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Περίληψη

Από τα τέλη του 2019, δισεκατομμύρια άνθρωποι έχουν μολυνθεί από ένα νέο στέλεχος κορονοϊού που ξεκίνησε από την Κίνα (SARS CoV-2), προκαλώντας κυρίως ήπια συμπτώματα από τον αναπνευστικό, αλλά ακόμη και θανατηφόρο αναπνευστική ανεπάρκεια σε κάποιους ασθενείς. Πρώιμα στην περιγραφή της νόσου, καταγράφηκε αυξημένη επίπτωση φλεβικής θρομβοεμβολής (ΦΘΕ) μεταξύ των ασθενών, οδηγώντας συχνά σε σοβαρή επιδείνωση της νόσου και θάνατο. Με σκοπό να αξιολογηθεί η επίπτωση της ΦΘΕ σε νοσηλευόμενους ασθενείς με COVID-19, καταγράφηκαν αναδρομικά όλα τα δεδομένα των ασθενών από τον Μάρτιο του 2020, καθώς και τα επεισόδια ΦΘΕ.

Μεταξύ των 1353 ασθενών με COVID-19, 10.9% αυτών εμφάνισε επεισόδιο ΦΘΕ (πνευμονική εμβολή ή σημείο αγγειακού "tree-in-bud") κατά τις πρώτες 72 ώρες νοσηλείας. Οι ταυτοποιημένοι παράγοντες κινδύνου συμπεριλαμβάνουν το αυξημένο ΔΜΣ, το ιστορικό υπέρτασης, μεγαλύτερη διάρκεια των συμπτωμάτων πριν τη νοσηλεία και την παρουσία πυρετού, μυαλγιών, δύσπνοιας, διαρροιών ή εμέτων στα αναφερόμενα συμπτώματα. Αντίθετα, η μεγαλύτερη ηλικία, ο εμβολιασμός έναντι του SARS CoV-2 και το ιστορικό στεφανιαίας νόσου φάνηκε να μειώνει τον κίνδυνο για ΦΘΕ. Περαιτέρω έρευνα και μεγαλύτερες μελέτες απαιτούνται ώστε να βρεθούν περισσότεροι παράγοντες κινδύνου ή προστατευτικοί παράγοντες για ΦΘΕ σε ασθενείς με COVID-19 και να ανακαλυφθούν πιθανοί παθοφυσιολογικοί μηχανισμοί.

Λέξεις κλειδιά: covid-19, φλεβική θρομβοεμβολή, πνευμονική εμβολή, αγγειακό "tree-in-bud", παράγοντες κινδύνου

Abstract

Since the end of 2019, billions of people have been infected with a new coronavirus originating in China (SARS CoV-2), causing mostly mild respiratory symptoms, but also fatal respiratory failure in some patients as well. Early in disease exploration, increased incidence of venous thromboembolism (VTE) was recorded among the patients, often leading to increased severity of the disease and death. In order to assess the incidence of VTE in hospitalized patients with COVID-19, we retrospectively recorded all patients' data since March 2020, as well as the episodes of VTE.

Among 1353 patients with COVID-19, 10.9% of them had an episode of VTE (pulmonary embolism or vascular "tree-in-bud" sign) in the first 72 hours of hospitalization. Identified risk factors include increased BMI, history of hypertension, longer duration of symptoms prior to hospitalization and the presence of fever, myalgia, dyspnea, diarrhea or vomiting in symptoms. Contrary, older age, vaccination against SARS CoV-2 and history of coronary artery disease seemed to decrease the risk for VTE. Further investigation and larger studies are needed to reveal more risk and protective factors for VTE in patients with COVID-19 and explore possible pathophysiology mechanisms.

Key words: covid-19, venous thromboembolism, pulmonary embolism, vascular "tree-in-bud", risk factors

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GENERAL PART

Chapter 1

1. Introduction

1.1 Description of the disease.

Since the December of 2019, a new pathogen causing many cases of severe respiratory infection was first described in China. It was a novel coronavirus named Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS CoV-2), a single stranded RNA virus belonging in the coronaviridae family of viruses, identified in Wuhan City, China. As the incidence of the disease rapidly increased in the following weeks, the World Health Organization (WHO) declared the infection a public health emergency of international concern on 30 January 2020. Further rapid spreading of the disease in many other countries led to the characterization of the SARS CoV-2 infection as a pandemic on 11 March 2020[1].

During the following months, COronaVIrus Disease 19 (COVID-19) cases were identified in every country and as of June 2022, more than 550.000.000 infections have been reported globally, accounting for more than 6.300.000 deaths. In a period of 31 months, more than ten different variants of the virus have been described, most notably the delta variant causing more severe respiratory disease and the omicron variant with higher contagion rate. In the battle against the disease, a number of vaccines have been approved since 11 December 2020 (first vaccine approved in the United States of America), while more than 4.700.000.000 persons have been fully vaccinated worldwide. In addition, a small number of antiviral drugs have been approved for use in hospitalized or non- hospitalized patients with COVID 19[2].

Disease transmission occurs with close contact and respiratory droplets, while the mean incubation period is approximately 6 days. The clinical course of the SARS CoV-2 infection widely varies among the patients. A small percentage will be

completely asymptomatic while the majority of the infected people will appear very mild to moderate severity symptoms of upper respiratory system infection (including fever, cough, sore throat, headache, fatigue, muscle pain, loss of taste and smell and diarrhea). A minority of patients will experience severe symptoms (high fever, difficulty breathing, hypoxia, chest pain) due to lower respiratory system infection (pneumonia) and will need hospitalization for oxygen supplementation and medical treatment. Moreover, a small percent of the hospitalized patients will be severely affected by the virus, demonstrating signs and symptoms of severe acute respiratory distress syndrome (ARDS) and respiratory failure, leading to need for intubation and transfer to the Intensive Care Unit (ICU). Finally, mortality rate is estimated around 1.1% of the infected, with more than 6.300.000 deaths attributed to SARS CoV-2 globally[1,2].

