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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

Μεταπτυχιακή Διπλωματική Εργασία
"ΦΛΕΓΜΟΝΗ ΚΑΙ ΦΛΕΒΙΚΗ ΘΡΟΜΒΟΕΜΒΟΛΗ ΣΕ ΝΟΣΗΛΕΥΟΜΕΝΟΥΣ ΑΣΘΕΝΕΙΣ ΜΕ COVID-19. ΑΝΑΛΥΣΗ ΑΠΟ ΜΙΑ ΜΕΓΑΛΗ ΚΟΟΡΤΗ ΑΠΟ ΕΝΑ ΑΚΑΔΗΜΑΪΚΟ ΚΕΝΤΡΟ ΣΤΗΝ ΕΛΛΑΔΑ"

υπό

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Ειδικευμένου Παθολόγου

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Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

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<u>Στην κόρη που περιμένουμε</u>

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του στη συλλογή, καταχώρηση των δεδομένων καθώς και την επεξεργασία αυτών με αποτέλεσμα την ολοκλήρωση της παρούσας διατριβής.

Περίληψη

Εισαγωγή και στόχοι

Αρκετές μελέτες έχουν δείξει μια συνολικά αρνητική συσχέτιση φλεγμονωδών δεικτών και του κινδύνου εμφάνισης φλεβικής θρομβοεμβολής στη νόσο COVID-19. Ο στόχος της μελέτης αυτής ήταν να περιγράψει την πιθανή συσχέτιση της φλεγμονώδους διαδικασίας και της έκβασης της νόσου σε ενήλικες νοσηλευθέντες ασθενείς με COVID-19. Το πρωτογενές καταληκτικό σημείο αφορούσε τη συχνότητα εμφάνισης φλεβικής θρομβοεμβολής, ενώ τα δευτερογενή καταληκτικά σημεία περιελάμβαναν το θάνατο, τη διασωλήνωση και τη διάρκεια παραμονής στο νοσοκομείο για περισσότερο από 7 ημέρες. Στην περαιτέρω έρευνα, πραγματοποιήθηκε ανάλυση στον υποπληθυσμό των ασθενών που νοσηλεύθηκαν με COVID-19 και φλεβική θρομβοεμβολή, με σκοπό για να περιγράψει τη συσχέτιση της φλεγμονής και των καταληκτικών σημείων της νόσου, δηλαδή το θάνατο, τη διασωλήνωση και τη διάρκεια παραμονής στο νοσοκομείο.

Μέθοδοι

Η μελέτη αυτή ήταν μια μελέτη παρατήρησης και διεξήχθη με αναδρομικό τρόπο. Συλλέχθηκαν ποσοτικά και ποιοτικά δεδομένα των συμμετεχόντων, όπως αποτελέσματα επιδημιολογικών, κλινικών και εργαστηριακών παραμέτρων, καθώς και απαντήσεις σε ερωτηματολόγιο. Συλλέχθηκαν συνολικά δεδομένα από 889 νοσηλευθέντες ασθενείς με COVID-19 στη Μονάδα Λοιμωδών Νοσημάτων του Πανεπιστημιακού Νοσοκομείου Ιωαννίνων, από την 1η Μαρτίου 2020 έως τις 31 Δεκεμβρίου 2021. Η λοίμωξη από τον SARS-CoV-2 διαγνώστηκε με δοκιμασία RT-PCR σε δείγματα ρινοφαρυγγικού επιχρίσματος. Το θετικό αποτέλεσμα για φλεβική θρομβοεμβολή θεωρήθηκε ως η παρουσία πνευμονικής εμβολής ή αγγειακού tree-in-bud στους πνεύμονες σε αξονική αγγειογραφία ή υψηλής ευκρίνειας αξονική τομογραφία πνευμόνων. Η ακτινολογική βαρύτητα της νόσου ορίστηκε ως το ποσοστό (%) του προσβεβλημένου πνευμονικού παρεγχύματος. Μετά τη διαδικασία αντιστοίχισης το τελικό δείγμα της μελέτης διαμορφώθηκε σε 574 ασθενείς. Για τη στατιστική επεξεργασία των δεδομένων χρησιμοποιήθηκε το Chi-squared test και univariate logistic regression analysis στο λογισμικό IBM SPSS 26.0.

Αποτελέσματα

Γενικός πληθυσμός: Η παρουσία λευκοκυττάρωσης καθώς και το πηλίκο Πολυμορφοπύρηνων/Λεμφοκυττάρων > 3,1 συσχετίστηκε με αυξημένο κίνδυνο θρομβωτικών συμβαμάτων στο συνολικό πληθυσμό (OR: 1,84 και OR: 0,05, αντίστοιχα). Τα επίπεδα CRP > 100 mg/L, ινωδογόνου > 600 mg/mL και πνευμονικής βλάβης > 50 %, συσχετίστηκαν επίσης με αυξημένο κίνδυνο (OR: 1,81, 3,01 και 2,2, αντίστοιχα). [Όλα, $p < 0,05$] .

Η λεμφοπενία και το πηλίκο Πολυμορφοπύρηνων/Λεμφοκυττάρων > 3,1 συσχετίστηκαν με αυξημένο κίνδυνο παραμονής στο νοσοκομείο > 7 ημέρες (OR: 1,64 και 1,58, αντίστοιχα). Αυξημένα επίπεδα CRP > 100 mg/L, IL-6 > 24 pg/mL, φερριτίνης >335 ng/mL, LDH > 230 IU/L και προκαλσιτονίνης > 0,5 ng/mL συσχετίστηκαν επίσης με αυξημένο κίνδυνο παραμονής στο νοσοκομείο > 7 ημέρες (OR: 1,56, 1,72, 1,44, 1,62 και 2,62, αντίστοιχα). Ομοίως, αυξημένος κίνδυνος για παρατεταμένη νοσηλεία παρατηρήθηκε σε ασθενείς με επίπεδα ινωδογόνου > 600 mg/ dL, επίπεδα δείκτη TyG > 8, 7 ή > 9,1 (σε σύγκριση τα επίπεδα δείκτη < 8,7) και πηλίκο TRG/HDL-C > 2, 5 (OR: 1,52, 1,79, 2,35 και 2,41, αντίστοιχα). Οι ασθενείς επίσης, με πνευμονική βλάβη > 50%, ήταν πιο πιθανό να χρειαστούν νοσηλεία > 7 ημέρες (OR: 4,14).[Όλα, $p < 0,05$].

Οι ασθενείς με λεμφοπενία, λευκοκυττάρωση και πηλίκο Πολυμορφοπύρηνων/Λεμφοκυττάρων > 3,1 εμφάνισαν μεγαλύτερο κίνδυνο διασωλήνωσης (OR: 3,68, 2,54 και 6,23 αντίστοιχα). Τα αυξημένα επίπεδα D-dimers > 2 μg/mL και LDH > 230 IU/L συσχετίστηκαν επίσης με αυξημένο κίνδυνο (OR: 2,39 και 2,96, αντίστοιχα), όπως και τα επίπεδα CRP > 100 mg/L και προκαλσιτονίνης > 0,5 ng/ mL(OR: 2,68 και 5,18, αντίστοιχα). Ο δείκτης TyG > 9,1 και η πνευμονική βλάβη > 50%, συσχετήσθηκαν επίσης με αυξημένο κίνδυνο διασωλήνωσης ((OR: 4,2 και OR: 21,23) επίσης. [Όλα $p < 0.05$].

Παρατηρήθηκε επίσης ότι, οι ασθενείς με λεμφοπενία, λευκοκυττάρωση και πηλίκο Πολυμορφοπύρηνων/Λεμφοκυττάρων > 3,1 είχαν αυξημένο κίνδυνο θανάτου (OR: 1,9, 2,01 και 3,26, αντίστοιχα). Τιμές IL-6 > 24 pg/mL, CRP > 100 mg/L, προκαλσιτονίνης > 0, 5 ng/mL και φερριτίνης > 335 ng/mL συσχετίστηκαν επίσης με αυξημένο κίνδυνο θανάτου (OR: 3,18, 2,00, 4,28 και 1,76, αντίστοιχα). Ο δείκτης TyG > 9,1 αύξησε την πιθανότητα θανάτου (OR: 4,65), ενώ αντίθετα τα επίπεδα δείκτη < 8,7 και < 9,1 συσχετίστηκαν με μειωμένο κίνδυνο (OR: 0,33). Η έκταση νόσου στην αξονική τομογραφία θώρακος > 50% αύξησε την πιθανότητα θανάτου, επίσης (OR: 3,91). [Όλα $p < 0,05$] .

Ομάδα ασθενών με φλεβική θρομβοεμβολή: η παρουσία λεμφοπενίας συσχετίστηκε με αυξημένο κίνδυνο διασωλήνωσης και θανάτου (OR: 5,33 και 3,63 αντίστοιχα). Το πηλίκο Πολυμορφοπύρηνων/Λεμφοκυττάρων στην ομάδα αυτή συσχετίστηκε επίσης με αυξημένο κίνδυνο θανάτου (OR: 7,15) όπως και ο δείκτης TyG > 9,1 (σε σύγκριση με τα επίπεδα < 8,7) (OR: 5,63). Η πνευμονική βλάβη συσχετίσθηκε με αυξημένη πιθανότητα εμφάνισης και των 3 καταληκτικών σημείων: παραμονή στο νοσοκομείο > 7 ημέρες (OR: 4.65) διασωλήνωση (OR: 14.64) και θάνατος (OR: 14.64). [Όλα p < 0.05]

Συμπέρασμα

Οι δείκτες φλεγμονής συσχετίστηκαν με την πιθανότητα εμφάνισης της φλεβικής θρομβοεμβολής. Η αύξηση αριθμού των λευκών αιμοσφαιρίων, η παρουσία λεμφοπενίας και του αυξημένου λόγου ουδετερόφιλων προς λεμφοκύτταρα συσχετίσθηκε με επιδείνωση της πρόγνωσης και της έκβασης της νόσου. Διαπιστώθηκε επίσης ότι ο δείκτης TyG συσχετίσθηκε με αυξημένο κίνδυνο δυσμενούς έκβασης. Κρίνεται σκόπιμο όμως να αξιολογηθεί περαιτέρω η συσχέτιση αυτών των δεικτών με την εξέλιξη της νόσου.

