OUTPATIENT TREATMENT OF PULMONARY EMBOLISM – A SINGLE-CENTER EXPERIENCE

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SUMMARY – *Background:* Pulmonary embolism (PE) is a common diagnosis in an emergency department. It also represents a large share of patients admitted to hospital wards. Patients with PE can be risk-stratified and discharged early from the emergency department. This results in better availability of hospital beds for other patients and a significant reduction of treatment costs for the healthcare system. This paper aims to describe the protocols used in our emergency department, with special emphasis on risk stratification, for adverse events and bleeding risk, treatment strategies, and outcomes for this type of protocol.

Materials and methods: This paper is a retrospective analysis of patients discharged from the emergency department in a of two-year period (2020-2021) with a low-risk pulmonary embolism.

Results: We have included in this study 42 patients discharged after a short-term observation from the emergency department (<24h) or short-term hospitalization; <24h). Ninety-one percent of patients were discharged with direct oral anticoagulant as a treatment for PE. We did not notice any adverse events (hemorrhage, progression of PE, or major cardiovascular issues).

Conclusion: In the cohort of patients with PE, early discharge and outpatient treatment was safe and effective, with lower healthcare costs and almost no adverse events for patients

Key words: *pulmonary embolism, emergency department, early discharge, outpatient treatment*

Introduction

Pulmonary embolism (PE) is a common diagnosis encountered by physicians working in the emergency department. In the United States, approximately two million patients are diagnosed with pulmonary embolism or deep vein thrombosis each year[1]. There is no clear data on the incidence in the literature in Croatia. Until recently, every patient with deep vein thrombosis and pulmonary embolism was admitted to the inpatient ward. In the last six years, in most cases (78.6%), patients with deep vein thrombosis have been discharged for outpatient treatment at the University hospital center Zagreb[2]. Such treatment strategy can lead to significant savings for the health care system

and has reduced the average costs at the emergency department (ED) of UHC Zagreb for the treatment of patients with DVT by approximately 50%[2]. Diagnostic procedures and treatment of pulmonary embolism are also a major burden on the health system, and the diagnosis itself has almost always been an indication for hospitalization[3]. In the last few years, there have been more and more papers describing the safety and usefulness of PE treatment in outpatient settings, although this concept has been known for more than the last 20 years. In the last 8 years, with studies that have proven the safety of treating pulmonary embolism with direct anticoagulants, and after introducing the recommendation of such treatment in the ESC guidelines, more and more centers have adopted such a treatment protocol. Various validated clinical tools are used to assess the risk of pulmonary embolism: HESTIA score[5]; simplified pulmonary embolism severity score (sPESI)[6] and pulmonary embolism severity score (PESI)[7]. Meta-analyzes have confirmed that

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outpatient treatment of pulmonary embolism is safe for patients[4].

This study aims to describe the population, diagnostic process, risk assessment, therapeutic options, and complications of outpatient treatment of pulmonary embolism at ED UHC Zagreb.

Methods

We retrospectively analyzed patients discharged from the emergency department or hospitalized for a maximum of one day in one of the departments of the University Hospital Center Zagreb, in the period from 1.1.2020. until 31.12.2021. The average annual number of patient visits at ED UHC Zagreb is about 100,000. The patients included in this analysis are adults (> 18 years of age) who were either examined in the emergency department and discharged with a diagnosis of pulmonary embolism after short-term observation (up to 24 hours) or were hospitalized in one of the hospital wards and discharged to home care within 24 hours of admission to the hospital. Patients excluded from the analysis were patients who were treated for a long time in the wards of UHC Zagreb or died during emergency treatment, or we could not obtain data on patients. Patient data from the Hospital Information System (BIS) of the University Hospital Center Zagreb were analyzed. The process itself was structured so that one researcher sought data on patients who could be included in the analysis, and another, a senior researcher, checked the data and made an analysis of the data obtained. The data included in the analysis were previously agreed upon and standardized before the beginning of the analysis. The data we analyzed were general patient data, clinical features of the disease, diagnostic procedures, risk quantification process for potential outpatient treatment, complications, and returns to the emergency department after discharge, for up to a total of two years after the first patient was discharged. All patients who entered this analysis underwent CT pulmonary angiography as a method of confirming the diagnosis of pulmonary embolism, in ED itself; or patients reported to ED with CTA report. The risk assessment tools - HESTIA score, PESI score, sPESI score, and the VTE-BLEED bleeding risk assessment tool - were also retrospectively analyzed. In addition, the therapy prescribed to the patient upon discharge was registered as well as potential complications that occurred after the patient was discharged from the hospital, for a total of up to 6 months after discharge.