1.1.1 COVID- 19 in Greece.

According to WHO, the first case of COVID-19 in Greece was recorded on 26 February 2020 in a woman who had recently traveled in Northern Italy and after a short hospitalization and isolation period recovered with no other sequelae. Since then and as of early July 2022, 3.792.674 cases of SARS CoV-2 infections were recorded in Greece (population approximately 11.000.000), indicating a national incidence of 34.4%. The highest daily incidence of new infections was recorded on 4 January 2022 with 50.126 cases. The number of deaths attributed to the virus was 30.400 and total mortality at around 0.8%. The first vaccination against SARS CoV-2 in Greece was performed on 23 December 2020, with a total of 21.161.653 vaccine doses delivered so far. As a result, 7.719.202 persons are considered fully vaccinated (70% of the total population)[3].

1.2 Thromboembolic disease in COVID-19

Even in the first days after the identification of the novel coronavirus and the cluster of hospitalizations for viral pneumonia in Wuhan City, China, it was prominent that except from pneumonia and respiratory failure, laboratory features of thrombosis (d- dimers) were significantly apparent in patients that ended up in the ICU[4]. In addition, acute pulmonary embolism (PE) without significant traditional risk factors for thromboembolism was recorded in a patient with severe bilateral pneumonia caused by SARS CoV-2[5]. One of the first studies in COVID-19 patients showed an increased incidence of Venous Thromboembolism (VTE) in critically ill patients of up to 25%, while expected incidence among the ICU patients (receiving thromboprophylaxis) was not exceeding 15% until then. Furthermore, studies and autopsies in European patients admitted to the ICU confirmed an increased incidence of VTE (31%, 32% and 58%)[6]. Other studies in France showed high incidence (16.7% and 21%) of PE in critically ill patients, along with other thrombotic complications, despite thromboprophylaxis. On top of that, extremely increased incidence of PE in critically ill patients with COVID-19 was observed despite not only prophylactic dose of anticoagulation (100%) but also therapeutic dose of anticoagulation (56%). Higher cumulative incidence of VTE was again detected in ICU patients after 21 days (59%), but it was significantly high (9.2%) in hospitalized non ICU patients[5].

1.2.1 Pathophysiology of VTE in COVID-19

Acute Respiratory Distress Syndrome (ARDS) is often observed in patients with severe SARS CoV-2 pneumonia, and one of its core pathophysiology mechanisms is the extravasation of neutrophils into the alveoli, resulting in intraalveolar inflammation, fluid concentration and gas exchange disturbances. Moreover, platelet

concentration and following deployment of neutrophil extracellular traps (NETs) further support thromboinflammation in lungs, worsening respiratory function.

The unique correlation between severe COVID-19 and coagulopathy seems to have both features of diffuse intravascular coagulation (DIC) and thrombotic microangiopathy (TMA), as indicated by the laboratory findings of increased levels of d-dimers, firbrinogen, fibrin degradation products and decrease levels of thrombocytes. In particular, thrombocytopenia in COVID -19 is not as severe as observed in DIC, while d-dimer levels are more elevated than that seen in DIC[7].

Coagulopathy specifically located in respiratory circulation has been observed in severe SARS CoV-2 pneumonia, associated with bilateral pulmonary inflammation. Lung autopsy findings from COVID-19 infected patients describe perialveolar vascular microthrombi occluding small vessels, pulmonary infarctions, blood vessel wall edema and fibrin thrombi, along with immune cell infiltrates. The abundant formation of small clots in alveolar capillaries seems to be characteristic for COVID-19 compared to other viral respiratory infections[7].

An interesting pattern of pulmonary vascular abnormalities in patients with COVID-19 is vascular “tree-in-bud” sign (VTIB) as revealed by lung CT imaging. In specific, peripheral pulmonary vessels become dilated, forming the “tree-in-bud” radiologic sign, where resolved small peripheral vessels account for the “bud” point in central vascular “tree”. So far, “tree-in-bud” sign in lung CT referred to peripheral airway abnormalities, attributed almost exclusively to infectious diseases. Most plausible pathophysiology of the sign is the hypercoaguability and impaired fibrinolysis specifically in lung vasculature of COVID-19 patients, leading to peripheral vessels’ dilation. Furthermore, VTIB is possibly another form of pulmonary thrombotic angiopathy located in peripheral vessels[8].

Apart from SARS CoV-2 associated immunothrombosis that significantly increases the risk for VTE, traditional risk factors are also very common among hospitalized patients, including older age, extended immobility and hospitalization, especially in an ICU setting, obesity, history or active cancer, history of previous VTE or thrombophilia[9].

1.3 Prevalence of VTE in COVID-19 patients.

In early observational studies, increased incidence of VTE was recorded in hospitalized patients with COVID-19. Lower extremity venous thrombosis was diagnosed in 25% of patients with SARS CoV-2 pneumonia. Elevated d-dimer level more than 1.5 μg /mL were sensitive and specific (85% and 88.5%, respectively) predictors of VTE in these patients[10]. Although the majority of them were asymptomatic, 46% of the hospitalized patients were diagnosed with deep vein thrombosis (DVT). The predicting factors were d-dimer levels, hypoalbuminemia and SOFA score[11]. In another study, cumulative incidence of VTE among hospitalized patients receiving thromboprophylaxis was 16% (in day 7), 33% (in day 14) and 42% (in day 21). DVT was observed in 13% of the patients whereas less often PE was noted in 6.6%. In addition, significant difference in the VTE incidence was observed between ICU patients (47% with VTE) and simple ward hospitalized patients (3.3% with VTE). Independent risk factors were once again elevated d-dimer levels, white blood cell and the neutrophil to lymphocyte ratio[12].