Λέξεις- Κλειδιά:

COVID-19, φλεγμονώδεις δείκτες, φλεβική θρομβοεμβολή, ιντερλευκίνη-6, λεμφοπενία, C-αντιδρώσα πρωτεΐνη, πηλίκο Πολυμορφοπύρηνων/Λεμφοκυττάρων

Abstract

Background and aims

Several studies have shown an overall positive association of inflammatory markers and venous thromboembolism (VTE) risk in COVID-19. Study aim was to describe the association of inflammation and outcomes in adult hospitalized COVID-19 patients. The primary outcome was incidence of venous thromboembolism. Secondary outcomes included death, intubation and length of hospital stay. Of further investigation aimed analysis was performed to describe the association of inflammation and outcomes in COVID-19 hospitalized patients and venous thromboembolism. The outcomes included death, intubation and length of hospital stay

Methods

This study was conducted with a retrospective observational design. Quantitative and qualitative data of the participants were collected, such as epidemiological, clinical and laboratory parameter results as well as questionnaire replies. Data were collected from 889 COVID-19 hospitalized patients in the Infectious Diseases' Unit of University Hospital of Ioannina, from 1st of March 2020 to 31st of December 2021. SARS-CoV-2 infection was diagnosed by reverse real time transcription–polymerase chain reaction (RT-PCR) test performed on nasopharyngeal swab specimens. Positive result for venous thromboembolism was consider the evidence of pulmonary embolism or vascular tree-in-bud in the lungs. Burden of disease was defined as the percentage (%) of the affected lung parenchyma After propensity score matching the final study sample was estimated in 574 patients. Chi-squared test and univariate logistic regression analyses were performed in IBM SPSS 26.0.

Results

General population: Leukocytosis was associated with increased risk of thrombotic events in the total population (OR: 1.84). Neutrophils-to-Lymphocytes (Neut/Lymph) ratio > 3.1 was also associated with this risk (OR: 0.05). CRP levels > 100 mg/L, fibrinogen > 600 mg/mL and lung injury (computed tomography burden of disease, CTBoD) > 50 %, were also associated with increased risk (OR: 1.81, 3.01 and 2.2, respectively), [All $p < 0.05$]. Lymphocytopenia and Neut/Lymph ratio > 3.1 were associated with a significant increased risk of length of stay (LoS) stay > days

(OR:1.64 and 1.58, respectively). Elevated levels of CRP > 100 mg/L, IL-6 > 24 pg/mL, ferritin >335 ng/mL, LDH > 230 IU/L and procalcitonin > 0.5 ng/mL were also associated with significant risk of LoS > 7 days (OR: 1.56, 1.72, 1.44, 1.62 and 2.62, respectively). Similarly, significant risk was shown in patients with fibrinogen levels > 600 mg/dL, TyG index > 8.7 or > 9.1 (compared to levels < 8.7) and TRG/HDL-C ratio > 2.5 (OR: 1.52, 1.79, 2.35 and 2.41, respectively). Patients with greater lung injury (CTBoD > 50%) were more likely to require LoS >7 days (OR: 4.14), [All p <0.05].

Regarding intubation, patients with lymphocytopenia, leukocytosis and Neut/Lymph ratio > 3.1 were at greater risk of intubation (OR: 3.68, 2.54 and 6.23 respectively). Elevated levels of D-dimers > 2 μg/mL and LDH > 230 IU/L were also associated with increased risk (OR: 2.39 and 2.96, respectively). Levels of CRP > 100 mg/L and procalcitonin > 0.5 ng/mL were also associated with increased risk (OR: 2.68 and 5.18, respectively). Similarly, Triglyceride-glucose (TyG) index > 9.1 showed increased risk (OR: 4.2), while CTBoD > 50% also increased the risk (OR: 21.23), [All p < 0.05].

Regarding death, it was found that patients with lymphocytopenia, leukocytosis and Neut/Lymph ratio > 3.1 were at increased risk (OR: 1.9, 2.01 and 3.26, respectively). IL-6 > 24 pg/mL, CRP > 100 mg/L, procalcitonin > 0.5 ng/mL and ferritin > 335 ng/mL were associated with higher risk of death (OR: 3.18, 2.00, 4.28 and 1.76, respectively). TYG index > 9.1 increased the risk of death (OR: 4.65) while levels between 8.7 and 9.1 were associated with reduced risk (OR: 0.33). CTBoD > 50% also increased the risk of death (OR: 3.91), [All p < 0.05].

VTE group of patients: Lymphocytopenia was associated with increased risk of intubation and death (OR: 5.33 and 3.63 respectively). Neut/Lymp ratio was also associated with increased risk of death in the VTE group (OR: 7.15) TyG > 9.1 (compared to levels < 8.7) was related with increased risk of death (OR: 5.63). Excessive lung injury (CTBoD > 50%) was associated with greater risk regarding all three outcomes; LoS > 7 days (OR: 4.65) intubation (OR: 14.64) and death (OR: 14.64), [All p < 0.05].

Conclusions

Indices of inflammation were associated with the prevalence of venous thromboembolism. Upregulation of white blood cells, lymphocytopenia and increased Neutrophils-to-Lymphocytes ratio aggravated the disease's prognosis and outcomes.

TyG index was also found to further increase the risk of worse outcomes. Whether these markers unfavorably affect outcomes must be further evaluated.

Key words:

COVID-19, inflammatory markers, venous thromboembolism, interleukin-6, lymphocytopenia, C-reactive protein, Neutrophils-to-lymphocytes ratio, Triglyceride-glucose index,

Trial registration:

The study protocol was published online in https://diavgeia.gov.gr/ (No: Ψ29Ψ46906H-9T0) via the Ministry of Digital Governance, after receiving approval from the Scientific Council and Administrative Council of University Hospital of Ioannina (No. of approval: 4/21-4-2021 [issue 24]).

https://diavgeia.gov.gr/decision/view/%CE%A829%CE%A846906%CE%97-9%CE%A40
https://diavgeia.gov.gr/doc/%CE%A829%CE%A846906%CE%97-9%CE%A40?inline=true

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Appendix 1. Figures and tables

Appendix 2. Abbreviations

AH: arterial hypertension,

aPTT: activated partial thromboplastin time

BMI: body mass index,

CAD: coronary artery disease,

CKD: chronic kidney disease

COVID-19: coronavirus disease 2019

CRP: C-reactive protein

CT: computed tomography

CTBoD: CT burden of disease

DM: diabetes mellitus

DVT: deep vein thrombosis

FiO2: fraction of inspired O2

HDL-C: high density lipoprotein cholesterol

ICU: intensive care unit

IL: interleukin

IL-6: interleukin-6

LDH: lactate dehydrogenase

LDL-C: low density lipoprotein cholesterol

LoS: length of hospital stay

Lymph: lymphocytes

Neut/Lymph ratio: neutrophil-to-lymphocyte ratio

Neut: neutrophils

PE: pulmonary embolism

PFR: pO2 / FiO2 ratio

pO2: partial pressure of O2

PSM: propensity score matching

RT-PCR: real time reverse transcription–polymerase chain reaction

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

T-C: total cholesterol

TE: thrombotic event

TRG: triglycerides

TyG index: triglyceride-glucose index

VTE: venous thromboembolism,

VTIB: vascular tree-in-bud

Chapter 1. Introduction

1.1. Disease description

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) had declared COVID-19 disease a global pandemic since March 2020 and an international public health emergency issue (1). As of May 25th, 2022, there have been 524,339,768 confirmed cases of COVID-19, including 6,281,260 deaths worldwide [World Health Organization, Coronavirus disease (COVID-19) outbreak (https://covid19.who.int/ accessed 25 May 2022)] (2).

Clinical manifestations range from an asymptomatic course of illness to critical disease (3,4). SARS-CoV-2 primarily affects the respiratory tract (5) and enters cells via the ACE2 receptors in the nasal and alveolar endothelium (6). Histopathological findings in patients with COVID-19 have shown diffuse alveolar damage and inflammatory infiltrates of the lung parenchyma as well as in extra-pulmonary sites, such as the gastrointestinal tract and cardiac muscle (7–10). It is estimated that 3-10% of patients infected with SARS-CoV-2 will require hospitalization due to progressive pneumonia (11,12) and 20% of those will progress to a more severe form of the disease, namely acute respiratory distress syndrome (ARDS) (11,12).

Severe COVID-19 is associated with cytokine overproduction and immune over-response of the host mediated by chemotaxis (13). This high inflammatory state and immune activation can induce cytokine release syndrome (14). This syndrome is characterized by elevated levels of circulating inflammatory mediators (interleukin-6 [IL-6], IL-1β, IL-2, IL-6, IL-7, IL-10, IL-18, IP-10, MCP-1, TNF-α, macrophage inflammatory protein 1 alpha, and granulocyte-CSF) and decreased levels of lymphocytes (13,15–19). Several markers have also served as indicators of the inflammatory process and severity in the course of the disease (20). Among these, low absolute lymphocyte number and platelet count, as long as elevated levels of troponin, ferritin, interleukin-6 (IL-6), neutrophil-to-lymphocyte ratio and others, implicate in disease progression and unfavorable outcomes (20,21,13,19,18,17,22–24).

Host infection with various pathogens leads to immune response which mediates formation of thrombi particularly in microvessels (25,26). COVID-19 coagulopathy and hypercoagulation have been identified since early days of the pandemic as emerging complications of the viral infection with increased risk of

arterial and venous thromboembolism (VTE) (27–29). Patients with more severe forms of COVID-19 exert this viral-induced prothrombotic state manifested by microrthrombosis as a result of uncontrolled immunothrombosis (30). The virus activates coagulation pathway by direct damage on endothelial tissue (31–34). Numerus pathways have been proposed to explain the cascade of immunothrombosis (30,35) that eventually leads to thrombus formation affecting various vascular beds (30). Possible pathways of COVID-19-related immunothrombosis are summarized in Figure 2.

