MORTALITY RISK ESTIMATION OF ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS TREATED WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION

PhD Thesis

Dominika Szabó, MD

Doctoral School of Basic and Translational Medicine

Semmelweis University

Supervisor:	István Hizoh, MD, PhD
Official reviewers:	András Komócsi, MD, D.Sc Dániel Aradi, MD, Ph.D
Head of the Complex Examination Committee:	István Karádi, MD, DSc
Members of the Complex Examination Committee:	Henriette Farkas, MD, DSc Hassan Charaf, PhD

Budapest, 2023

1. Introduction

Risk estimation is an integral part of the daily medical practice. To assess the individual mortality risk of ST-segment elevation myocardial infarction (STEMI) patients, a number of mathematical models (scoring algorithms) have been developed and validated in the last quarter of a century. Yet, as treatment approaches evolve over time with improving outcomes and as even older patients with complex disease patterns are treated invasively, there is a need to identify new predictors, and build new algorithms to maintain / increase prognostic accuracy. Moreover, by using calculators on mobile devices and computers instead of old-fashioned scoring tables and even nomograms, some predictors may be used as continuous or even non-linear variables further improving discriminative ability of the model.

In many of the risk estimation algorithms for patients with STEMI, heart rate and systolic blood pressure are key predictors. Yet, these parameters may also be altered by the applied medical treatment / circulatory support without concomitant improvement in microcirculation / survival.

We hypothesised that lactate as a biomarker of microcirculatory failure may have an added prognostic value in the risk assessment of patients with STEMI treated with primary percutaneous coronary intervention (PCI).

In the setting of STEMI, intravenous morphine is traditionally employed to relieve pain, reduce pulmonary congestion, and anxiety. International guidelines on STEMI recommend its application in these conditions based on expert consensus. Nevertheless, according to recent studies, morphine delays and decreases the effects of all currently available oral platelet $P2Y_{12}$ receptor inhibitors in vitro, which may result in poorer myocardial reperfusion and larger infarct size. In the light of that, the current European guidelines add a note of caution that the diminished effects of clopidogrel, ticagrelor, and prasugrel may lead to early treatment failure. Yet, there are few data available about the impact of this interaction on clinical outcomes and the effect on long-term mortality is barely investigated.

2. Objectives

2.1. Admission lactate level as a predictor of mortality

We investigated whether venous lactate level, a well-known marker of microcirculatory failure, may have an added prognostic value on top of the conventional variables of the GRACE 2.0 model for predicting 30-day all-cause mortality of STEMI patients treated with primary PCI.

2.2. Impact of morphine use on mortality

Using a prospective registry, we studied the impact of periprocedural morphine application on all-cause mortality in STEMI patients treated with primary PCI.

3. Methods

3.1. Venous lactate level

In a pilot real-world prospective single-centre registry, data of 334 STEMI cases were collected from May 2020 through April 2021. All patients were treated with primary PCI using standard techniques within 12 hours from symptom onset. All but 10 of them underwent venous blood gas analysis at cardiac care unit admission.

Nested logistic regression models were built using the GRACE 2.0 score alone and with the addition of venous lactate with 30-day all-cause mortality as the primary outcome measure. Model performance was characterised by receiver operating characteristic curve analysis (ROC, c-statistic). Difference in model performance was primarily analysed by the likelihood ratio (LR) test. Though the application of the integrated discrimination improvement (IDI, i.e. the change in the discrimination slope) and the widely used receiver operating characteristic curve analysis or model selection has been criticised, they have also been performed. Independence of the predictors (lack of collinearity) was evaluated by the variance inflation factor (VIF).

3.2. Impact of morphine use on mortality

We analysed observational data of 1255 consecutive STEMI patients of a single-centre prospective registry who were treated with primary PCI from September 2007 through December 2011. Of them, 397 (31.6%) received morphine intravenously based on physician's judgment in the periprocedural period.

Primary outcome measure of the study was time to all-cause death, whereas predischarge left ventricular ejection fraction (LVEF) assessed by echocardiography was used as secondary endpoint. Median follow-up time was 7.5 years.

Following descriptive statistical analysis, to adjust for confounders, two distinct propensity score-based techniques were applied. We used 1 to 1 nearest neighbour propensity score matching with a caliper width of 0.2 to estimate the average treatment effect for the treated (ATT) yielding a total of 728 cases. In addition, we also assessed the average treatment effect (ATE) by inverse probability of treatment weighting (IPTW) using stabilised weights retaining data from all patients.

The propensity score model included all measured baseline covariates that could affect treatment assignment and / or are known to be associated with the primary endpoint. Balance on baseline covariates between the treated and control groups was evaluated using absolute standardised differences. A value less than 0.1 was considered as an acceptable standardised bias.