Furthermore, higher incidence of thrombotic complications (in total 31%) was found in ICU hospitalized patients receiving thromboprophylaxis, not only in the venous branch, presenting as PE in 25% and other venous sites in 3%, but also in the arterial branch, as ischemic strokes were observed in 3%[13]. Similar results were also

showed in a study from Italy where 7.7% of the hospitalized patients had at least one thromboembolic event despite thromboprophylaxis. In particular, PE was diagnosed in 2.8% of the patients, DVT in 1.7% of the patients, ischemic stroke in 2.5% and acute coronary syndromes (ACS) in 1.1% of the patients. Regarding the intensity of care needed for these patients, thromboembolic events appeared in 16.7% of the ICU hospitalized patient and in 6.4% of those in general wards[14]. In a recent meta-analysis, among 3.973 patients hospitalized for COVID-19, PE was reported in 32%, while the estimated prevalence of DVT among 2.552 patients was 27%. Interestingly, VTE was common despite thromboprophylaxis, while patients with COVID-19 related VTE had higher risk for death compared to patients with VTE and other underlying causes[15].

Increased prevalence of thrombotic events was observed among 289 COVID-19 patients hospitalized in non ICU wards, with the majority of them receiving standard dose thromboprophylaxis. Specifically, PE was present in 14.5%, DVT in 4.2% and cerebral venous thrombosis (CVT) in 1% of the patients. Increased leukocyte and D-dimer levels at admission, peak D-dimer levels during hospitalization and lower hemoglobin level at discharge were observed in VTE patients. In addition, time from onset of symptoms to admission, Improve score and lack of thromboprophylaxis were associated with VTE. Both death and admission to ICU rates were almost double in VTE patients and the independent risk factors for these endpoints were VTE, fever at admission, lymphopenia and the extent of COVID-19 assessed by chest CT. [16]

In a retrospective study in France, increased prevalence of VTE (22.5%) and PE (10%) was also observed among non severe COVID-19 patients, hospitalized in non ICU medical wards, receiving adequate thromboprophylaxis. A D-Dimer threshold of 1μg/mL could be of predictive value for the risk of VTE.[17] Similarly, increased PE

prevalence (6.4%) was also observed among 452 non critically ill patients, despite standard thromboprophylaxis regimen. In this study, the best predictive factor for PE (OR 3.77) was a peak D-dimer level of >5000 μg/dL (50 μg/mL). Significantly, the risk for PE was 9 times higher in non dyslipidemic patients. [18]

Diagnosis of both PE and DVT can often be challenging in the setting of COVID-19 units. Elevated d-dimer levels are usually elevated on admission regardless of an underlying thromboembolic event. Clinical instability and severe isolation protocols restrict the otherwise easier access to diagnostic imaging tests. Clinical signs and symptoms of DVT or PE as acute leg swelling or rapid respiratory deterioration, should lead to targeted further evaluation[7,9].

In a meta-analysis of 39 studies revealed high incidence of VTE (42%) and specifically PE (17%) among patients with severe COVID-19 (defined as having signs of pneumonia and one from tachypnea, respiratory distress or hypoxia). Moreover, male patients with VTE were predominant accounting for 69% of cases, while average BMI was higher than normal at 27.2 kg/m^2. Compared to controls, a series of laboratory values were significantly different in patients with VTE, including higher D-dimer and fibrinogen levels, neutrophil counts and CRP, but decreased lymphocyte counts. In addition, male gender and advanced age were associated with higher prevalence of VTE. In contrast, common comorbidities like cancer, coronary artery or respiratory disease, hypertension and diabetes were not associated with VTE presence. Finally, as expected, the presence of VTE augmented both the need for critical care and severe deterioration.[19]

Similarly, increased levels of D-dimers, lactate dehydrogenase (LDH) and WBC with decreased lymphocytes were observed in COVID-19 thrombotic patients (vs non thrombotic) in another meta-analysis. In general wards, thrombosis was present in

22% of patients, while the prevalence almost doubled to 43% after admission to ICU wards.[20] Significant difference in the prevalence of VTE was also associated with disease severity, as 38% of the severely ill patients had been diagnosed with VTE, while VTE prevalence was less than half (17.2%) in non severe COVID-19. In the same meta-analysis, the prevalence of PE is slightly lower than DVT both in general (17.6% and 18.3%) and in severe cases (21.7% and 22.1%) of COVID-19 patients.[21]

In another meta-analysis of 20 studies, weighted mean prevalence of DVT was 19.8% and PE 18.9% in patients with COVID-19. In addition, no significant difference in the prevalence of both DVT and PE was observed despite hospitalization in an ICU or treatment with thromboprophylaxis. Regression analysis revealed association between increased age and total VTE, DVT and PE prevalence, while increased BMI was positively associated only with PE prevalence. No difference was observed between males and females.[22] Another meta-analysis revealed increased risk for thrombotic events in patients above 60 years of age, increased D-dimer levels (above 3.17 μg/mL), while traditional thrombotic risk factors such as hypertension, diabetes, cardiovascular or respiratory diseases, chronic kidney disease and active cancer were found irrelevant.[23]

1.4 Thromboprophylaxis in COVID-19 patients.

In hospitalized patients with COVID-19, thromboprophylaxis with standard dose of unfractioned heparin (UFH) or low molecular weight heparin (LMWH) should be started, except if contraindicated. Especially in high risk ICU hospitalized patients, intermediate dose of LMWH should be considered. In selected high risk for VTE patients, extended thromboprophylaxis up to 30 or 45 days post discharge could be recommended. Treatment of diagnosed VTE should follow current therapeutic

guidelines and should last at least 3 months[9,24]. In contrast, the American Society of Hematology guidelines suggest prophylactic over higher intensity anticoagulation in both critical and acute illness from SARS CoV-2 in hospitalized patients without suspected or confirmed VTE[25].