All analyzes were performed in MedCalc 14.1. The results are presented as absolute and relative frequencies and median with interquartile range (IQR).

Results

Demographic characteristics of patients

This analysis included 42 patients who were discharged from the University Hospital Center Zagreb and treated according to the protocol for the treatment of pulmonary embolism in outpatient settings. The total number of patients diagnosed with pulmonary embolism in the two years was 457. 9.2% of patients were treated in outpatient settings. The mean age of the patient was 54 years, ranging from 42-72 years, and the proportion of women was 57.1%. Of these patients, 19 (45.2%) had a history of COVID-19 infection. Other demographic data, as well as previous diseases that are important in the treatment of these patients, are listed in Table 1.

Table 1. Demographic characteristics of patients

Variable	Number	Percentage
Age (in years)	54 (42-72)	/
Female sex	24	57.1%
Male sex	18	42.9%
Previous history of pulmonary embolism	8	19%
Previous history of deep vein thrombosis	9	21.4%
Hypertension	17	40.5%
Coronary heart disease	7	16.7%
Heart failure	6	14.3%
History of malignancy	12	28.6%
History of COVID-19	19	45.2%

Clinical characteristics of the patients

The predominant symptom experienced by the patients included in the study was shortness of breath, which occurred in 47.6% of patients. Patients had a normal heart frequency (median pulse 81/min (range 75-94) and normal respiratory rate (respiratory rate 16/min (range 12-18 / min). Oxygen saturation was nor-

Table 2. Clinical characteristics of patients

Variable	Number	Percentage
Chest pain	19	45.2%
Shortness of breath	20	47.6%
Elevated body temperature	6	9.5%
Swelling of the leg	4	6.5%
Syncope	2	4.8%
Palpitations	5	11.9%
Heart rate (min-1)	81 (75-94)	/
Respiratory rate (min-1)	16 (12-18)	
Blood pressure (systolic value)		
<100mmHg	3	3.14%
100-120mmHg	9	21.43%
120-140mmHg	14	33.33%
140-160mmHg	11	26,19%
>160mmHg	5	11.9%
Oxygen saturation (%)	97 (96-97)	/
D-dimers	2.4 (1.6-4.6)	/
NTproBNP	156 (117-509)	/
Troponins (hsTnI)	5 (3-11)	/
CT angiography of the lungs		
Large vessels	2	4.76%
Lobar branches	6	14.29%
Segmental branches	15	35,71%
Subsegmental branches	12	28,57%
Bilateral pulmonary embolism	7	16.67%
Ultrasound of the heart		
Significant RV disfunction	0	0
Mild RV disfunction	7	16.67%
No RV disfunction	35	83,33%
Ultrasound of the leg veins		
Proximal DVT	2	4.76%
Distal DVT	11	26,19%
Without DVT	29	69,05%
Arterial blood gas analysis		
Normal findings	40	95,24%
Respiratory alkalosis	2	4.76%

mL (ranging between 117 and 509.) All patients analyzed were diagnosed with CT pulmonary angiography, 35.71% of patients had a segmental pulmonary embolism. It was interesting to note that 7 (16.67%) patients had a bilateral pulmonary embolism. All patients underwent cardiac ultrasound, which was normal in 83.33% of patients. All patients were examined with color doppler of leg veins, in 4.76% of patients we found proximal deep vein thrombosis, and in 26,9% of cases distal deep vein thrombosis. Analysis of arterial blood gases in the majority of patients was normal. Clinical characteristics of patients are shown in Table 2.

Assessment of severity of pulmonary embolism and assessment for the risk of bleeding

Several validated tools were used to assess the severity of pulmonary embolism and to assist. The HESTIA score was negative in all patients. The SPESI score in 14 patients (33.33%) indicated a high risk for outpatient treatment. The PESI score showed a very low or low risk of pulmonary embolism severity in 73% of patients. The VTE-BLEED score in 14 patients (33.33%) indicated a high risk of bleeding during treatment with direct oral anticoagulants. Other risk assessment data are listed in Table 3.

