 30 days in highly-selected COVID-19 patients who were previously hospitalized to reduce the risk of major thromboembolism and death in the post-discharge period. (197) Based on the results of the MICHELLE and ACTIV-4c trial, the NIH

recommends against the routine use of VTE prophylaxis in hospitalized COVID-19 patients after discharge and suggests a case-by-case approach for patients at high risk for VTE, similar to other acute medically ill hospitalized patients. (53)

Our findings support extended thromboprophylaxis with an anticoagulant (either LMWH or preferably a DOAC because of oral route of administration) in high-risk patients with COVID-19 at low bleeding risk at the time of discharge, especially because a majority of post-discharge MB events in our study (82.4%) occurred in patients not receiving post-discharge anticoagulants. High-risk criteria for major thromboembolism and death include advanced age >75 years, presence of cardiovascular risk factors (personal history of VTE, CAD, CAS, PAD), CKD, IMPROVE-DD VTE score ≥4, or ICU stay.

Our subgroup analysis of 608 adult hospitalized patients with COVID-19 at a mean follow-up of 93.3 days after hospital discharge represents one of the largest analyses to date of post-discharge major thromboembolic events and death conducted in a population with a prior history of cardiovascular disease, including CAD, CAS, PAD, and stroke. Our analysis revealed a major thromboembolism and ACM rate of 35.2%, including a 27.3% rate of ATE driven by stroke, MI, major adverse limb event, and systemic embolism, a 6.9% rate of VTE, and a 9.5% rate of ACM during the 90-day post-discharge period. Significant independent predictors of major thromboembolism and death after discharge included age > 75 years, ICU stay, and cardiovascular risk factors (PAD, CAS, CHF, and a personal history of VTE).

A major finding of our subgroup analysis is the markedly increased rate of post-discharge ATE, which is at least 15-fold greater than previously published rates from studies showing an increase of ATE during the post-discharge period. (97,206–209) Our

data showing a very elevated risk of ATE up to 90 days after hospital discharge is consistent with previous observational study data showing that the risk for ATE remains high up to 49 weeks after discharge, with a 14-fold increased risk for first arterial thrombosis during the first week after COVID-19 hospitalization and a 1.46-fold increased risk during weeks 27 to 49. (115) Rates of post-discharge ATE have been estimated up to 39.8/1000 person-years in a large population-level study of 118,879 hospitalized patients with COVID-19 in the United Kingdom. (115) In the US, a recently published retrospective observational study of 40,524 hospitalized patients with COVID-19 reported post-discharge rates of ischemic stroke, myocardial infarction, and acute limb ischemia of 1.18%, 1.53%, and 0.10%, respectively at a mean follow-up of 70.7 days and time to first-event 71.6, 52.6, and 83.5 days, respectively, while an overall 9.62% of the population received antiplatelets at discharge. (37) Data from a recent meta-analysis of 7,816 discharged patients with COVID-19 showed an ATE rate of 1.46% for a post-discharge follow-up period of up to 6 months among the included studies, while another large meta-analysis of 20,875,843 patients in the post-acute phase of COVID-19 showed a cumulative post-discharge rate of incident MI between 0.1 to 1.1% with a mean follow-up of 8.5 months. (116,117) Lastly, the REMAP-CAP trial in hospitalized severe COVID-19 patients showed a benefit on 90-day mortality, at the cost of a significantly increased risk of major bleeding in patients receiving antiplatelets (OR = 2.97; 95% CI, 1.23–8.28). (122) The observed benefit of antiplatelet therapy at 90 days and the persistently increased risk of arterial thromboses for several months after the diagnosis of COVID-19 indicate the need for well-designed trials investigating the risks and benefits of antiplatelets in the post-discharge period.

The risk of arterial thrombosis in hospitalized COVID-19 patients may reflect the modified effect of COVID-19 induced inflammation on a chronically damaged endothelium. Atherosclerosis is associated with low-grade inflammation contributing to endothelial damage, accumulation, and disruption of atherosclerotic plaques, and acute arterial thromboembolic complications. (109–111) Indeed, cardiovascular outcomes one year after COVID-19 suggest an increased risk of cardiovascular events, including ATE, VTE, and all-cause mortality, with implications for long-COVID-19. (114) Against this backdrop, viral infections have been associated with myocardial and systemic vascular injury and exacerbation of pre-existing arterial disease. (103,104) Thus, it has been suggested that antiplatelet therapy may mitigate risk in the hospitalized COVID-19 population with baseline cardiovascular disease. An association between antiplatelet drug use and improved prognosis in COVID-19 patients was reported in early observational studies, but was not confirmed by randomized trials. (160–163) In the early phases of the pandemic most observational studies included patients receiving antiplatelets prior to confirmed COVID-19 diagnosis in contrast to during hospitalization in randomized trials. (119,120,122,160,164) These findings may be partially explained by the effects of chronic antiplatelet therapy that prevented platelet activation prior to disease onset and progression to severe COVID-19; there was greater benefit with increased duration of treatment or antiplatelet administration in the early stages of COVID-19, prior to onset of overt inflammation. (119,160) In addition, the effect of antiplatelets may have been skewed by concomitant use of treatment dose anticoagulants or other experimental therapies tested at the early stages of the pandemic.