SPECIFIC PART

Chapter 2

2. Methodology

2.1 Aim of the study

The aim of this study was to describe the incidence of VTE among patients hospitalized for COVID-19 in simple clinical wards from the start of the pandemic in Greece on March 2020 up to September 2022 in the University Hospital of Ioannina, in Northwestern Greece. In addition, specific characteristics of the patients diagnosed with VTE will be addressed. Finally, various risk factors associated with VTE outcomes will be described as well. As risk factors we defined patient comorbidities and reported symptoms. The outcome was defined as the onset of Venous Thromboembolic Event (VTE) during the first 72 hours of hospitalization. We considered as VTE the presence of radiologically evident Pulmonary Embolism (PE) or vascular tree-in-bud sign (VTIB).

The foreground questions of this study are presented by PICO statement (84) in figure 1.

P	Patient / Population	Adult hospitalized COVID-19 patients
I	Intervention / Indicator / Exposure	Presence of comorbidities and symptoms
C	Compare / Control	Absence of comorbidities and symptoms

O	Outcome	Thrombotic Event
T	Time / Type of Study or Question	Retrospective cohort

Figure 1: PICO statement as formed for this study

2.2 Inclusion and exclusion criteria

Between March 2020 and September 2022, all patients older than 16 years old, positive for SARS CoV-2 (RT-PCR test) hospitalized in the Infectious Diseases' Unit of the University Hospital of Ioannina (Ioannina, Northwestern Greece) were recorded, after providing consent form. In total, 1353 patients were eligible for inclusion in the study, all hospitalized in simple wards. Main admission criteria used in the emergency department were hypoxia (SPO2 <94%) or respiratory failure, imaging findings indicating pneumonia in chest x-ray, severity or prolongation of symptoms (high fever, dyspnea, cough, chest discomfort) and derailed laboratory findings (e.g. white blood cells abnormalities, electrolyte disorders, cardiac or renal injury). Exclusion criteria were defined as: consent form not provided, onset of TE after the first 72 hours of hospitalization. All patients requiring intubation or hospitalization in an Intensive Care Unit at the time of admission were excluded from the study as well.

2.3 Study design and data record.

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

We collected data from COVID-19 hospitalized patients admitted to the Infectious Diseases Unit of the University Hospital of Ioannina, from March 1st, 2020 to September 31st, 2022. SARS-CoV-2 infection was diagnosed by reverse transcriptace–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 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 Supplementary Table 1.

Patient demographics, anthropometric characteristics, medical history, comorbidities, and concomitant medications were documented on admission (baseline characteristics). Specifically, demographic parameters (age, gender, body mass index, history of smoking), as well as medical history and comorbidities (coronary artery disease, cancer, autoimmune disease, diabetes mellitus, arterial hypertension, pulmonary disease, dyslipidemia, chronic kidney disease, obesity, hypothyroidism) were recorded. All data were obtained as reported by patients or through patients' electronic records. Regarding long term pharmaceutical therapy as well as recent drug administration for other reasons, information was obtained in a similar way.

Radiological findings and indices were obtained by computed tomography (CT) pulmonary angiogram or high-resolution chest CT. Radiographic evidence of PE or VTIB in either examination was considered as a positive result. 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.

2.5 Statistical analysis

Statistical analyses and table syntheses were performed via the Statistical Package for Social Sciences (SPSS) 28.0 software (SPSS, IBM corp), provided by the University of Ioannina. Continuous numeric variables are expressed as mean ± standard deviation. Categorical data are presented as total number (N) and percentage. Analyses were performed comparing different groups of patients. Exposure group was identified as the group of patients diagnosed with each comorbidity or symptom. Control group was identified as the group of patients without a diagnosis of

comorbidity or symptom. Chi-squared test was used to compare categorical data among study groups, Mann-Whitney test for continuous data, Kolmogorov-Smirnov test for ratio data. The presented results are derived from multivariate binary logistic regression for each risk factor, while adjusting for patient age and sex. Two-tailed significance was defined as p-value < 0.05.

Chapter 3

3. Statistical results

3.1 Demographics

In a period of 31 months (March 2020 to September 2022), 1353 patients eligible for the study were recorded. Most of them were Greeks, older than 16 years old (adolescents over 16 years of age are admitted in adults' COVID-19 units rather than pediatric unit as per hospital's protocol), living mainly in Ioannina city, but also in the greater area of Northwestern Greece. Baseline demographic characteristics of the study population and comorbidities are presented in Table 2.

Mean age was 65.1 years (16 to 97 years old), while the majority of them (80%, 1082 patients) were more than 50 years old. More than half of study population were men (56.9% male and 43.1% female gender). Furthermore, mean body mass index (BMI) was 28.8 kg/m^2, indicating that most patients were overweight, if not obese. On the other hand, only 13.3% of patients were current smokers.

3.2 Medical history and comorbidities

The most common comorbidities among patients were metabolic disorders with almost half of them (47.7%) having a history of arterial hypertension (mostly under treatment) and one third of them (35.2%) having dyslipidemia. Obesity (BMI over 30 kg/m^2) was present in 23.5% of the patients, while diabetes mellitus was also very common concerning 23.1% of study population. Importantly, a history of coronary artery disease (CAD) was recorded in 20.2% (including myocardial infarction, angina or previous percutaneous coronary intervention).

Furthermore, thyroid disease was present in 11.3% of the patients, while 7.3% reported a pulmonary disease (predominantly chronic pulmonary disease or asthma).

Moreover, 6.7% of the patients had an autoimmune disorder (mostly rheumatoid arthritis), while chronic kidney disease (CKD) was present in 6.9% and dementia in 4.7% of the patients. Finally, active or history of cancer, a well known risk factor for VTE, was recorded in 8.4% of study population.

Another critical factor for both disease severity and final outcome was the history of vaccination against SARS CoV-2. Thus, 32.6% of the patients were fully vaccinated prior to their infection, a relatively small percentage compared to almost 70% of fully vaccinated adult population in the country. Some obvious explanation for this is the initial delay in vaccine production and distribution, as for more than a year since the start of the study, vaccines were not available for the majority of the population.