Table 3. Assessment of the severity of the PE and assessment of the risk of bleeding

Variable	Number	Percentage
HESTIA score	42	100%
sPESI score		
Low risk	28	66,67%
High risk	14	33,33%
PESI score		
Very low risk	23	54,76%
Low risk	8	19.05%
Medium-high risk	7	16.67%
High risk	4	9.52%
Very high risk	0	0
VTE-BLEED score		
Low risk of bleeding	28	66,67%
High risk of bleeding	14	33,33%

Treatment and complications after discharge from hospital

The majority (78.6%) of patients were discharged from the emergency department after observation for

mal in all patients. The median d-dimer level in patients was 2.4 micromoles / mL (range 1.6-4.6 micromoles / mL) The median NTproBNP level was 156 pg/

Table 4. Treatment and complications

Variable	Number	Percentage
Type of discharge:		
Patients discharged from ED	33	78.6%
Patients discharged after hospitalization <24h	9	21.4%
Medication for treatment:		
Rivaroxaban	33	78.6%
Dabigatran	0	0
Apixaban	4	9.5%
Edoxaban	1	2.3%
Warfarin	1	2.3%
Dalteparin	3	7.1%
Complications		
Bleeding	0	
Thrombosis progression	0	9.52%
Major cardiovascular event	0	
Return to ED	4	

up to 24 hours, and 21.4% of patients were discharged from inpatient wards within 24 hours from admission. The medication predominantly started for outpatient treatment was rivaroxaban (78.6% of patients). Bleeding, progression of pulmonary embolism, or major cardiovascular event, including death, has not been observed in any patient. Four patients returned to the ED after discharge from the ED or hospital. First patient returned to the emergency department due to chest pain, his workup was fine, and the patient was discharged from the emergency department. Second patient developed pericarditis, as part of the non-recognized immune disease, he was hospitalized, and after stabilizing the condition with high doses of nonsteroidal antirheumatic drugs, he was discharged home. The third patient came to the emergency room due to symptoms of respiratory infection, with workup we found pneumonia in the territory of the vessels affected by pulmonary embolism, and the patient was discharged to home care with a recommendation for antibiotic treatment. A fourth patient was admitted to the emergency room due to symptoms of acute exacerbation of chronic obstructive pulmonary disease and was discharged home with a recommendation for treatment with steroids and antibiotics. We would like to point out a patient that was diagnosed with deep vein thrombosis of the arm and pulmonary embolism in the emergency department, which was also success-

fully treated in outpatient conditions without complications. In table 4 the types of treatment and complications after discharge are shown.

Discussion

Our retrospective analysis examined the demographic, clinical-diagnostic, and therapeutic characteristics of patients treated for pulmonary embolism in an outpatient setting. It is interesting to note that the greatest risk factor for the development of pulmonary embolism in the last two years was COVID-19 infection. The protocol used in ED UHC Zagreb requires adequate workup before the decision for discharge. This protocol includes the use of CT pulmonary angiography as a method of confirming pulmonary embolism, analysis of highly sensitive troponins and NT-PROBNP to rule out biochemical signs of right heart loading, orientational cardiac ultrasound to rule out signs of right ventricular stress, and leg vein ultrasound to confirm or exclusion of the existence of deep vein thrombosis. In addition, the risk assessment of the severity of the clinical picture is determined using the HESTIA score, and the PESI or sPESI score. These tools can adequately identify patients at low risk of mortality and morbidity within 30 days of discharge[8,9,10]. In addition, part of the protocol is to assess the risk of bleeding in the patient. For this purpose, we used the VTE-BLEED score[11], a clinical tool developed to assess the risk of bleeding in patients receiving anticoagulant therapy for the first time. Unlike the HAS-BLED clinical tool, which is most often used in clinical practice, the VTE-BLEED score was designed and subsequently validated in the group of patients with venous thromboembolic disease, while the HAS-BLED score was validated for the group of patients with nonvalvular atrial fibrillation. In addition, the VTE-BLEED score has been studied in patients receiving direct oral anticoagulant therapy and is therefore specific for bleeding that may occur during treatment with these drugs. As can be seen in the analysis, even patients with higher VTE-BLEED scores (> 2) can be treated safely and without complications with DOAC in an outpatient setting. More than 90% of patients were discharged from the emergency department with DOAC therapy, in most cases with rivaroxaban. Rivaroxaban is a drug that has been validated multiple times in the outpatient treatment of

