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Original article

What we have learned from the Regional Pulmonary Embolism Registry (REPER)?

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Abstract

Introduction. The management of acute pulmonary embolism (PE) is still full of controversies, and the number of randomized trials in this field is relatively small. For the individual doctor and the health system who deal with acute pulmonary embolism it is very important to analyze the number of treated patients, hospital and out of hospital mortality and morbidity, how the patients' treated, what are the most important obstacles for the management of the disease.

Methods. Here, we present the Regional PE registry (REPER), in brief its development, purposes and the scientific results published in the journals on the scientific citation list, doctor thesis and studies accepted and presented at the European Society of Cardiology annual congress. This is academic initiated, non-interventional research and the patients are informed and gave their permission to be part of the registry. However, no public patient's personal data was used. The basic criterion for the enrollment is objectively proven (positive CT-pulmonary angiography) acute PE.

Results. The REPER was found as the single center PE registry at 2011 which enrolled patients hospitalized for the acute PE in the clinic of Internal Emergency Medicine of Military Medical Academy. As we realized that one institution could not have enough patients with acute PE to create the valid registry, we started to join other institutions under the principles of transparency and equality, and the first two were Institute for Pulmonary Diseases Vojvodina and Clinical Center Nis, which enrolled high number of patients from 2015. The registry became an international when the Clinical Center of Banja Luka joined as, followed by Clinical Center of Podgorica and Skopje. Till now, 1776 patients with acute PE are enrolled in the data base with more than 300 variables. During the last 5 years, 15 original scientific articles were published with the cumulative impact factor of 39.2, 5 doctor thesis were defended, and 5 scientific researches were presented at the ESC meeting.

Conclusion. For the clinician scientist it is crucial to develop qualitative data-base with as many as possible variables which are important for the understanding pathophysiology, diagnostic process and therapy management of the disease in focus. For that it is vital to cooperate with other doctors and institutions. We think that this registry full-filled their purpose, and thanks for these data our knowledge about PE is much deeper and we become better doctors.

Kew words pulmonary embolism, registry, treatment, risk stratification, bleeding

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Introduction

The Regional Pulmonary Embolism Registry (REPER) has been found as the single center registry of the hospitalized acute pulmonary patients in the Military Medical Academy at 2011. As we could not enroll enough patients for the qualitative scientific work, we decided to call other institutions to join us. The Institute of Pulmonary Diseases Vojvodine has become the first hospital that become the member of the multicenter PE registry. After that, permanently or transiently, several institutions joined to the registry, and from the period of 2015 to 2022 we enrolled 1776 patients with acute PE in our regional registry. Besides the Institute for pulmonary diseases Vojvodine, Clinical Center Nis, Kragujevac, Zemun and Zvezdara (for some period) and general hospital Pancevo became the part of the registry. From 2016 Clinical Center Banja Luka and after that Clinical Center Podgorica and Skopje became the multinational members of the registry. The number of enrolled patients regarding the institutions are presented in Figure 1.

During the period of 2015-2022, we managed to publish 15 articles in-extenso in the journals on the SCI list with the cumulative impact factor of 39.265, we had 6 accepted abstracts on the European Society of Cardiology congress, 5 doctor thesis are defended till know and one monography was published[1-27]. Several studies from our registry are currently under review in the journals ranking M21 and M22.

Here, we aimed to summarize the main published results from the REPER registry.

Risk stratification

We studied the role of pre-existing heart failure in the respect of all-cause, and PE-related hospital mortality in patients with acute PE. Heart failure with reduced ejection fraction was the independent predictor for 7-day hospital death in our cohort of 1201 patient (hazard ratio 2.22, 95% confidence interval 1.25-4,38.41, P=0.021)[1]. Glomerular filtration rate was also independent risk factor for hospital death, HR was 7.109 for GFR<30 ml/min, and 2.554 for GFR<60 ml/min)[2].

Electrocardiographic changes during acute PE were also important for the early risk stratification and the estimation of the efficacy of initial therapy. In the subgroup of 110 patients with intermediate-high and high risk PE we have found that early resolution (<72 h) of S waves in the first precordial lead and aVL lead were associated to better right ventricle function after few days and lower hospital mortality rate[3]. Early resolution od S waves was more often and earlier achieved in patients who were treated with thrombolytic therapy. This result is similar to the significance of ST segment resolution during the treatment of ST elevation myocardial infarction and shdismal owed the presence of re-perfused lungs.