3.3 Prevalence and duration of symptoms

All reported symptoms were recorded in present illness of the patients. Among them, fever was by far the most common symptom, reported by three quarters of the patients (77.6%), followed by dry cough by almost half of them (45.9%). Dyspnea was already present at admission in 25.4% of the patients, while other common symptoms included fatigue (27.2%), diarrhea or vomiting (24.8%) and myalgia (15%). Less common symptoms with prevalence smaller than 10% in study population were (from most to least common) headache, sputum production, anorexia, sore throat, dysgeusia, anosmia and rhinorrhea.

Mean time from symptoms' onset to admission was 5.9 days, while mean duration of hospitalization was 10.7 days.

3.4 Incidence of VTE in study population and specific characteristics.

Data of 1353 hospitalized COVID-19 patients were included in the analysis. Incidence of VTE was 10.9%. Most cases of VTE consisted of VTIB (80%), while CT confirmed PE was 20%. The population was split in two sub-groups; the VTE group consisting of 147 patients and the non-VTE group consisting of 1206 patients.

The VTE group of patients had younger mean age ($p<0.001$), in opposition to mean BMI values that where greater ($p=0.012$), compared to the non-VTE group. The most frequent commorbidities in the VTE group were arterial hypertension, dyslipidemia, obesity and diabetes mellitus. Also, a significant percentage of these patients (15.0%) reported a smoking habit.

The most frequently reported symptoms in the VTE group of patients were fever, dry cough, fatigue, dyspnea, myalgia and diarrhea/vomiting. Also, the vaccination coverage in the VTE group was significantly lower compared to the non-VTE group (14.3% vs 34.8%).

Moreover, the main comorbidities in the non-VTE group of patients were arterial hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, obesity and smoking. The most frequent symptoms in this group were fever, dry cough, fatigue, dyspnea, myalgia and diarrhea/vomiting.

Finally, the VTE group of patients reported longer duration of symptoms during the pre-hospital stages (more than 2 days) and eventually required longer hospitalization (for a mean of 3.5 days) compared to the non-VTE group ($p<0.001$ for both comparisons).

3.5 Association of risk factors with the incidence of VTE

The results of multivariate binary logistic regression for each risk factor are summarized in Table 3. The odds ratios are adjusted for patient age and sex.

Age was negatively associated with the incidence of VTE (OR=0.98, p-value=0.004), while higher BMI values slightly increased it (OR=1.03, p-value=0.050). Similarly, arterial hypertension was associated with increased incidence of VTE (OR=1.53, p-value=0.037) and CAD was associated with decreased incidence (OR=0.55, p-value=0.032). Of note, vaccination against SARS-CoV-2 was associated with significantly decreased incidence of VTE (OR=0.33, p-value<0.001). Concerning the reported symptoms, fever and dyspnea significantly increased the incidence of VTE (OR=2.18, p-value=0.004 and OR=1.57, p-value=0.015, accordingly). Patients who reported myalgia and diarrhea/vomiting, also, presented higher incidence of VTE compared to the total population (OR=1.96, p-value=0.001 and OR=1.48, p-value=0.040, accordingly). Finally, longer duration of reported symptoms was associated with slightly increased incidence of VTE compared to the total population (OR=1.08, p-value<0.001).

3.6 VTE incidence during the waves of the pandemic (SARS CoV-2 predominant variant)

Figure 3 summarizes the alterations of VTE incidence during each pandemic wave. VTE incidence was quite low during the first 2 waves of the pandemic, that were mostly attributed to wild-type variants of the virus. During the third wave, which was marked by an increased circulation of the Delta variant, the incidence of VTE peaked at 102 cases documented in a 6 month period. During the fourth and the

current pandemic wave (mostly attributed to the Omicron variants) the incidence of VTE gradually decreased.

CHAPTER 4

4.0 Discussion

It has been almost 3 years since a new respiratory virus named SARS CoV-2 appeared in Wuhan, China and spread across the globe, causing the largest pandemic of the 21st century so far. Having affected billions of people, the virus's burden of disease can range from fully asymptomatic to fatal acute respiratory distress syndrome. Apart from that, an increased incidence of thrombotic events among patients with COVID-19 was observed early in the course of the pandemic.

In the same way, thousands of patients were infected and hospitalized in Greece, some of them in the University Hospital of Ioannina. Since March 2022, 1353patients were recorded, including anthropometric and medical data, present illness and incidence of thrombotic events in particular. The aim of this study was to record the incidence of VTE events in this population and investigate the specific characteristics of the thrombotic group, as well as any factors associated with increased risk of thrombotic event.

The data analysis revealed that 10.9% of the patients had an episode of VTE (PE or VTIB) within the first 72 hours from admission. The majority of VTE events consisted of VTIB sign (80%) as described by radiologists in lung CTs performed to all recorded patients. Although not completely investigated, radiologic "tree-in-bud" sign in pulmonary vasculature of patients with COVID-19 could be perceived as a thrombotic event in the level of smaller pulmonary vessels, reflecting impaired mechanisms of coagulation[8]. Further studies in this field will determine the exact meaning and role of this sign in the course of the disease. On the other hand, 20% of VTE events were PE as described in CT pulmonary angiography.

Furthermore, the study suggests that, comparing to the non-VTE group, patients with VTE were younger, had greater BMI, reported longer time from symptom's onset to admission and were later discharged from hospital. In addition, younger age and greater BMI were associated with higher incidence of VTE, along with the history of hypertension. On the other hand, the presence of coronary artery disease in medical record was associated with fewer VTE episodes. Gender, obesity, dyslipidemia, diabetes mellitus, history of smoking, cancer, respiratory, autoimmune or other diseases were not significantly associated with the risk for VTE.

When it concerns to reported symptoms, fever, myalgia, dyspnea, diarrhea or vomiting were positively associated with the risk for VTE, while the rest of the symptoms (dry cough, fatigue, anorexia, sputum production, anosmia, dysgeusia, headache, sore throat and rhinorrhea) were not associated with VTE. Vaccination against SARS CoV-2 was more frequent in the non VTE group and seemed to significantly decrease the risk for VTE. Interestingly, during the 3rd pandemic wave correlated to the delta variant, a peak in VTE events was observed, although it was not the most populous of the waves.