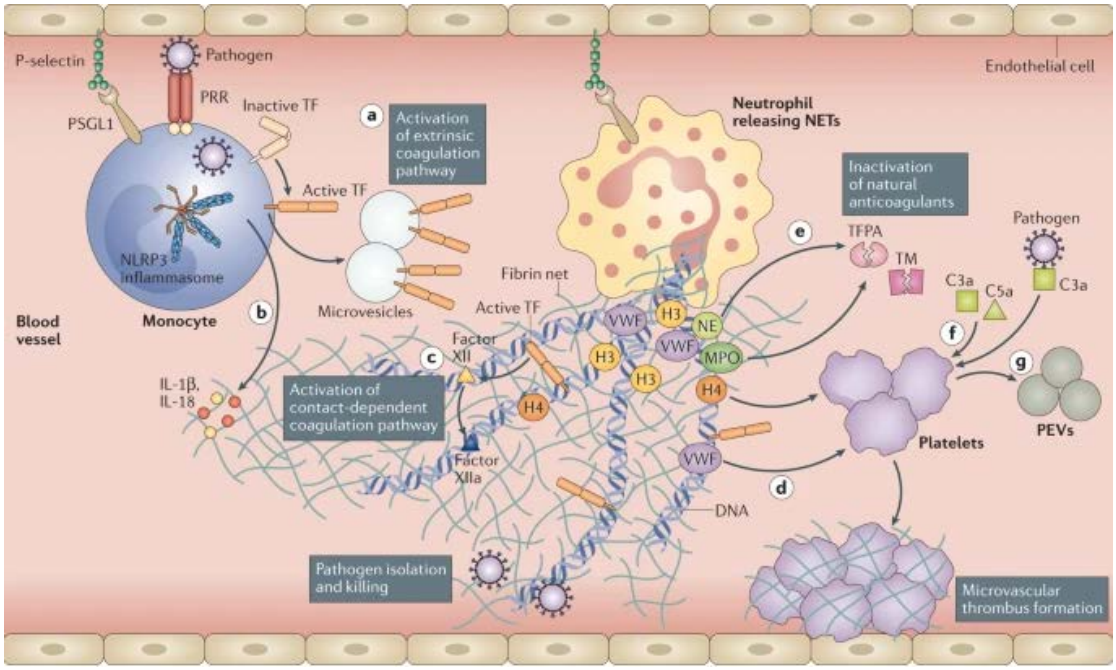

Figure 1. Immunothrombosis pathways

Possible immunothrombosis pathways (30): direct endothelial cells injury and consequent activation of the coagulation; neutrophils infiltration; tissue factor upregulation induced by hypoxemia causing formation of clots; activation of complement activation and subsequent activation of platelets, monocytes and neutrophils, thus promoting further tissue factor expression; direct cell damage by the increased levels of inflammatory cytokines (30).

1.2. Literature research

1.2.1. Venous thromboembolism and COVID-19

Venous thromboembolic events in acute illness, including deep vein thrombosis (DVT) and pulmonary embolism (PE) are considered a common complication (36). VTE in COVID-19 patients include three distinct events, namely PE, vascular tree-in-bud (VTIB) and DVT primarily in the lower extremities (37–40). VTIB was primarily reported as thrombotic microangiopathy of pulmonary tumors. (41). Similarly, this pattern of pulmonary microthrombosis was identified by computed tomography of the lungs in COVID-19 patients (38).

1.2.2. Epidemiology of VTE in COVID-19

Various studies and meta-analyses reported on the incidence of VTE in COVID-19 patients. Prevalence of thrombotic events in COVID-19 disease presents increased variability and a wide range, due to multiple reasons (42). Among these, time of assessment of possible VTE, screening tests and diagnostic algorithms for thrombotic events as well as disease severity affect the accurate estimation of incidence (42).

Infection with SARS-CoV-2 has been associated with a higher risk of VTE in hospitalized patients with either moderate or severe disease compared to other patients (non-COVID-19) (OR: 2.79 and 5.94, respectively) (43). Similarly, VTE and PE were more frequent (4.9% and 3.4%, vs. 1.7% and 0.9%), in hospitalized patients with COVID-19 (n =89,530) vs. in patients hospitalized with influenza (n = 45,819) (44). Similar results were observed in a large meta-analysis of 1,013,495 patients; COVID-19 patients had a greater risk of VTE and PE vs. non-COVID-19 patients (Risk difference; 6% and 3%, respectively) (45). In addition, in patients requiring intensive care unit (ICU) admission, a higher risk of VTE in COVID-19 patients vs. non-COVID-19 (risk difference: 16% and 11% of VTE and PE, respectively) was observed (45).

In a meta-analysis of observational studies (n = 9249), VTE occurred in 18.4% (12.0-25.7) of COVID-19 patients, PE in 13.5% (8.4-19.5) and DVT in 11.8% (7.1-17.4) (37). In another meta-analysis (n = 18,093), VTE overall occurred in 17.0% (95% CI, 13.4-20.9) of patients, DVT in 12.1% (95% CI, 8.4-16.4) and PE in 7.1% (95% CI, 5.3-9.1), respectively (39). Comparable results were shown in the meta-analysis of Tan et al. (n = 64,503) on the incidence of VTE (overall), PE and DVT (14.7%, [95% CI 12.1%, 17.6%], 7.8% [95% CI 6.2% 9.4%] and 11.2% [95% CI

8.4%, 14.3%], respectively) (Tan et al., 2021). A higher incidence of thrombotic events was shown in the meta-analysis by Kollias et al. (n = 6,459); PE and DVT occurred by 32% (95% CI: 25%, 40%) and by 27% (95% CI: 21%, 34%), respectively (46).

It has been shown that the majority of VTE events are often diagnosed at hospital admission (n = 346, 20% of 27% overall estimate) (47). Similar results were also shown in another study (n =388, 50% of 21% overall estimate) (48). In a large analysis (n = 374,244) of 188 hospitals, it was observed that 78.0% of VTE events (n = 17,346) were diagnosed at admission (49). Of note, in another study (n = 54,354) a 29% increase in the rate of VTE was observed during the first seven days following acute infection (50).

Severity of COVID-19 is positively associated with the risk of VTE (46). Regarding VTE's prevalence in COVID-19 patients not requiring ICU admission vs. ICU-admitted patients, a higher percentage in the later was observed (22% vs. 43%) (51). Similarly, in the meta-analysis of Tan et al., non-ICU-admitted patients exerted a lower incidence of VTE vs. ICU-admitted patients (9.0% [95% CI 6.9%, 11.4%], vs. 23.2% [95% CI 17.5%, 29.6%], $p<0.0001$) (28).

1.2.4. Pathophysiology of VTE in COVID-19

Several pathophysiological mechanisms are identified in the effect of SARS-CoV-2 and the incidence of thromboembolism. Two major interrelated pathways are held responsible for both micro- and large vessel thrombosis (42,52). The overall hypercoagulable state leading to large vessel embolism and the immune mediated microthrombosis as well, exert a key role in the resulting venous thrombotic events in COVID-19 (7,42,53,54). Direct activation of platelets through the viral spike protein and by inflammatory cytokines (IL-1β, IL-6, and IL-8) aggravates the risk of thrombosis (54). Furthermore, this thrombotic state is enhanced by endothelial dysfunction; SARS-CoV-2 leads to endothelial damage through its capacity to directly infect ACE2-expressing cells, in the lungs and vessels (53,54). The affected endothelium enhances the activation of the coagulation pathway, further platelet dysfunction and tissue factor expression (53,54). Platelet tissue factor interacts with factor VII, resulting in thrombin and fibrin production (31-34). Immune and coagulation system interaction mainly via thrombin and fibrinogen increases the prothrombotic burden (55). Hyperinflammation leads to the adhesion of platelets and

incite thrombi formation in microvessels through cytokine overproduction and associated chemotaxis (30,35,53).

1.2.3. Inflammation cascade and COVID-19

1.2.3.1. Coagulation markers and inflammation in COVID-19

Platelets and other factors

Platelets primarily regulate thrombosis and hemostasis (56,57). Growing evidence has also shown their role in immune responses and inflammation (56–58). Activated platelets adhere to endothelial cells and promote the chemotaxis of monocytes and neutrophils. This process is mediated among other mechanisms by secretion of inflammatory cytokines (59). In this setting, their role in COVID-19 associated coagulopathy is of great importance (24). In addition to increased platelets, COVID-19-coagulopathy is associated with elevated D-dimers and fibrinogen levels as well as prolonged activated partial thromboplastin (aPTT) time (60,47,61). Hence, increased coagulation markers are related to higher probability of thrombotic events and more severe disease.

Neutrophils

Neutrophils represent the first-line cell defense of the immune system and represent the most abundant circulating leukocytes (62). Increased neutrophil counts is considered as a clinical feature of COVID-19 and were associated with its severity (63,64).

Neutrophils have been associated with the risk of thrombosis in COVID-19 patients. Elevated levels of blood neutrophils and neutrophil extracellular traps (NETs) have recently been described in patients with COVID-19 (65,66). Neutrophil activation by the virus, enhances NET formation, platelet aggregation and adhesion and cell damage (65,66).

Lymphocytes

Lymphocytopenia is one of the hallmarks of COVID-19 severity and its predictive role for worse outcomes has been shown (67,68).

1.2.3.1. Lipid parameters and inflammation in COVID-19

It has been shown that high-density lipoprotein cholesterol (HDL-C) plays a key role in inflammatory and infectious diseases through its effect on immune cell reactivity (69,70). It has been suggested that SARS-CoV2 infection alters HDL-C metabolism through the hyperinflammation state and the resulting cytokine storm (71). HDL-C exerts various anti-inflammatory, as well as anti-thrombotic, anti-apoptotic and anti-oxidative effects in COVID-19 disease (72) and plays a pivotal role in the inflammatory response in COVID-19 disease (73).

Similarly, triglycerides (TRG) are related to vascular inflammation (74,75) and induce endothelial dysfunction, through complement and coagulation cascade activation (76–78). In this regard, data from several studies have shown that TRG are implicated in COVID-19 and were associated with more severe forms of the disease (79).