Finely, we studied the role of gender to the prediction of acute PE. Hence, we have found that syncope has negative predictive value for hospital mortality only in women, and not in men[4]. One of the important finding

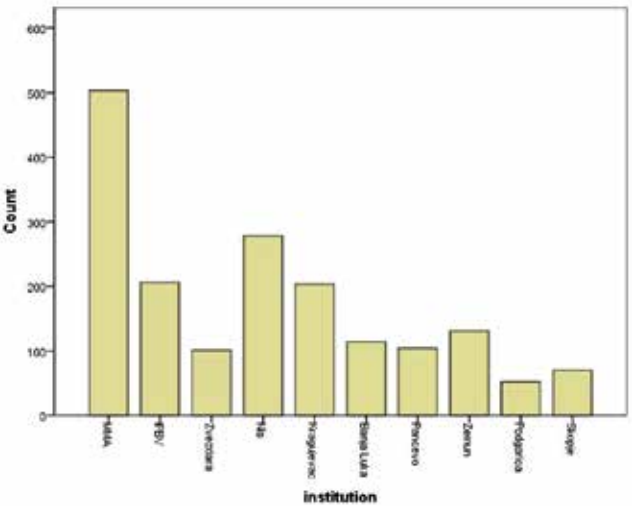

Figure 1. The number of patients from the various institutions which participate in the REPER

from our registry is that tachycardia at admission have had predictive value for early death only in women, and not in men[5]. Sinus tachycardia was also more important dismal sign for younger PE patients that for older[6] (ESC congress 2017).

We also investigated the prognostic role of symptomatic lower limb deep vein thrombosis, and our results pointed out that the presence of these symptoms at admission in patients with intermediate-high PE was associated with better prognosis and that was safe to use thrombolytic therapy in these patients[7].

Biomarkers

Considering biomarkers, we compare the predictive values regarding early death, for four biomarkers, cardiac troponin (cTn), brain natriuretic peptides (BNPs), C reactive protein and D-dimer in spontaneous versus provoked PE, and in the subgroups of provoked PE (major transient, major persistent, minor transient and minor persistent factors). We have found that elevated BNP is the most useful biomarker for predicting early death in acute PE whatever the cause of PE[8-10]. We also directly compared BNP-s x URL and cTn-s x URL (upper rate limit) in the cohort of 758 patients who had measured both markers at admission, and our data is going to conclusion that quantitative elevation of BNPs are much more accurate for prediction early PE death than cTn-s[11] (ESC Congress 2022).

We also studied the value of admission glycaemia for the prediction of hospital death in diabetic versus non-diabetic acute PE patients. We have found than only in diabetic patients, admission glycaemia had significant association with hospital death[12].

The special attention we dedicated to the prognostic role of various coagulation and anticoagulation protein activities during the first 24 hours from admission to PE severity and early death. We have found that lower antithrombin activity was associated to more severe PE presentation and early death[13,14].

Inflammation might play important role for the outcome of spontaneous PE, since CRP levels were signifi-

cant predictor of hospital mortality in this cohort of patients[15,16].

Bleeding in acute pulmonary embolism patients

The problem of bleeding was a central problem and the focus of our investigation for many years. Indeed, the foundation of REPER has begun as an attempt to make a score for the prediction of bleeding in acute PE, and to use it as a tool for the choice of treatment modality. We started with the small study presented at the ESC 2016 Congress, with comparison of 3 scores (simplified PESI, CHA2DS2-VASc and HAS-BLED scores) for the prediction of net adverse event (both death and major bleeding), and the HAS-BLED score had the best performance for this goal[17].

After a very long and hard scientific journey we succeeded to publish our investigation – Pulmonary Embolism Bleeding Score Index (PEBSI score) in the Thrombosis Research this year. We created 5-element's score for the prediction of low risk for bleeding on thrombolytic therapy[18]. Patients who had low risk for major bleeding according to the score have had 2.8% chance of major bleeding during the first seven days from the admission to hospital compare to patients with higher score who had 18.6% chance for major bleeding.

Therapy in acute pulmonary embolism

At the 2015 ESC Congress we presented the study about the efficacy and safety of rivaroxaban in patients with acute PE who were previously treated with thrombolytic therapy[19]. These kind of patients were excluded from the direct oral anticoagulant (DOAC) trials in venous thromboembolism. We have showed that in this high-risk group of patients rivaroxaban was efficacious and safe as the combination of heparins and vitamin K antagonists was.

Military Medical Academy is the pioneer for the catheter directed therapy (CDT) in acute PE. The first balloon angioplasty in subacute PE was performed at 2003 (20), and the first catheter directed thrombolysis with ultrasound facilitated system was used in October 2013. Since then Institute of Pulmonary Diseases Vojvodine and Clinical Center Kragujevac also developed teams which performed catheter directed therapy. 101 patients with acute PE treated with CDT were included in our REPER registry till now.

We published part of these results comparing no-reperfusion to classic systemic thrombolytic therapy with ultrasound assisted catheter thrombolysis in patients with intermediate-high risk PE patients[21,22]. We have achieved the lowest mortality rate in CDT therapy group with the similar rate of major bleeding with systemic thrombolysis.