High-quality randomized trial data in hospitalized COVID-19 patients reveal that antiplatelet medications have yet to show benefit in the prevention of major thromboembolism and death, and in fact may cause harm in non-critically ill hospitalized COVID-19 patients. (119,164) The ACTIV-4a randomized clinical trial explored the effects of combined P2Y12 inhibitors (ticagrelor or clopidogrel) and treatment dose heparin versus treatment dose heparin only in non-critically ill COVID-19 patients (n=562) for 14 days or until hospital discharge, and showed no benefit in the antiplatelet group in terms of major thromboembolism, including ATE (ischemic stroke, myocardial infarction, and systemic embolism), or death at 28 days. (119) The REMAP-CAP trial investigated the effect of aspirin and P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in hospitalized critically ill COVID-19 patients, and despite showing a benefit on 90-day mortality (HR: 1.22; 95% CI, 1.06–1.40), demonstrated comparable rates of ATE in patients receiving antiplatelets compared to control (3.7% vs 2.3%, respectively). (122) The RECOVERY trial was a randomized, open-label, multicenter trial that included more than 14,000 hospitalized COVID-19 patients receiving either aspirin 150 mg daily or standard of care until discharge and evaluated 28-day mortality. Despite a reduction in length of stay until discharge and a slightly greater chance of being discharged alive within 28 days, there was no benefit from aspirin in terms of mortality, need for mechanical ventilation, or ATE events, including ischemic stroke, myocardial infarction, and systemic embolism, while major bleeding risk was increased by 55%. (164) The recently published COVID-PACT trial, a multicenter, open-label, randomized controlled trial, included COVID-19 patients receiving ICU-level care that were assigned to either antiplatelet therapy with clopidogrel 300 mg at randomization, followed by 75 mg daily, versus no

antiplatelet therapy for the prevention of ATE and VTE. Reported ATE events were low in both groups and there was no benefit from clopidogrel use, with consistently nonsignificant results in prespecified subgroup analyses, including patients with atherosclerotic cardiovascular disease, diabetes, or age > 65 years, with comparable moderate and severe bleeding rates (4.0% vs 6.4%). (120) Lastly, the ACT trial was a multicenter, randomized, controlled trial that assigned hospitalized patients with COVID-19 to rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily for 28 days versus neither therapy and found no difference in terms of mortality, major thromboembolism including ATE (stroke, myocardial infarction, acute limb ischemia) and PE at 45 days, and revealed a statistically significant increased risk of bleeding in the anticoagulant/antiplatelet arm (1.6% vs 0.66%, respectively). (165) The recently published ISTH guidelines consider the use of antiplatelets to reduce mortality in select critically ill hospitalized COVID-19 patients as an adjunct to prophylactic dose heparins, (122,152,164) and recommend against the use of antiplatelets in non-critically ill patients due to potential harm. (152)

Interestingly, in our main analysis post-discharge anticoagulants were associated with a 46% decreased risk of major thromboembolism and death, but the effect was not consistent in the subgroup analysis of patients with cardiovascular comorbidities. This difference may be attributed to the fact that the composite endpoint (35.2%) in the subgroup with cardiovascular comorbidities was mainly driven by ATE (27.3%). Similarly, the MICHELLE trial reported no benefit in terms of prevention of arterial thromboembolism with rivaroxaban 10 mg daily for 30 days after discharge compared to no anticoagulation. (139) The identification of high risk COVID-19 patients with established atherosclerotic

or cardiovascular disease as seen in our study (especially patients with PAD, a personal history of VTE, and ICU admission) may provide additional targets and prognostic indicators for the prevention of thromboembolic disease in the post-discharge period.