Furthermore, several markers concerning lipid profile have been proposed to assess the severity of COVID-19. TRG/HDL-C, CRP/HDL-C, ratio, Neut/HDL-C, Lymph/HDL-C ratio have been associated with more sever forms of COVID-19 disease (80,81). Of note, a marker of insulin resistance, namely triglyceride-to-glucose (TyG) index, primarily used in prediabetic patients as a marker of the increased risk of diabetes and cardiovascular disease, has also been proposed for the estimation of disease severity and outcome. TyG index showed a positive association with disease severity and worse outcomes (82).

1.2.3.2. Inflammatory markers in COVID-19

Several randomized controlled trials and meta-analyses have shown an overall positive association of inflammatory markers and VTE risk in COVID-19. Elevated IL-6 (among cytokines), CRP, LDH and ferritin levels in COVID-19 patients, are indicative of a more severe course of illness. In addition, It has been reported that IL-6, CRP, and ferritin can induce coagulation independently, through many mechanisms (83).

Chapter 2. Methods

2.1 Aim of the study

Primary aim: To describe the association of inflammation and outcomes in adult hospitalized COVID-19 patients. The primary outcome was incidence of venous thromboembolism. Secondary outcomes included death, intubation and length of hospital stay.

Secondary aim: To describe the association of inflammation and outcomes in COVID-19 hospitalized patients and venous thromboembolism. The outcome included death, intubation and length of hospital stay.

The foreground questions of this study are presented by PICO statement (84) in figure 2.

		PICOT #1	PICOT #2
P	Patient / Population	Adult hospitalized COVID-19 patients	
I	Intervention / Indicator / Exposure	Inflammation (moderate to severe illness)	Venous thromboembolism
C	Compare / Control	Inflammatory markers (elevated)	Inflammatory markers
O	Outcome	Primary: Venous thromboembolism Secondary: death, intubation, length of stay	Venous thromboembolism associated outcome: death, intubation, length of stay
T	Time / Type of Study or Question	Admission to discharge / Retrospective cohort, cross-sectional	

Figure 2. PICOT flow diagram

2.2 Inclusion and exclusion criteria

Patients with the following were included in the study. Inclusion criteria: provided consent form, age >16 years, SARS-CoV-2 positive testing, patient meet outcomes during hospitalization.

Patient with the following criteria were excluded from the study. Exclusion criteria: consent form not provided, death post-discharge

2.3 Study design and data extraction

This is a retrospective study. Quantitative and qualitative patient data were collected from the hospital medical records. Epidemiological, clinical and laboratory parameters were recorded.

We collected data from COVID-19 hospitalized patients in the Infectious Diseases Unit of the University Hospital of Ioannina, from March 1st, 2020 to December 31st, 2021. SARS-CoV-2 infection was diagnosed by reverse real time transcription–polymerase chain reaction (RT-PCR) test performed on nasopharyngeal swab specimens. Data were obtained retrospectively using patients' medical records (hard copy and digital records). All medical records were imported in a digital database anonymously with a personal identifier code for each patient, as prespecified by study protocol.

All data were collected following the highest standards set by the respective European Guidelines for Good Clinical and Laboratory Practice in Research Studies/Protocols and in accordance with the Helsinki Declaration. All participants in the study received a personal identifier code and were kept anonymous. The epidemiological, clinical and laboratory data were collected and stored without being linked to personal data of the patients, but only to the personal identifier code. biological samples were not collected. The collected clinical and laboratory data were archived in electronic databases encrypted with electronic codes. Due to the retrospective study design of the study and the anonymized nature of the database used, a consent form was waived. The study is part of a larger COVID-19 hospitalized patient cohort study, which has been approved by the Institutional Ethics Committee of the University Hospital of Ioannina [Protocol Number: 5/11-03-2021 (issue:3)]

2.4 Definitions

All recorded variables, definitions and outcomes are summarized in Table 1 (supplementary).

Patient demographics, anthropometric characteristics, medical history, comorbidities, and concomitant medications were documented on the day of admission, namely baseline. All data were obtained as reported patients or through patients' electronic records. Regarding at home medications as well as recent drug administration for other reasons, information was obtained in a similar way.

The laboratory results of inflammatory markers and other parameters were also obtained through medical records and documented at baseline.

Novel markers of inflammation in COVID-19 disease, were also calculated at baseline. The triglyceride-glucose (TyG) index was calculated as the natural logarithm (Ln) of the product of fasting glucose and triglycerides (TRG) using the formula: Ln (TRG [mg/dL] × fasting glucose [mg/dL]/2) (85).

Partial pressure of O2 (pO2) was measured by arterial blood gas analyser. Fraction of inspired O2 (FiO2) was obtained from medical records as O2 supply (liters per minute) by specific device (nasal canula, venturi mask, non-rebreather mask, bi-pap c-pap or high flow nasal canula). Horowitz index (PO2 / FiO2 ratio, PFR) was calculated by partial O2 to FiO2 values.

Radiological findings and indices were obtained by computed tomography (CT) pulmonary angiogram or high-resolution chest CT. Positive result for VTE was considered when there was radiographic evidence of PE or VTIB in either examination. CT burden of disease (CTBoD) was defined as the percentage (%) of the affected lung parenchyma. Vascular ultrasonography was not available routinely in the COVID-19 wards and COVID-19 ICUs and therefore suspected DVT could not be confirmed. Hence, only PE and VTIB were included as VTE. Only patients with VTE diagnosed within the first 72 hours were included in the study.

Outcomes were also collected from patient medical records. The outcome of death was recorded at the site where it occurred (either COVID-19 ward or COVID19-ICU), and day of death was noted. Deaths post-discharge from hospital, were not included.

Category	Variables	Description	Values	SI units
Personal Information				
	Date of admission	Determines patient's date of admission	day/month/year	NA
	Date of Discharge	Determines patient's date of discharge	day/month/year	NA
	Patient Study ID	Unique numeric code for each patient	Numerical	NA
	Gender	Gender of the patient	Male Female	-
	Age	Age of the patient at admission	Numerical > 16	years
	BMI	Body mass index of the patient	Numerical	kg/m^2
Past medical history/ Comorbidities				
	CAD	Past cardiac medical history, type: coronary artery disease, myocardial Infraction, prior cardiac catheterization, self-reported or by patient's medication or else documented (visits at clinic, other documents)	no yes	-
	Hyperlipidemia	Past medical history of the patient, self-reported or by patient's medication or else documented (visits at clinic, other documents)	no yes	-
	Arterial Hypertension	Past medical history of the patient, self-reported or by patient's medication or else documented (visits at clinic, other documents)	no yes	-
	Diabetes mellitus	Past medical history of the patient, self-reported or by patient's medication or else documented (visits at clinic, other documents)	no yes	-
	Cancer	Past medical history of the patient of known cancer, self-reported or by medication patient was receiving, or else documented (visits at clinic, other documents)	no yes	-
	Autoimmune	Past medical history of the patient of autoimmune disease, self-reported of by medication patient was receiving (visits at clinic, other documents)	no yes	-
	COPD	Past medical history of the patient of chronic obstructive pulmonary disease	no yes	-
	CKD	Chronic kidney disease, a type of renal medical history, self-reported or by patient's medication or else documented (visits at clinic, other documents)	no yes	-
	Thyroid disease	Thryoid disease, a type of endocrine medical history self-reported or by patient's medication or else documented (visits at clinic, other documents)	no yes	-
	Morbid Obesity	Defined by BMI values	< 35	Kg/m^2

	(categorical)		> 35 no yes	
	Dementia	Medical history of dementia	no yes	-
	Smoking	Current smoker	no yes	-
Hospital Summary				
	CTBoD	Burden of disease in Computed Tomography as affected lung parenchyma	Numerical	%
	CTBoD (categorical)	Burden of disease in Computed Tomography as affected lung parenchyma	> 50 < 50	%
	Duration of symptoms	Days of reported symptoms prior to hospitalization	Numerical	days
	Days of hospitalization	Hospital LoS: days to discharge or death	Numerical	days
	Days to death	Days to death	Numerical	days
	FiO2	Fraction of inspired O2	Numerical	%
	pO2	Partial pressure of O2	Numerical	mmHg
	PFR	PO_2/FiO_2 ratio on admission	Numerical	-
	PFR-150	PO_2/FiO_2 ratio on admission	< 150 > 150	-
	PFR-300	PO_2/FiO_2 ratio on admission	< 300 > 300	-
Laboratory parameters				
	aPTT	Activated Partial Thromboplastin Time	Numerical	sec
	CRP	C-reactive protein serum concentration	Numerical	mg/L
	CRP (categorical)	C-reactive protein serum concentration	< 100 > 100	mg/L
	CRP/HDL-C	CRP/HDL-C ratio	Numerical	-
	D-dimers	D-dimer plasma concentration	Numerical	μg/mL
	D-dimers (categorical)	D-dimer plasma concentration	< 2 > 2	μg/mL
	Ferritin	Ferritin serum concentration	Numerical	ng/mL
	Ferritin (categorical)	Ferritin serum concentration	< 335 > 335	ng/mL
	Fibrinogen	fibrinogen	Numerical	mg/dL
	Fibrinogen (categorical)	fibrinogen	> 600 < 600	mg/dL
	HDL-C	serum HDL-Cholesterol	Numerical	mg/dL
	IL-6	Interleukin 6 serum concentration	Numerical	pg/mL
	IL-6 (categorical)	Interleukin 6 serum concentration	< 24 > 24	pg/mL
	LDH	Lactate dehydrogenase serum concentration	Numerical	IU/L
	LDH (Categorical)	Lactate dehydrogenase serum concentration	< 230 > 230	IU/L
	LDL-C	serum LDL-Cholesterol	Numerical	mg/dL
	Leukocytosis	Leukocytes count	> 11,000	#/μL