We also have showed that slow-low dose tPA, (1-5 mg/h, maximum dose 20-50 mg) given either by intravenous or local infusion through the catheter, reduced hospital mortality compare to classic high-dose, faster tPA protocols in the intermediate-high risk patients[23].

Different DOACs have different risk for bleeding, especially gastrointestinal bleeding. We tested the hypothesis that all three DOACs used in Serbia (dabigatran, rivaroxaban and apixaban) have different hemostasis profile one month after stable anticoagulation in patients with acute PE. Patients on apixaban have the highest activity of prothrombin under the drug, and that could explain the lowest rate of bleeding on apixaban together with the most balanced anticoagulation pharmacokinetics[24,25]. This also might partly explain the less efficacy of the lower apixaban dose for the prevention of thromboembolic events. Dzudovic J et al, also developed the original method for the measurement of apixaban blood concentrations[26].

Timing for death in acute PE in respect of PE mortality risk is important for the strategy of planning PE management. According to our results 50% of fatal cases were occurred during the first hospitalization day in high risk PE, and 10% of fatal cases (from the whole group of patients who died during hospitalization) per day for the first 5 days occurred in intermediate-high risk PE. Interestingly about 50% of patients who died from PE died after the fifth hospitalization day in the intermediate-high risk subgroup[27].

Finely, the work on this registry resulted to our participation in the current ESC guidelines for the catheter directed therapy in acute pulmonary embolism[28].

Conclusion

For the clinician scientist, it is crucial to develop qualitative data-base with as many as possible variables which are important for the understanding pathophysiology, diagnostic process and therapy management of the disease in focus. For that it is vital to cooperate with other doctors and institutions. We think that this registry fullfilled their purpose, and thanks for these data our knowledge about PE is much deeper and we become better doctors.

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Sažetak

Šta smo naučili iz regionalnog registra za plućnu emboliju (REPER)?

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Uvod. *Lečenje I dijagnostika akutne plućne embolije (PE) je još uvek puno kontroverzi, I broj randomizovanih studija je relativno mali. Za pojedinačnog lekara I zdravstveni system koji zbrinjava pacijente sa PE veoma je važno da se analizira broj bolesnika, bolnički I van bolnički mortalitet I morbiditet, kako su pacijenti lečeni I koje su najvažnije prepreke u tretmanu ovih bolesnika.*

Metodi. *Ovim radom predstavljamo Regionalni PE registar (REPER), u kratko njegov razvoj, ciljeve, i naučne rezultate, publikovane u časopisima sa SCI liste, doktorske teze i radove koji su prezentovani na Evropskim kongresima*

kardiologa. Ovo je akademski registar, ne-intervencijski, i pacijenti su informisani i dali pristanak za učešće u njemu. Ne koriste se javno personalizovani podaci bolesnika. Osnovni kriterijum za ulazak u studiju je objektivno dokazana akutna PE i hospitalizacija bolesnika.

Rezultati. *REPER je nastao kao registar bolesnika sa akutnom plućnom embolijom jednog centra – Klinike za urgentnu internu medicinu, Vojnomedicinske akademije 2011 godine. Kako smo shvatili da kao jedna bolnica ne možemo da napravimo validan registar, odlučili smo se da pozovemo druge bolnice da nam se priključe po principu jednakosti i otvorenosti. Prvo nam se priključio Institut za plućne bolesti Vojvodine I Klinički Centar u Nišu – klinika za kardiologiju koji su počeli da uključuju svoje bolesnike u registar od 2015-te godine. Registar je postao internacionalni kada nam se pridružila Klinika za kardiologiju Banja Luke prvo, a zatim i Klinika za kardiologiju iz Podgorice i iz Skoplja. Do danas je 1776 bolesnika uključeno u registar, u bazu sa više od 300 varijabli. Tokom proteklih 5 godina, 15 originalnih radova je proisteklo iz registra sa kumulativnim impact faktorom 39,2, odbranjeno je 5 doktorskih teza i 5 radova je prikazano na ESC-u. Zahvaljući ovom radu smo postali i deo najnovijih ESC preporuka o kateterskom lečenju akutne PE.*

Zaključak. *Za kliničara-naučnika, je jako važno da razvija baze podataka od interesa, sa što više kvalitatetnih varijabli što je neophodno za shvatanje patofiziologije bolesti, dijagnostičkog procesa I terapijskih opcija. Zbog toga je od vitalnog značaja da se sarađuje sa drugim doktorima i institucijama. Mi mislimo da je ovaj registar ispunio svoje ciljeve, i zahvaljujući sopstvenim podacima naše znanje o tretmanu akutne PE je postalo dublje i postali smo bolji doktori.*

Klučne reči: *plućna embolija, registri, lečenje, stratifikacija rizika, krvarenje*