The incidence of VTE in the present study (10.9%) is within the range of VTE incidence reported from similar retrospective studies from around the globe (7.7% - 46%), but mostly towards the lower end. The inclusion of patients hospitalized only in simple wards and not in an ICU environment as in other studies, could in part explain that difference. Furthermore, the inability to identify episodes of DVT due to lack of necessary equipment and strict access policies, factors restricting other studies too, may have led to not recording almost half of VTE events, taking into account that similar incidence of PE and DVT was seen in other studies. In addition, VTE events were only recorded if revealed within the first 72 hours and not throughout the whole

of hospitalization. As VTE events seemed to accumulate during the course of hospitalization[12], absence of late VTE events record could further shrink the documented incidence of VTE.

Having a thrombotic event (PE or VTIB) added on average two more days of hospitalization to the patients. This prolongation is interpreted not only in added burden of disease and suffering for the patient, increasing among others the risk for clinical deterioration and transfer to an ICU[19], but also in increased needs for available medical facilities and staff in the particularly demanding period of a pandemic.

Demographic data showed controversial results, as no difference in VTE incidence between genders was revealed (while men predominated in other[19]), younger age was associated with increased incidence of VTE (in contrast to other findings[19,22,23]) and BMI was associated with greater risk for VTE (in agreement with other studies[19,22)]. Further investigation with bigger meta-analyses could clarify these uncertainties. Although cardiovascular and metabolic risk factors were not associated with increased risk for VTE in other studies[19,23] (or even associated to decreased risk[18]), arterial hypertension was positively associated to VTE risk. Surprisingly, data suggest the history of CAD as a predictive factor for VTE. The possible favorable effect of antiplatelate and other medical treatment (common in patients with CAD) in both endothelial function and coagulation mechanisms could explain this finding, but more data are needed to clarify this relation.

From the perspective of symptoms, the duration seems to be significantly longer in the VTE group by 2.2 days. Similar results were also described in other studies[16], possibly reflecting the disease severity in this group, but also the later appearance of thrombotic complications in disease progress. In other words, longer symptoms'

duration increased VTE risk. Among symptoms, mainly fever but also the presence of myalgia, dyspnea, diarrhea or vomiting increased the thrombotic risk. Fever at admission has been described to increase VTE risk[16], but its exact contribution to thrombotic mechanisms (e.g. dehydration, inflammation, viral load, disease severity) remains unclear.

Possible limitations of this study include the relatively small number of patients recorded in the cohort, as the population of 1353 patients remains far from the according number in other large cohorts. Furthermore, VTE and especially PE is a relatively rare complication and the aforementioned number of patients may not be enough to reveal precise results. In addition, data were recorded retrospectively, limitating the recorded variables and partly through electronic data records increasing the risk for systematic biases.

Another significant limitation was the inability to investigate the possibility of DVT, mainly due to strict isolation protocols and poor availability of needed sources. As a result, one significant aspect of VTE was systematically not recorded, shrinking the VTE outcome to only PE and VTIB. On the other hand, outcomes of PE or VTIB were systematically assessed to all hospitalized patients, as CT scan was performed to all patients regardless of clinical signs and symptoms. Thus, systematic biases associated to subjective clinical judgment, decision making strategies, confirmation and other clinical practice aspects were prevented. Additional limitations include the lack of data for the incidence of VTE after the first 72 hours of hospitalization, either during the rest of hospitalization, or later after discharge. In this case, new CT scan was performed based on clinical signs, disease worsening or prolongation of hospitalization.

Thromboprophylaxis with low molecular weight heparin was given to all patients based on standard protocols, according to body weight, initiating the same day of admission. In addition, tinzaparin was unanimously used in all recorded patients, excluding specific substance differences. As of the patients receiving anticoagulation on admission (direct oral anticoagulants or acenocumarol) mostly due to atrial fibrillation, their number was small and were excluded from study.

CHAPTER 5

5.0 Conclusion

Higher incidence of thromboembolic events was observed in patients with COVID-19, in relation to patients suffering from similar viral or respiratory diseases. In order to assess the incidence of VTE in patients with COVID-19 hospitalized in the University Hospital of Ioannina, a cohort was recorded retrospectively. So far 1353 patients have been recorded and analyzed, particularly for demographic data, medical history, symptoms, vaccination history and the presence of PE or VTIB in the first 72 hours since admission.

The incidence of VTE was 10.9%, mainly VTIB and lesser PE, but higher incidence can be suspected as severe restrictions made the diagnosis of DVT impossible, thus excluding it from this study. Patients with VTE seemed to have younger age, greater BMI, longer period of symptoms and ended up with more days of hospitalization. In addition, risk factors for VTE included increased BMI, history of hypertension, longer duration of symptoms prior to admission and the presence of fever, myalgia, dyspnea, diarrhea or vomiting. In opposition, the history of vaccination and previous coronary artery disease seemed to strongly reduce the risk for VTE, while older age marginally reduced that risk.

Retrospective character of the study and the number of patients were the main limitations of the study. Continuing patients' and variables' record will further expand available data leading to more reliable results. In addition, future meta-analyses will reveal possible new risk factors for VTE in patients with COVID-19. Finally, new studies are needed to further enlight the pathophysiology mechanisms behind increased incidence of VTE in COVID-19 patients, as well as effective thromboprophylaxis to prevent these episodes.