	Lymphopenia (categorical)	Lymphocytes count	< 1,000	#/μL
	Lymph/HDL-C	Lymph/HDL-C ratio	Numerical	-
	Neut/HDL-C	Neut/HDL-C ratio	Numerical	-
	Neut/Lymph ratio	Neutrophils to Lymphocytes ratio of the patient	Numerical	-
	Neutr/Lymph ratio (Categorical)	Neutrophils to Lymphocytes ratio of the patient, categorical	< 3.1 > 3.1	-
	Neutrophis	White blood cell count of the patient, absolute count	Numerical	#/μL
	Platelet Count	Platelet count of the patient	Numerical	#/μL
	Procalcitonin	Procalcitonin serum concentration	Numerical	ng/mL
	Procalcitonin (categorical)	Procalcitonin serum concentration	< 0.5 > 0.5	ng/mL
	T-C	serum Total Cholesterol	Numerical	mg/dL
	Thrombocytopenia (categorical)	Platelets count	< 150000	#/μL
	TRG	serum Triglycerides	Numerical	mg/dL
	TRG/HDL-C	TRG/HDL-C ratio	Numerical	-
	TRG/HDL-C (categorical)	TRG/HDL-C ratio	< 2.5 > 2.5	-
	TyG	TyG index	Numerical	-
	TyG 1 (categorical)	TyG index	< 8.7 >8.7 and < 9.1	-
	TyG 2 (categorical)	TyG index	< 9.1 > 9.1	-
	TyG 3 (categorical)	TyG index	< 8.7 > 9.1	-
Outcomes				
	VTE	Venous thromboembolism was considered the radiographic evidence of pulmonary embolism and vascular tree-in-bud	no yes	-
	LoS (categorical)	Hospital length of stay: days to discharge or death	< 7 > 7	days
	Intubation/Mechanical ventilation (categorical)	Need for invasive mechanical evntilation during hospitalization	no yes	-
	Death (categorical)	Patient death during hospitalization, general COVID-19 ward and/or ICU	no yes	-

Table 1. Supplementary. Definitions and Dictionary of variables in study's registry database

2.5 Statistical analysis

Propensity score matching and Statistical analysis

Statistical analyses and table syntheses were performed via the Statistical Package for Social Sciences (SPSS) 26.0 software (SPSS, IBM corp), provided by the University of Ioannina. Continuous numeric variables are expressed as mean ± standard deviation or median (interquartile: IQR) if Gaussian or non-Gaussian distributed, respectively. Categorical data are presented as total number (N) and percentage. Propensity score matching (PSM) through Python script FUZZY ver. 2.0.1 extension package for SPSS was used to reduce the bias due to confounding variables. Confounding variables used for matching process were gender, age, morbid obesity, medical history of CAD, DM, AH, dyslipidemia, cancer and smoking. The matching ratio was 1 case: 3 controls with a match tolerance of 0.05. Analyses were performed comparing different group of patients. Exposure group was identified as the group of patients diagnosed with VTE (PE and VTIB). Control group was identified as the group of patients without a diagnosis of VTE. Chi-squared test was used to compare categorical data among study groups, Mann-Whitney test for continuous data and binary logistic regression with the outcomes as dependent variables. Two-tailed significance was defined as p-value < 0.05.

Chapter 3. Results

3.1 Characteristics of study population

The flow diagram of the study is displayed in Figure 3. During the study period, a total of 889 consecutive patients were initially included. 144 patients were diagnosed with thrombotic event (PE or VTIB) on admission or within the first 72 hours from admission.

After propensity matching, a total of 574 eligible patients were included in the final analysis. A total of 144 patients were allocated in the VTE group. In the non-VTE group, there were 430 patients (controls).

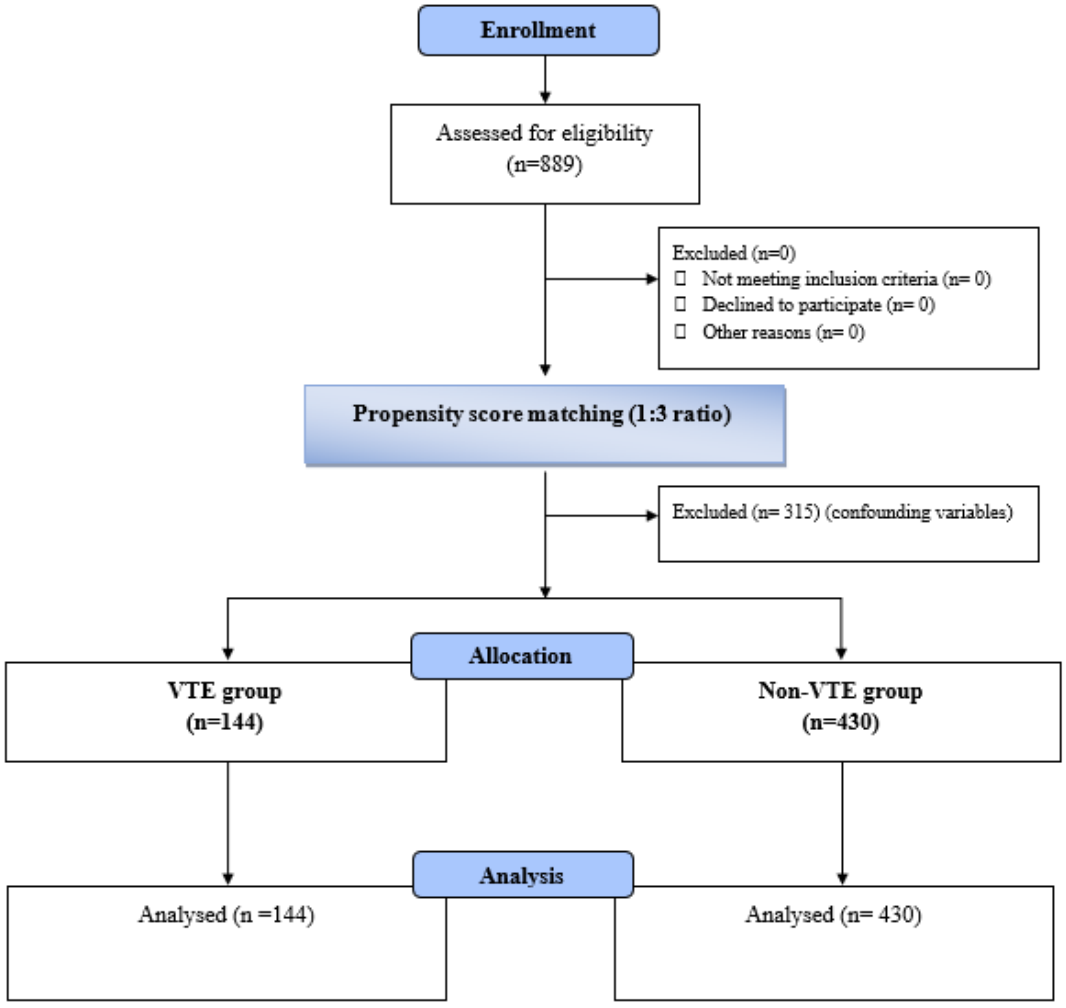

Figure 3. Flow diagram of the study

Baseline demographic characteristics of the study population and comorbidities are presented in Table 1.

The mean age of the study population was 61.3 years. Malepatients had a higher representation than females, in all three groups.

Concerning the prevalence of comorbidities, AH and dyslipidemia were the most common among participants and across all groups. Tobacco use was similar among all patients, while prevalence of morbid obesity was higher in the VTE group vs. non-VTE.

	Total (N=574)		**VTE group (N=144)**		**non-VTE group N=430**	
	(n)	(%)	(n)	(%)	(n)	(%)
Demographics						
Gender (male/female)	318/256	55.4/44.6	81/63	56.2/43.7	237/193	55.1/44.8
Age (mean-years)	61.3	-	61.7	-	61.1	-
BMI (mean-kg/m^2)	29.3	-	30.1	-	29.0	-
Vaccination	77	13.4	11	7.6	66	15.3
Comorbidities- risk factors						
AH	262	45.6	69	47.9	193	44.8
Dyslipidaemia	192	33.4	53	36.8	139	32.3
DM	107	18.6	27	18.7	80	18.6
CAD	84	14.6	16	11.1	68	15.8
Thyroid disease	64	11.1	12	8.3	52	12.0
Pulmonary disease	29	5.0	7	4.8	22	5.1
Autoimmune	33	5.7	6	4.1	27	6.2
CKD	27	4.7	6	4.1	21	4.8
Cancer	23	4.0	6	4.1	17	3.9
Dementia	19	3.3	2	1.3	17	3.9
Smoking	59	10.2	16	11.1	43	10.0
Morbid obesity	39	6.7	12	8.3	27	6.2

Table 2. Patient characteristics at baseline

Data are presented as: mean values, cases (n) and percentage (%)

BMI: body mass index, VTE: venous thromboembolism, CAD: coronary artery disease, DM: diabetes mellitus, AH: arterial hypertension, CKD: chronic kidney disease

3.2 Results synthesis

3.2.1. Disease severity and outcomes of the studied population

Disease severity and outcomes of the studied population are summarized in table 3. VTE patients had a larger duration of symptoms prior to hospitalization, by 2 days, vs. non-VTE patients (8.5 vs. 6.5, $p < 0.01$). Similarly, VTE patients had significantly greater lung injury by COVID-19 assessed by CT burden of disease vs. non-VTE (61.4% vs. 51.0%, $p < 0.01$) and required prolonged hospitalization (15.3 vs. 11.7 days, $p < 0.01$).

Incidence of all three outcomes was higher in the VTE group vs. non-VTE, overall. Patients with VTE were more likely to require hospitalization beyond seven days and showed higher rates of intubation and death.

Groups		**Total (n = 574)**		**VTE group (n =144)**		**non-VTE group (n =430)**		Mann-Whitney test
Variables	units	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	p-value*
Duration of symptoms	days	6.9	4.9	8.5	5.9	6.5	4.5	< **0.01**
PFR	-	276.0	119.6	262.7	112.5	280.5	121.8	0.18
CTBoD	%	54.6	23.6	61.4	20.1	51.0	24.5	< **0.01**
Days to death	days	22.0	14.5	26.5	16.5	19.9	13.2	0.21
Days of hospitalization	days	12.6	9.5	15.3	10.5	11.7	9.0	< **0.01**
Outcomes	-	(n)	(%)	(n)	(%)	(n)	(%)	-
LoS (> 7)	days	374	65.1	115	79.8	259	60.2	-
Intubation	-	41	7.1	19	13.1	22	5.1	-
Death	-	59	10.2	19	13.1	40	9.3	-

Table 3. Indices of disease severity and incidence of outcomes

Data are presented as mean values, standard deviation, SI units.