Absolute risk differences in all-cause mortality were captured by Kaplan-Meier survival curves which were compared using log-rank tests. The relative change in the hazard of death was estimated using univariable Cox models. As to the secondary outcome measure, distributions of predischarge LVEFs in the treated and control groups were compared by rank tests.

4. Results

4.1. Lactate as a predictor of mortality

Receiver operating characteristics analysis of the admission lactate level as a single predictor revealed good discriminative ability for predicting both in-hospital and 30-day mortality. According to these analyses, the optimal cut-off point was 3.65 mmol/L.

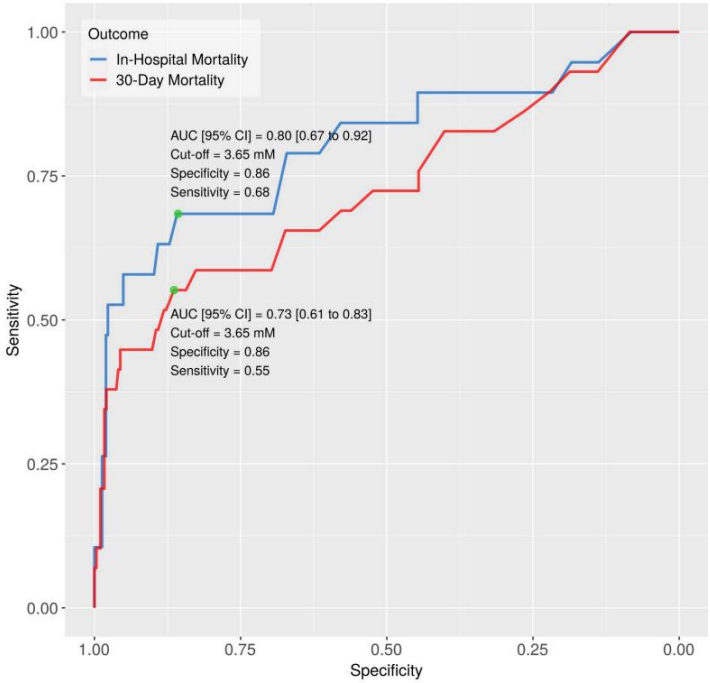

Figure 1.: ROC curves for lactate as predictor. Lactate level alone may have good predictive ability for predicting both in-hospital and 30-day mortality. ROC: Receiver Operating Characteristics; AUC: area under curve).

Compared with the base model (GRACE 2.0 score), the addition of lactate improved the model's performance as assessed by both likelihood ratio test (LR Chi-square = 8.7967, p = 0.0030), and integrated discrimination improvement (IDI [95% CI]: 0.0685 [0.0031 to

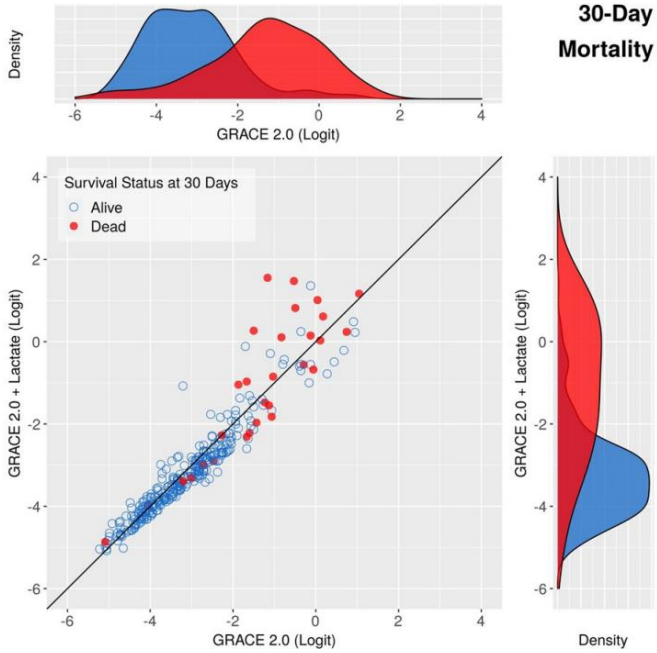

Figure 2.: Combined scatter and density plots for 30-day mortality. Two logistic regression models are shown: the horizontal axis represents the GRACE 2.0 score, while the vertical axis shows the model expanded with the lactate levels. The diagonal line represents identical predictive ability. With the inclusion of lactate, the probability of dying within 30 days was shifted downwards in most survivors (blue circles), whereas the majority of non-survivors (red dots) were shifted towards higher risk. The change in density plots suggest an increased discriminatory power of the expanded model.

0.1338], p = 0.0402), suggesting that the expanded model may have better predictive ability than the GRACE 2.0 score. The variance inflation factor (VIF) was 1.1203, indicating lack of collinearity, i.e. the measured lactate values were independent of the calculated GRACE 2.0 scores.