pulmonary embolism[12]. The HOT-PE study[13] showed that rivaroxaban changes were safe and effective, with a very low risk of bleeding (1.6%) and an extremely low risk of thrombosis progression (0.6%), which is why the study was discontinued earlier than necessary because the null-hypothesis was statistically satisfied[14]. Finally, our analysis showed that low-risk pulmonary embolism outpatient treatment is safe. There were no cases of thrombosis progression, bleeding, or major cardiovascular events. The reason for this may be that this is a group of patients who are already at low risk for adverse events, but this does not change the fact that this analysis shows that the treatment protocol is safe for patients. Adverse events in terms of returning the patient to the emergency department were treated without hospitalization, were not serious, or were unrelated to pulmonary embolism, disease complications, treatment with direct oral anticoagulants, or treatment complications. The limitations of this study are primarily evident from the design itself. Namely, it was a retrospective analysis, and the cohort of patients was not large (42 patients). In addition, we studied complications of the disease or treatment if the patient came back to our hospital. The study also included patients who were hospitalized for a short time but who were discharged within 24 hours of treatment. The hospitalized patients were predominantly patients with bilateral pulmonary embolism, and although the protocol did not state that this was a contraindication for outpatient treatment, for patient safety they were still hospitalized for a short time. To correct the limitations of this retrospective analysis, it is necessary to do additional research, but still, monitor the cohort of patients who were treated in this way. Therefore, a prospective study is planned to study outpatient treatment of pulmonary embolism at OED UHC Zagreb.

Conclusion

In this retrospective analysis of patients who were discharged from the University Hospital Center Zagreb after short-term treatment (up to 24 hours) with a diagnosis of pulmonary embolism, it is evident that this is a safe and effective method of treatment. No patient had a disease complication (thrombosis progression), no treatment complication (bleeding), or any other major cardiovascular event. Outpatient treatment of pulmonary embolism with such a proto-

col could be implemented in the work of other health care institutions in the Republic of Croatia.

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Sažetak

IZVANBOLNIČKO LIJEČENJE PLUĆNE EMBOLIJE – ISKUSTVA JEDNOG CENTRA

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Uvod: Plućna embolija (PE) predstavlja jednu od čestih dijagnoza u svakodnevnom radu hitnog prijema i dovodi do velikog broja prijema u bolnicu, što nije uvijek nužno. Pošto se pacijenti na temelju obrade i stratifikacije rizika mogu obraditi i otpustiti iz hitnog prijema, to može dovesti do rasterećenja bolničkih odjela, te smanjenja troškova u sustavu zdravstva. Cilj ovog rada je opisati protokol koji se koristi u našem centru, koji uključuje obradu stratifikaciju rizika za kompliciranu kliničku sliku i krvarenje, terapijske opcije i neželjene događaje ovakve vrste liječenja

Materijali i metode: Ovo je retrospektivna analiza pacijenata koji su u razdoblju od dvije godine (2020 i 2021 godina) otpušteni iz hitnog prijema kao plućna embolija niskog rizika.

Rezultati: U studiju je uključeno 42 pacijenata koja su otpuštena iz OHBP KBC Zagreb nakon kratkotrajne opservacije (do 24h) ili su otpuštena iz bolnice nakon kratkotrajne hospitalizacije (do 24h). U 91% slučaja je pacijentu u terapiju uveden direktni oralni antikoagulans. Kod niti jednog pacijenta nije bilo neželjenih događaja (krvarenje, progresija tromboze ili veliki kardiovaskularni incident)

Zaključak: U ovoj kohorti jasno se vidi da je rani otpust pacijenata sa plućnom embolijom niskog rizika siguran način za liječenje ove bolesti, te da dovodi do većeg zadovoljstva pacijenata, manjeg boja hospitalizacija, manjih troškova za bolnice, te zanemarivog broja neželjenih učinaka liječenja.

Ključne riječi: *plućna embolija, hitni prijem, izvanbolničko liječenje, rani otpust*