BMI: body mass index, pO2: partial pressure of O2, FiO2: fraction of inspired O2, CT: computed tomography, PFR; PO2 / FiO2 ratio, VTE: venous thromboembolism, LoS; length of hospital stay

* p- value (Mann-Whitney test); non-VTE compared to VTE group (significance; $p < 0.05$)

3.2.2. Inflammatory markers in VTE vs non-VTE patients

Results of group comparisons regarding variables related to inflammation, are summarized in Table 4.

Patients with VTE, had significantly higher levels of fibrinogen and d-dimers vs. patients without VTE (549.7 vs 509.3 mg/dL and 1.9 vs. 1.4 μg/mL, $p < 0.01$ and $p = 0.047$, respectively). Ferritin and LDH levels were also significantly higher in the VTE group vs. the non-VTE group (519.9 vs. 464.0 ng/mL, $p = 0.27$ and 353.2 vs. 330.9 IU/L, $p = 0.03$, respectively). IL-6 and CRP levels were higher in the VTE group vs. the non-VTE group (43.2 vs 43.1 pg/mL, $p = 0.26$ and 78.8 vs. 61.5 mg/L, $p < 0.001$). Procalcitonin levels at baseline, were lower in the VTE group vs. the non-VTE group (0.3 vs. 0.4 ng/mL, $p = 0.02$).

HDL-C was lower in the VTE group vs. the non-VTE group (34.8 vs. 37.6 mg/dL, $p = 0.06$), while TRG levels were higher in the first group (121.4 vs. 118.5 mg/dL, $p = 0.32$).

Neut/Lymph ratio was significantly higher in the VTE vs. the non-VTE group (6.7 vs. 5.7, $p = 0.04$). Ratios of CRP/HDL-C and Neut/HDL-C were also significantly higher in the VTE group vs. the non-VTE group (2.4 vs. 1.9, $p = 0.01$ and 167.7 vs. 145.1, $p = 0.13$, respectively). TyG index was also higher in the VTE group (8.9 vs. 8.8, $p = 0.42$).

Of note, regarding neutrophils, lymphocytes and platelets, patients with VTE had higher levels of absolute counts but no statistically significant difference was shown. Similarly, no significant difference was shown in TRG / HDL-C and Lymph / HDL-C ratios, though both were also higher in the VTE group.

Groups		Total (n = 574)		VTE group (n =144)		non-VTE (n =430)		Mann-Whitney test
Variables	units	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	p-value*
Neutrophils (count)	#/μL	5,239	3,127	5,622	3,508	5,110	2,981	0.17
Lymphocytes (count)	#/μL	1,207	1,998	1,373	3,842	1,151	603	0.12
Platelet count	#/μL	208,865	88,220	210,648	92,338	208,264	86,893	0.80
Fibrinogen	mg/dL	520.2	137.9	549.7	126.4	509.3	140.7	**< 0.01**
D-dimers	μg/mL	1.5	2.8	1.9	3.8	1.4	2.5	0.47
aPTT	sec	34.0	11.7	34.0	7.9	34.0	12.8	0.36
Ferritin	ng/mL	478.4	616.0	519.9	621.2	464.0	614.5	0.27
LDH	IU/L	336.5	135.0	353.2	133.3	330.9	135.3	**0.03**
IL-6	pg/mL	43.0	104.0	43.2	59.0	43.1	117.5	0.26
Procalcitonin	ng/mL	0.3	1.5	0.3	1.1	0.4	1.8	**0.02**
CRP	mg/L	65.8	68.9	78.8	74.6	61.5	66.4	**< 0.01**
T-C	mg/dL	151.1	38.8	152.7	37.6	150.7	39.4	0.56
TRG	mg/dL	119.2	60.8	121.4	58.7	118.5	61.6	0.32
HDL-C	mg/dL	36.9	11.8	34.8	9.1	37.6	12.5	**0.06**
LDL-C	mg/dL	90.6	33.4	96.6	35.3	88.6	32.7	**0.08**
Novel-markers								
Neut/Lymph ratio	-	5.9	5.1	6.7	5.7	5.7	5.0	**0.04**
TRG/HDL-C ratio	-	3.5	2.1	3.7	2.1	3.5	2.1	0.16
CRP/HDL-C ratio	-	2.0	2.0	2.4	2.2	1.9	2.0	**0.01**
Neut/HDL-C ratio	-	150.7	93.2	167.7	110.6	145.1	86.2	0.13
Lymph/HDL-C ratio	-	36.4	89.3	51.0	176.4	31.6	17.9	0.72
TyG index	-	8.8	0.5	8.9	0.6	8.8	0.6	0.42

Table 4. Variables related to inflammation in the cohort analyzed and between group comparisons.

Data are presented as mean values, standard deviation, SI units.

VTE: venous thromboembolism, aPTT: activated partial thromboplastin time, LDH: lactate dehydrogenase, IL-6: interleukin-6, T-C: total cholesterol, TRG: triglycerides, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, Neut: neutrophils, Lymph: lymphocytes

* p- value (Mann-Whitney test); non-VTE compared to VTE group (significance; $p < 0.05$)

3.2.3. Association of inflammatory markers, thrombotic events and disease outcomes

3.2.3.1. Total population

Results are summarized in Table 5.

Thrombotic events (TE)

Leukocytosis was associated with increased risk of thrombotic events in the total population (OR: 1.84). Neut/Lymph ratio > 3.1 was also associated with this risk (OR: 0.05). CRP levels > 100 mg/L, fibrinogen > 600 mg/mL and lung injury (CTBoD) > 50 %, were also associated with increased risk (OR: 1.81, 3.01 and 2.2, respectively).

Inflammatory markers and LoS > 7 days

Lympopenia and Neut/Lymph ratio > 3.1 were associated with a significantly increased risk of LoS stay > 7 days (OR:1.64 and 1.58, respectively). Elevated levels of CRP > 100 mg/L, IL-6 > 24 pg/mL, ferritin >335 ng/mL, LDH > 230 IU/L and procalcitonin > 0.5 ng/mL were also associated with significant risk of LoS > 7 days (OR: 1.56, 1.72, 1.44, 1.62 and 2.62, respectively). Similarly, significant risk was shown in patients with fibrinogen levels > 600 mg/dL, TyG index > 8.7 or > 9.1 (compared to levels < 8.7) and TRG/HDL-C ratio > 2.5 (OR: 1.52, 1.79, 2.35 and 2.41, respectively). Patients with greater lung injury (CTBoD > 50%) were more likely to require LoS >7 days (OR: 4.14). PFR > 150 and > 300 were related with lower risk (OR: 0.23 and 0.45, respectively).

Inflammatory markers and Intubation/Mechanical Ventilation

Patients with lymphocytopenia, leukocytosis and Neut/Lymph ratio > 3.1 had greater risk of intubation (OR: 3.68, 2.54 and 6.23 respectively). Elevated levels of D-dimers > 2 μg/mL and LDH > 230 IU/L were also associated with increased risk (OR: 2.39 and 2.96, respectively). Levels of CRP > 100 mg/L and procalcitonin > 0.5 ng/mL were also associated with increased risk (OR: 2.68 and 5.18, respectively). TyG index > 9.1 showed increased risk (OR: 4.2). CTBoD > 50% increased the risk (OR: 21.23) while PFR > 150 and 300 were protective (OR: 0.15 and 0.07, respectively).

Inflammatory markers and Death

Patients with lymphocytopenia leukocytosis and Neut/Lymph ratio > 3.1 were at increased risk of death (OR: 1.9, 2.01 and 3.26, respectively).

IL-6 > 24 pg/mL, CRP > 100 mg/L, procalcitonin > 0.5 ng/mL and ferritin > 335 ng/mL were associated with higher risk of death (OR: 3.18, 2.00, 4.28 and 1.76, respectively). TYG index > 9.1 increased the odds of death (OR: 4.65) while levels between 8.7 and 9.1 were associated with reduced risk (OR: 0.33). PFR > 150 and 300 were associated with lower risk of death (OR: 0.23 and 0.27, respectively). CTBoD > 50% increased the risk of death (OR: 3.91).

Total Population	LoS > 7 days		Intubation		Death		TE	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value
Leukocytosis	1.04	0.87	**2.54**	**0.01**	**2.01**	**0.05**	**1.84**	**0.02**
Lymphocytopenia	**1.64**	**< 0.01**	**3.68**	**<0.01**	**1.90**	**0.02**	1.25	0.24
Thrombocytopenia	1.00	0.99	0.72	0.42	1.24	0.47	0.96	0.85
Neut/Lymp ratio > 3.1	**1.58**	**0.01**	**6.23**	**<0.01**	**3.26**	**< 0.01**	**1.50**	**0.05**
Fibrinogen > 600	1.52	0.21	2.78	0.11	1.44	0.42	**3.01**	**< 0.01**
D-dimers > 2	0.90	0.77	**2.39**	**0.05**	1.61	0.19	0.85	0.63
LDH > 230	**1.62**	**0.02**	2.96	0.06	1.75	0.17	1.28	0.33
IL-6 >24	**1.72**	**0.02**	2.00	0.12	**3.18**	**<0.01**	1.25	0.35
Ferritin > 335	**1.44**	**0.05**	1.41	0.34	**1.76**	**0.05**	1.24	0.27
Procalcitonin > 0.5	**2.62**	**0.02**	**5.18**	**< 0.01**	**4.28**	**<0.01**	1.24	0.53
CRP > 100	**1.56**	**0.04**	**2.68**	**< 0.01**	**2.00**	**0.01**	**1.81**	**< 0.01**
PFR > 150	**0.23**	**< 0.01**	**0.15**	**< 0.01**	**0.23**	**< 0.01**	0.68	0.13
PFR > 300	**0.45**	**< 0.01**	**0.07**	**< 0.01**	**0.27**	**< 0.01**	0.77	0.20
CTBoD > 50%	**4.14**	**< 0.01**	**21.23**	**< 0.01**	**3.91**	**< 0.01**	**2.20**	**< 0.01**
TRG/HDL-C >2.5	**2.41**	**< 0.01**	2.05	0.15	1.51	0.27	1.28	0.33
8.7 < TyG < 9.1	**1.79**	**0.03**	0.49	0.28	**0.33**	**0.04**	1.06	0.82
TyG > 9.1	1.31	0.38	**4.20**	**0.02**	**4.65**	**< 0.01**	1.09	0.76
TyG > 9.1 (compared to < 8.7)	**2.35**	**< 0.01**	2.06	0.10	1.54	0.23	1.16	0.58

Table 5. Association of inflammatory markers and outcomes in the entire matched cohort (n=574) (Odds Ratio)

TE: thrombotic event, Neut/Lymph ratio: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, IL-6: interleukin-6, LDH: lactate dehydrogenase, PFR: pO2 / FiO2 ratio, CTBoD: CT burden of disease, TyG: triglyceride-glucose index, LoS: length of stay

*cut-off values and units are summarized in Table 1[supplementary], (significance; $p < 0.05$)

3.2.3.2. Association of inflammatory markers and outcomes in the VTE group

Results are summarized in Table 6.