4.1 Limitations

Our study has several strengths including the large sample size, the prospective collection of data from consecutive patients of a diverse population, and the multimodal approach of collecting and cleaning the data to ensure a high-quality dataset that supports the generalizability of our findings. In addition, the use of a standardized data collection instrument and unified datamart reflects the high integrity of data collection and the use of adjudicated outcomes using record review reflects the high quality of outcome capture. Another potential strength when interpreting study results is the well-defined protocol (criteria) that was applied regarding post-discharge thromboprophylaxis. Limitations of our study include the observational design, lack of controls, biases related to nonresponse/patients lost to follow-up, and lack of data granularity regarding adherence to antiplatelets or anticoagulants after discharge. Another study limitation when interpreting results is the relatively small subgroup of patients who received post-discharge thromboprophylaxis. Our registry was conducted during the initial wave of the COVID-19 pandemic, which exhibited very high thrombotic rates and for which use of advanced or targeted antiviral and anti-inflammatory medications, in addition to vaccination rates, was suboptimal compared to more recent waves/variants of COVID-19 with associated improved hospital-based care. Further, the reinfections, emerging new variants, and vaccination have altered the thrombogenic potential of COVID-19. Furthermore, the logistical challenges of the early pandemic, specifically with regard to contacting patients

several months after discharge, limited our ability to collect full data despite a large team of dedicated abstractors. The remaining sample may not be representative of the original hospitalized population, which may introduce bias. However, no major baseline differences or comorbidities were seen between the original follow-up non-responders and responders, suggesting this is less likely.

Chapter 5. Conclusion and future directions

In summary, our prospective multihospital registry of 4,906 adult hospitalized patients with COVID-19 followed for a mean of 92 days reveals that VTE, ATE, and ACM occur with a higher frequency during the post-discharge period than previously reported. Key predictors of post-discharge thromboembolic events and death include advanced age, cardiovascular risk factors, CKD, IMPROVE-DD VTE score ≥4, and ICU stay. The use of post-discharge anticoagulants, mostly at prophylactic doses, was associated with a reduction of the risk of major thromboembolic events and death by 46%.

Our prospective subgroup analysis of hospitalized COVID-19 patients with cardiovascular comorbidities in the early phase of the COVID-19 pandemic showed that major thromboembolism and ACM occurred at a frequency of 35% during the first 3 months after discharge. Advanced age (>75 years), PAD, CAS, CHF, a personal history of VTE, and admission to the ICU were among the key predictors of major thromboembolism and death in the post-discharge period.

The identification of high-risk hospitalized COVID-19 patients, including those with established cardiovascular disease, may provide additional targets and prognostic indicators for the prevention of major thromboembolism and mortality after hospital discharge. Randomized controlled trials are needed to explore the role of antithrombotic agents, especially anticoagulant and add-on antiplatelet therapy, in the immediate post-discharge period.

Chapter 6. Publications and presentations

Publications

1. **Giannis D**, Goldin M, Rahman H, Sison CP, Lesser ML, Ngu S, Tsang J, Qiu M, Sanghani S, Yeh J, Matsagkas M, Arnaoutoglou E, Spyropoulos AC. Risk factors for post-discharge major thromboembolism and mortality in hospitalized patients with COVID-19 with cardiovascular comorbidities: Insights from the CORE-19 registry. Thrombosis and Haemostasis, Thromb Haemost.2023 Jun 1. doi: 10.1055/a-2087-3003. PMID: 37146648. Show publication
2. **Giannis D**, Allen SL, Tsang J, Flint S, Pinhasov T, Williams S, Tan G, Thakur R, Leung C, Snyder M, Bhatia C, Garrett D, Cotte C, Isaacs S, Gugerty E, Davidson A, Marder GS, Schnitzer A, Goldberg B, McGinn T, Davidson KW, Barish MA, Qiu M, Zhang M, Goldin M, Matsagkas M, Arnaoutoglou E, Spyropoulos AC. Post-Discharge Thromboembolic Outcomes and Mortality of Hospitalized COVID-19 Patients: The CORE-19 Registry. Blood. 2021 May 20;137(20):2838-2847. doi: 10.1182/blood.2020010529. PMID: 33824972; PMCID: PMC8032474. Show publication

Presentations

1. **Giannis D**, Allen SL, Davidson A, Marder GS, Flint S, Garrett D, Thakur R, Snyder M, Ghiuzeli C, McGinn TG, Davidson KW, Qiu M, Barish M, Spyropoulos AC. Thromboembolic Outcomes of Hospitalized [Oral Presentation]. COVID-19 Patients in the 90-Day Post-Discharge Period: Early Data from the Northwell CORE-19 Registry American Society of Hematology Conference; December 2020 [Virtual Conference during the COVID-19 Pandemic] Show publication
2. **Giannis D**. The CORE-19 Registry. IMETHA 9th Panhellenic congress of Thrombosis and Antithrombotic Treatment. October, 2021, Volos, Greece

Chapter 7. References

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