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SUPPLEMENTARY MATERIALS

Category	Predictor 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 value for each patient	Numerical	NA
	Gender	Gender of the patient	0 = Male 1 = Female	
	Age	Age of the patient at admission	Numerical > 16	years
	BMI (Body mass index)	Body mass index of the patient	Numerical	kg/m^2
Past medical history of the patient / 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)	0 = no 1 = yes	
	Hyperlipidemia	Past medical history of the patient, self-reported or by patient's medication or else documented (visits at clinic, other documents)	0 = no 1 = yes	
	Arterial Hypertension	Past medical history of the patient, self-reported or by patient's medication or else documented (visits at clinic, other documents)	0 = no 1 = yes	
	Diabetes mellitus	Past medical history of the patient, self-reported or by patient's medication or else documented (visits at clinic, other documents)	0 = no 1 = yes	

Past medical history of the patient / Comorbidities	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)	0 = no 1 = yes	
	Autoimmune	Past medical history of the patient of autoimmune disease, self-reported of by medication patient was receiving (visits at clinic, other documents)	0 = no 1 = yes	
	COPD	Past medical history of the patient of chronic obstructive pulmonary disease	0 = no 1 = 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)	0 = no 1 = yes	
	Thyroid disease	Past medical history of thyroid dysfunction	0 = no 1 = yes	
	Dementia	Past medical history of dementia	0 = no 1 = yes	
	Obesity	Defined by BMI values	< 30 = no > 30 = yes	
	Smoking	Current smoker	0 = no 1 = yes	
Hospital Summary	Fever	Patient reported fever	0 = no 1 = yes	
	Dry cough	Patient reported dry cough	0 = no 1 = yes	
	Fatigue	Patient reported fatigue	0 = no 1 = yes	
	Anorexia	Patient reported anorexia	0 = no 1 = yes	
	Myalgia	Patient reported myalgia	0 = no 1 = yes	
	Dyspnea	Patient reported dyspnea	0 = no 1 = yes	

	Sputum production	Patient reported sputum production	0 = no 1 = yes	
	Anosmia	Patient reported anosmia	0 = no 1 = yes	
	Dysgeusia	Patient reported dysgeusia	0 = no 1 = yes	
	Diarrhea/Vomiting	Patient reported diarrhea or vomiting	0 = no 1 = yes	
	Headache	Patient reported headaches	0 = no 1 = yes	
	Sore throat	Patient reported sore throat	0 = no 1 = yes	
	Rhinorrhea	Patient reported rhinorrhea	0 = no 1 = yes	
	Duration of symptoms	Days of reported symptoms prior to hospitalization	Numerical	days
	Days of hospitalization	Days to discharge or death	Numerical	days
Outcome	VTE	Presence of PE or VTIB on CT imaging	0 = no 1 = yes	

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

	Total (N=1353)		VTE group (N=147)		non-VTE group (N=1206)		P-value
	(n)	(%)	(n)	(%)	(n)	(%)	
Demographics							
Gender (male/female)	770/583	56.9/43.1	87/60	59.2/40.2	683/523	56.6/43.4	-
Age (mean-years)	65.1	-	61.1	-	65.6	-	**<0.001**
BMI (mean-kg/m^2)	28.8	-	29.9	-	28.7	-	**0.012**
Vaccination	441	32.6	21	14.3	420	34.8	-
Comorbidities- risk factors							
AH	646	47.7	73	49.7	573	47.5	-
Dyslipidaemia	476	35.2	53	36.1	423	35.1	-
DM	312	23.1	28	19.0	284	23.5	-
CAD	273	20.2	17	11.6	256	21.2	-
Thyroid disease	153	11.3	13	9.5	140	12.2	-
Pulmonary disease	99	7.3	6	4.1	93	7.7	-
Autoimmune	91	6.7	9	6.1	82	6.8	-
CKD	94	6.9	4	3.4	89	7.4	-
Cancer	113	8.4	9	6.1	104	8.6	-
Dementia	63	4.7	2	1.4	61	5.1	-
Smoking	180	13.3	22	15.0	158	13.1	-

Obesity	318	23.5	48	32.7	270	22.4	-
Symptoms							
Fever	1050	77.6	130	88.4	920	76.3	-
Dry cough	621	45.9	75	51.0	546	45.3	-
Fatigue	368	27.2	40	27.2	328	27.2	-
Anorexia	89	6.6	10	6.8	79	6.6	-
Myalgia	203	15.0	37	25.2	166	13.5	-
Dyspnea	344	25.4	50	34.0	294	24.4	-
Sputum production	99	7.3	11	7.5	88	7.3	-
Anosmia	83	6.1	10	6.8	73	6.1	-
Dysgeusia	85	6.3	13	8.8	72	6.0	-
Diarrhea/Vomitting	335	24.8	48	32.7	287	23.8	-
Headache	116	8.6	20	13.6	96	8.0	-
Sore throat	87	6.4	15	10.2	72	6.0	-
Rhinorrhea	48	3.5	1	0.7	47	3.9	-
Duration of reported symptoms (mean-days)	5.9	-	7.9	-	5.7	-	**<0.001**
Duration of hospitalization (mean-days)	10.7	-	13.8	-	10.3	-	**<0.001**

Table 2: Baseline characteristics and symptoms reported upon admission of the total population and sub-populations (P-value refers to the statistical significance of Mann-Whitney test comparing the VTE and non-VTE subgroups).

Comorbidities- risk factors	OR	P-value
Gender	0.90	0.556
Age	**0.98**	**0.004**
BMI	**1.03**	**0.050**
Vaccination	**0.33**	**<0.001**
AH	**1.53**	**0.037**
Dyslipidaemia	1.25	0.237
DM	0.87	0.547
CAD	**0.55**	**0.032**
Thyroid disease	0.78	0.427
Pulmonary disease	0.56	0.236
Autoimmune	0.90	0.780
CKD	0.50	0.148
Cancer	0.74	0.411
Dementia	0.34	0.147
Smoking	1.08	0.742
Obesity	1.32	0.147
Fever	**2.18**	**0.004**
Dry cough	1.17	0.367
Fatigue	1.00	0.988
Anorexia	1.12	0.747
Myalgia	**1.96**	**0.001**

Dyspnea	**1.57**	**0.015**
Sputum production	1.00	0.986
Anosmia	0.99	0.982
Dysgeusia	1.33	0.368
Diarrhea/Vomitting	**1.48**	**0.040**
Headache	1.67	0.052
Sore throat	1.70	0.075
Rhinorrhea	0.14	0.054
Duration of symptoms	**1.08**	**<0.001**

Table 3: Odds Ratios of each risk factor in association with the incidence of VTE (derived from multivariate binary logistic regression). The odds ratios are adjusted for patient age and sex.