In the VTE group of patients, lymphocytopenia was associated with increased risk of intubation and death (OR: 5.33 and 3.63 respectively). Neut/Lymp ratio was also associated with increased risk of death (OR: 7.15) TyG > 9.1 (compared to levels < 8.7) was related with increased risk of death (OR: 5.63). Excessive lung injury (CTBoD > 50%) was associated with greater risk regarding all three outcomes; LoS > 7 days (OR: 4.65) intubation (OR: 14.64) and death (OR: 14.64).

PFR > 150 was shown to not to increase LoS > 7 days and was protective in regards to mortality (OR: 0.24 and 0.32, respectively). PFR > 300 was similarly, associated with a lower risk of intubation (OR: 0.20).

VTE group	**LoS > 7 days**		**Intubation**		**Death**	
	OR	**p-value**	**OR**	**p-value**	**OR**	**p-value**
Leukocytosis	0.86	0.79	0.97	0.97	0.57	0.47
Lymphocytopenia	2.20	0.06	**5.33**	**< 0.01**	**3.63**	**0.02**
Thrombocytopenia	0.98	0.98	0.75	0.64	0.55	0.36
Neut/Lymp ratio > 3.1	1.01	0.98	3.24	0.11	**7.15**	**0.03**
Fibrinogen > 600	2.14	0.34	2.17	0.48	2.57	0.38
D-dimers >2	0.46	0.21	1.66	0.45	1.38	0.62
LDH > 230	0.87	0.81	1.63	0.53	0.96	0.95
IL-6 >24	1.62	0.39	1.88	0.33	1.47	0.53
Ferritin > 335	0.66	0.38	1.42	0.52	1.19	0.73
Procalcitonin > 0.5	2.72	0.33	5.20	0.12	5.20	0.12
CRP > 100	1.90	0.19	1.32	0.58	1.32	0.58
PFR > 150	**0.24**	**0.05**	0.46	0.18	**0.32**	**0.04**
PFR > 300	0.83	0.67	**0.20**	**0.02**	0.34	0.09
CTBoD > 50%	**4.65**	**< 0.01**	**14.64**	**< 0.01**	**14.64**	**< 0.01**
TRG/HDL-C >2.5	2.48	0.09	1.33	0.67	0.96	0.95
8.7 < TyG < 9.1	0.90	0.86	2.31	0.36	0.70	0.69
TyG > 9.1	2.57	0.20	2.43	0.22	3.80	0.10
TyG > 9.1 (compared to < 8.7)	2.32	0.23	**5.63**	**0.02**	2.66	0.14

Table 6. Association of inflammatory markers and outcomes in the VTE (n=144) group (Odds Ratio)

VTE: venous thromboembolism, Neut/Lymph ratio: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, IL-6: interleukin-6, LDH: lactate dehydrogenase, PFR: pO2 / FiO2 ratio, CTBoD: CT burden of disease, TyG: triglyceride-glucose index, LoS: length of stay

*cut-off values and units are summarized in Table 1[supplementary], (significance; $p < 0.05$)

3.2.3.3. Association of inflammatory markers and outcomes in the non-VTE group

Results are summarized in table 7.

Outcomes in non-VTE patients were overall associated with lympocytopenia, elevated levels of Neut/Lymph ratio, procalcitonin and CTBoD. TyG index >9.1 was also found to increase the incidence of all three outcomes in this group.

Non-VTE group	LoS > 7 days		Intubation		Death	
	OR	p-value	OR	p-value	OR	p-value
Leukocytosis	0.96	0.90	**4.34**	**< 0.01**	**3.30**	**< 0.01**
Lymphocytopenia	**1.50**	**0.04**	**2.73**	**0.03**	1.46	0.25
Thrombocytopenia	1.01	0.94	0.69	0.52	1.66	0.14
Neut/Lymp ratio > 3.1	**1.62**	**0.02**	**10.96**	**< 0.01**	**2.60**	**0.02**
Fibrinogen > 600	1.24	0.57	2.18	0.35	1.09	0.87
D-dimers >2	1.20	0.65	**4.01**	**0.03**	1.73	0.21
LDH > 230	**1.79**	**0.01**	5.22	0.07	2.31	0.11
IL-6 >24	1.69	0.06	1.94	0.30	**4.93**	**< 0.01**
Ferritin > 335	**1.64**	**0.02**	1.29	0.60	**2.05**	**0.04**
Procalcitonin > 0.5	**2.59**	**0.04**	**5.04**	**< 0.01**	**3.98**	**< 0.01**
CRP > 100	1.32	0.26	**3.92**	**< 0.01**	**2.34**	**0.01**
PFR > 150	**0.23**	**< 0.01**	**0.07**	**< 0.01**	**0.20**	**< 0.01**
PFR > 300	**0.40**	**< 0.01**	**0.91**	**< 0.01**	**0.26**	**< 0.01**
CTBoD >50%	**3.53**	**< 0.01**	**24.12**	**< 0.01**	2.31	0.06
TRG/HDL-C >2.5	**2.35**	**< 0.01**	2.86	0.16	1.83	0.20
8.7 < TyG < 9.1	**2.13**	**0.01**	**0.94**	**0.03**	**0.21**	**0.03**
TyG > 9.1	1.12	0.74	**1.06**	**0.02**	**5.49**	**0.01**
TyG > 9.1 (compared to < 8.7)	**2.38**	**< 0.01**	1.09	0.88	1.19	0.69

Table 7. Association of inflammatory markers and outcomes in the non-VTE (n=430) group (Odds Ratio)

VTE: venous thromboembolism, Neut/Lymph ratio: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, IL-6: interleukin-6, LDH: lactate dehydrogenase, PFR: pO2 / FiO2 ratio, CTBoD: CT burden of disease, TyG: triglyceride-glucose index, LoS: length of stay

*cut-off values and units are summarized in Table 1[supplementary], (significance; $p < 0.05$)

3.2.3.4. Univariate logistic analysis. Inflammation and outcomes in VTE patients

Results are summarized in Table 8.

Age was associated with a greater risk of death in patients with VTE (OR: 1.04). Lymphocytopenia was associated with the risk of intubation and death (OR: 5.33 and 3.63, respectively). Neut/Lymph ratio was also associated with the risk of intubation and death (OR: 1.13 and 1.1).

There was a slight increase in the risk of death with higher IL-6 levels at baseline (OR: 1.01). An increased risk of intubation and death was observed in VTE patients with procalcitonin levels > 0.5 (all, OR: 5.2). TRG/HDL ratio and TyG index at baseline, were associated with an increased risk of intubation (OR: 1.27 and 2.64 respectively). The excessive lung injury assessed by CTBoD > 50% was associated with the risk of occurrence of all three outcomes; LoS > 7 days, intubation, and death (OR: 4.65, 14.64 and 14.64 respectively). In the multivariate logistic regression model, none of the variables showed statistical significance.

VTE group	LoS > 7 days		Intubation		Death	
	OR	p-value	OR	p-value	OR	p-value
Age	1.01	0.40	1.02	0.20	**1.04**	**0.01**
BMI	1.05	0.42	0.85	0.16	0.85	0.16
Duration of symptoms	1.05	0.22	1.04	0.25	1.05	0.19
Neutrophil count	1.00	0.57	1.00	0.11	1.00	0.13
Lymphocyte count	1.00	0.87	0.99	0.28	1.00	0.42
Platelet count	1.00	0.56	1.00	0.78	1.00	0.80
Leukocytosis	0.79	0.86	0.97	0.97	0.57	0.48
Lymphocytopenia	2.20	0.06	**5.33**	**0.01**	**3.63**	**0.02**
Thrombocytopenia	0.98	0.98	0.75	0.64	0.55	0.37
Neut/Lymph ratio	1.10	0.07	**1.13**	**< 0.01**	**1.10**	**< 0.01**
Neut/Lymph ratio > 3.1	1.01	0.98	3.24	0.12	7.15	0.06
Fibrinogen	1.00	0.30	1.00	0.23	**1.00**	**0.04**
Fibrinogen > 600	0.35	2.14	2.17	0.49	2.57	0.40
D-dimers	0.92	0.09	1.03	0.56	1.04	0.38
D-dimers > 2	0.46	0.22	1.66	0.45	1.38	0.62
LDH	1.00	0.24	**1.005**	**<0.01**	**1.00**	**< 0.01**
LDH > 230	0.87	0.81	1.63	0.53	0.96	0.95
aPTT	1.02	0.47	1.01	0.73	0.99	0.93
IL-6	0.99	0.38	1.00	0.29	**1.01**	**< 0.01**
IL-6 > 24	1.62	0.40	1.88	0.34	1.47	0.53
Ferritin	1.00	0.49	1.00	0.16	1.00	0.21
Ferritin > 335	0.66	0.38	1.42	0.52	1.19	0.73
Procalcitonin	3.93	0.30	1.28	0.19	1.30	0.16
Procalcitonin > 0.5	2.72	0.34	**5.20**	**0.02**	**5.20**	**0.02**
CRP	1.00	0.28	1.00	0.27	1.00	0.18
CRP > 100	1.90	0.19	1.32	0.58	1.32	0.58
PFR	0.99	0.12	**0.99**	**0.01**	**0.99**	**0.01**
PFR >150	0.24	0.06	0.46	0.19	**0.32**	**0.05**
PFR > 300	0.83	0.67	**0.20**	**0.04**	0.34	0.10
CTBoD > 50%	**4.65**	**< 0.01**	**14.64**	**0.01**	**14.64**	**0.01**
Troponin	1.04	0.13	1.00	0.37	1.00	0.36
TRG/HDL-C ratio	1.29	0.16	**1.27**	**0.05**	1.22	0.09
TRG/HDL-C>2.5	2.48	0.09	1.33	0.68	0.96	0.95
CRP/HDL-C ratio	1.12	0.41	0.88	0.46	1.03	0.80
Neut/HDL-C ratio	1.00	0.15	1.00	0.54	1.00	0.24
Lymph/HDL-C ratio	1.00	0.74	0.99	0.65	0.99	0.71
TyG index	1.47	0.41	**2.64**	**0.03**	1.82	0.18
8.7 < TyG < 9.1	0.90	0.86	2.31	0.37	0.70	0.69
TyG > 9.1	2.57	0.21	2.43	0.23	3.80	0.11
TyG > 9.1 (compared to <8.7)	2.32	0.24	**5.63**	**0.04**	2.66	0.15

Table 8. Univariate logistic analysis of inflammatory markers and outcomes in the VTE group

OR: odds Ratio, VTE: venous thromboembolism, Neut/Lymph ratio: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, IL-6: interleukin-6, LDH: lactate dehydrogenase, aPTT: activated partial thromboplastin time PFR: pO2 / FiO2 ratio, CTBoD: CT burden of disease, TyG: triglyceride-glucose index, LoS: length of stay.

Variables are presented as continuous and categorical (categorical; if noted: “variable” > “of”)

*cut-off values and units are summarized in Table 1[supplementary], (significance; $p < 0.05$)

Chapter 4. Discussion

This study evaluated the association of markers of inflammation on the incidence of TE in COVID-19 patients requiring hospitalization. Among indices of inflammation, Leukocytosis (> 11000/μL) and elevated fibrinogen levels (cut-off > 600 mg/dL) were associated with greater risk of thrombotic events in the general population. Similarly, Neutr/Lymph ratio > 3.1 and a CRP cut-off level > 100 mg/L were found to be indices of high likelihood of TE. Concerning the group of patients with confirmed VTE at baseline, we found that low levels of lymphocytes (< 1000/μL) and TyG index > 9.1 (compared to <8.7) were associated with higher incidence of intubation. Similarly, lymphocytopenia, Neutr/Lymph ratio and its cut-off value of > 3.1 were associated with higher risk of death. Procalcitonin levels > 0.5 were also associated with greater risk of death and intubation in the VTE group of patients.

Data regarding the association between inflammatory markers on admission, and VTE occurrence are scarce. In addition, only a few clinical trials have evaluated the role of these markers on outcomes in patients with diagnosed VTE.

It has been postulated that excessive activation of neutrophils and production of neutrophil extracellular traps, may contribute to cytokine storm and adversely affect the progression of disease leading to organ damage, thrombosis, and death (86). Patients with VTE exert a higher risk of severe disease. It was estimated that 45% (95% CI, 24%–67%) of COVID-19 patients who developed VTE were in severe or critical condition (87).

Comparable to our results on markers of inflammation, in a meta-analysis by Wu et al. (n = 1,562) in COVID-19 patients, it was shown that VTE patients had higher white blood cell counts vs. non-VTE patients (7.62×10^9/L; 95% CI, 6.57–8.68×10^9/L for VTE, mean difference: 1.34×10^9/L; 95% CI, 0.84–1.84×10^9/L) (87). Results on other indices reported significantly higher fibrinogen and CRP levels in TE vs. non-TE patients (6.01 g/L; 95% CI, 5.29–6.72 g/L, mean difference: 0.49 μg/ml; 95% CI, 0.18–0.79 g/L and 136.99 mg/L; 95% CI, 103.60–170.37 mg/L, mean difference: 21.89 mg/L; 95% CI, 11.44–32.34 mg/L, respectively) (87).

Analysis from a small study showed that VTE in COVID-19 patients was associated with higher CRP levels vs. controls (214 vs. 153 mg/L, p = 0.035) (88). In a multicenter cohort study (n = 3,531), Lee et al. showed that CRP and LDH levels were significantly higher in the VTE group [9.8 mg/dL (8.1) vs. 7.6 mg/dL (5.8), p < 0.001 and 438.1 IU/L (378.4) vs. 380.0 IU/L (369.0), p = 0.036, respectively] (89).

In addition, among others white blood cell count and CRP at baseline showed a possible association with the incidence of VTE (OR: 1.03 (1.02-1.05, $p < 0.001$) for maximum white blood cells levels and OR: 1.04 (1.03-1.06, $p < 0.001$) for CRP) (89). Similar results on differences in CRP and LDH levels were reported in another study. CRP and LDH were higher in the VTE group (169 ± 20.0 mg/L vs. 92 ±156 mg/L, $p = 0.042$ and 378 ± 50 IU/L vs 347 ± 21, $p < 0.001$, respectively) (90). Similarly, in a meta-analysis (n = 1,803) it was shown that VTE vs. non-VTE patients had increased LDH and white blood cell count levels (mean difference: 112.71 IU/L, 95 % CI 62.40–163.02 IU/L, mean difference: $1.14*10^9$/L, 95 % CI 0.47–$1.81*10^9$/L) (Xiong et al., 2021). Higher leukocyte levels and CRP levels were also associated with the incidence of PE (OR 1.09, 95% CI 1.02–1.16, $p = 0.028$; OR 1.33, 95% CI 1.11–1.59, $p = 0.013$), in another study (91).

Regarding lymphocytes in the meta-analysis by Wu et al., a lower count was observed in VTE patients (0.77×10^9/L; 95% CI, 0.70 0.84×10^9/L, mean difference: -0.15×10^9/L; 95% CI, -0.23 -0.07×10^9/L) (87). Similarly, lower lymphocyte counts were observed by Cui et al. in the subgroup of VTE patients (0.8 ± 0.4 vs. 1.3 ± 0.6 × 10^9/L, $p < 0.001$). Fibrinogen is related to venous thrombosis; levels of 4.0-4.9 mg/ml vs. < 3 mg/ml exerted a 1.6-fold higher thrombotic risk, while levels ≥ 5 mg/mL had an high adjusted risk for venous thrombosis (OR: 4) (92).

In the study by Xiong et al. CRP and fibrinogen levels did not exert any difference between groups (VTE vs. non-VTE) (Xiong et al., 2021).

In our study Neut/Lymph ratio was associated with increased incidence of TE in the general population as well as with the risk of death in the VTE group of patients. Neut/Lymph ratio has been proposed as a marker of disease severity in COVID-19 patients since early days of the pandemic (64,93). In a study by Grimnes et al. Neut/Lymph ratio was considered to be a more consistent predictor for the risk of TE compared to CRP (94). In another study by Toori et al., it was shown that the cut-off level of Neut/Lymp ratio > 3.0 was associated with poorer outcomes and increased mortality (95).

Thrombotic events are associated with increased risk of death. In the meta-analysis of Xiong et al., patients with VTE were at a higher risk of death (OR: 2.39, 95 % CI 1.36 4.20) (51).

In our study, increased levels of TyG were associated with the need of intubation. TyG index has been proposed as a marker of insulin resistance (96). This index can identify those at greater risk of cardiovascular disease development (96). It

is evident that cardiovascular disease is inversely correlated with COVID-19 outcomes (97). It has been shown that patients with TyG levels > 9.2 have higher concentrations of white blood cells, LDH and CRP levels, yet lower lymphocyte counts. TyG index was also associated with severe COVID-19 (OR: 2.9) (98). TyG > 9.6 was considered to be predictor of mortality (98).

To our knowledge, only this study reported on the possible association of TyG index and outcomes in COVID-19 patients

Our findings should be interpreted in the light of certain limitations. This was a retrospective observational study and should be assessed by the limitations of its design. Population matching was performed considering only known confounding parameters which can intervene in the coagulation process. On the other hand, screening for PE or VTIB was not performed by standard protocol but upon clinician’s judgement regarding patient’s overall status.

Chapter 5. Conclusions

Indices of inflammation were associated with the prevalence of venous thromboembolism. Upregulation of white blood cells, lymphocytopenia and increased Neutrophils-to-Lymphocytes ratio aggravated the disease's prognosis and outcomes. Triglyceride-glucose (TyG) index was also found to increase the risk of worse outcomes. Large-scale clinical studies are needed to reach more robust conclusions regarding the clinical significance of these markers as predictors of COVID-19 associated venous thromboembolism. Future studies should consider including lipid profile, TyG index as well as inflammatory cytokines in the screening for thrombotic events in COVID-19 infected patients. Although promising, there is uncertainty if altered inflammatory markers represent a prognostic tool of COVID-19 severity risk, based on the existing evidence. Whether these markers unfavorably affect outcomes of thrombosis must be further evaluated. However, we strongly suggest that COVID-19 patients may benefit from monitoring more closely these markers.

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Chapter 6. Synopsis

- Several pathophysiological mechanisms are identified in the effect of SARS-CoV-2 and the incidence of thromboembolism.
- Two major interrelated pathways are held responsible for both micro- and large vessel thrombosis
- Hypercoagulable state leading to large vessel embolism and the immune mediated microthrombosis as well, exert a key role in the resulting venous thrombotic events in COVID-19
- Hyperinflammation leads to the adhesion of platelets and incite thrombi formation in microvessels through cytokine overproduction and associated chemotaxis
- VTE patients are at greater risk of adverse events in the course of the disease and an overall a more severe of illness.

Chapter 7. References

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