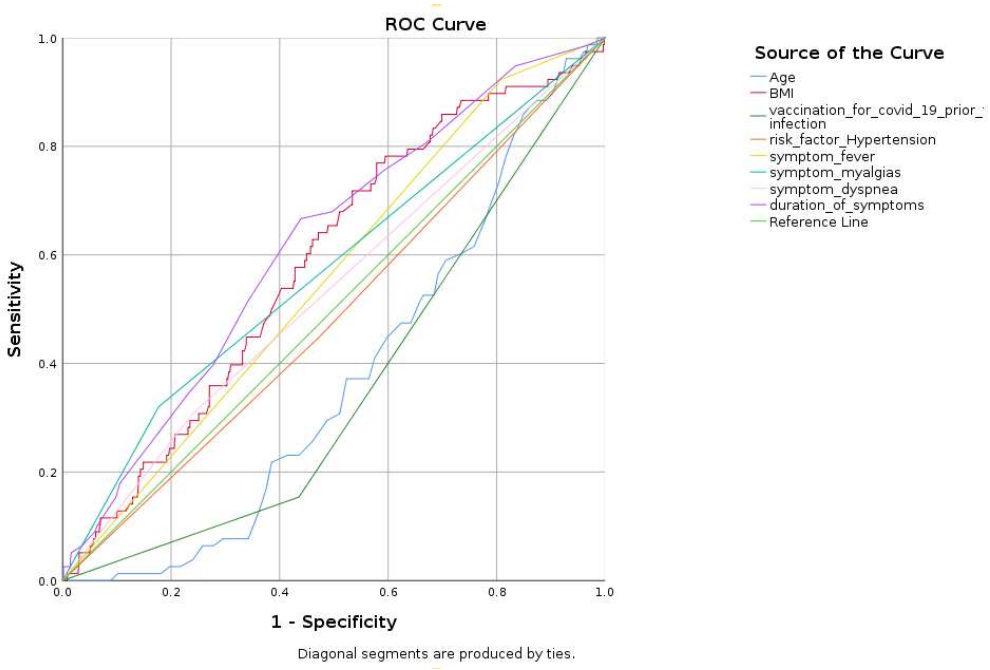

Figure 2: ROC analysis of the most important risk factors for the outcome of VTE.

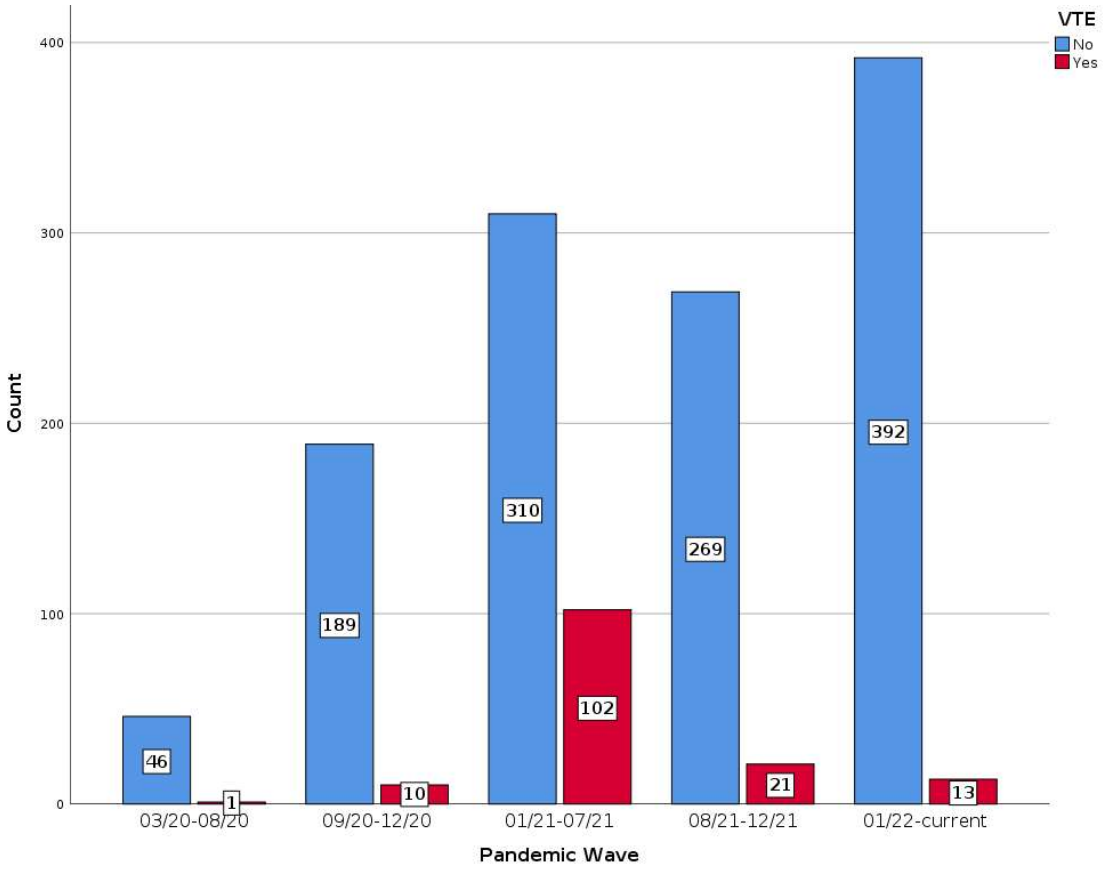

Figure 3: VTE incidence distribution documented during each pandemic wave.