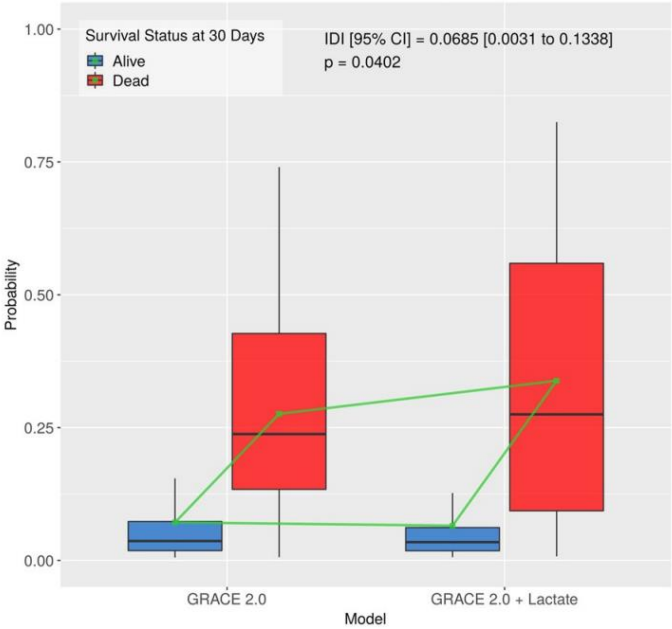

Figure 3.: Box-and-whisker plots for 30- mortality. The boxes represent the median and interquartile range (IQR), whereas the whiskers extend to the most extreme data point which is no more than 1.5 times the IQR from the box. The difference of mean probabilities (green squares) between non-survivors and survivors is known as discrimination slope, whereas the difference of discrimination slopes is defined as the integrated discrimination improvement (IDI). The results suggest that the expanded model may have better predictive ability than the GRACE 2.0 score.

4.2. Impact of morphine use on mortality

Systematic differences between treated and untreated patients in the original cohort have been eliminated in both matched and weighted samples.

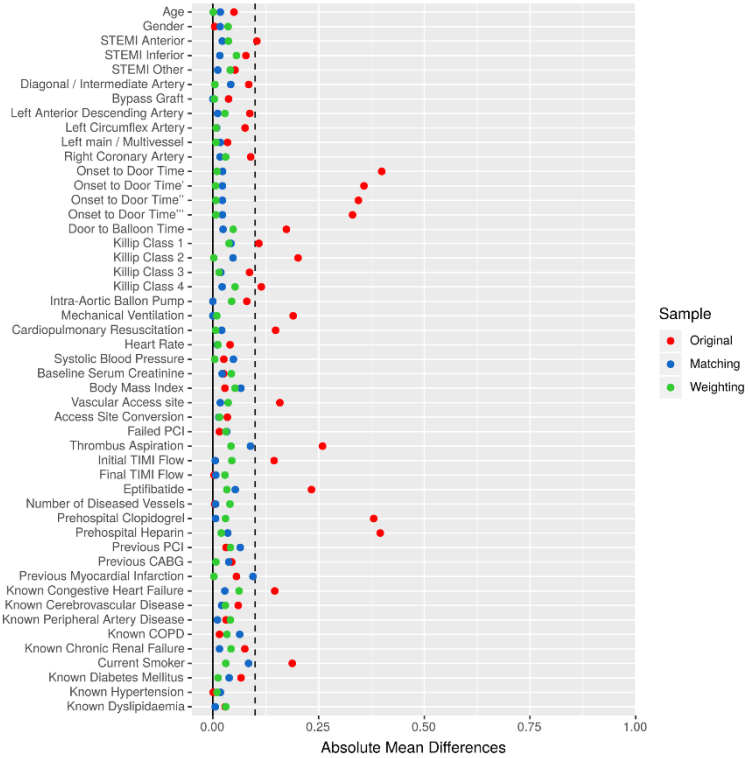

Figure 4.: Covariate balance between the original, the matched and the weighted population. The dot chart shows absolute standardised differences between control and treated groups across all measured baseline covariates. A value less than 0.1 was considered as an acceptable standardised bias. Adequate balance on baseline covariates has been achieved in both matched and weighted sets since potentially prognostically important covariates have been balanced between the treated and control groups.

Comparison of the Kaplan-Meier survival curves using the log-rank test revealed a statistically significant absolute all-cause mortality risk difference between the control and treated cohorts favouring treatment with morphine (p = 0.0229). Similarly, analysis of the relative effect size using a naïve, univariable Cox model, the hazard ratio (HR) was 0.79, 95% CI: 0.64 to 0.97, p = 0.0233.

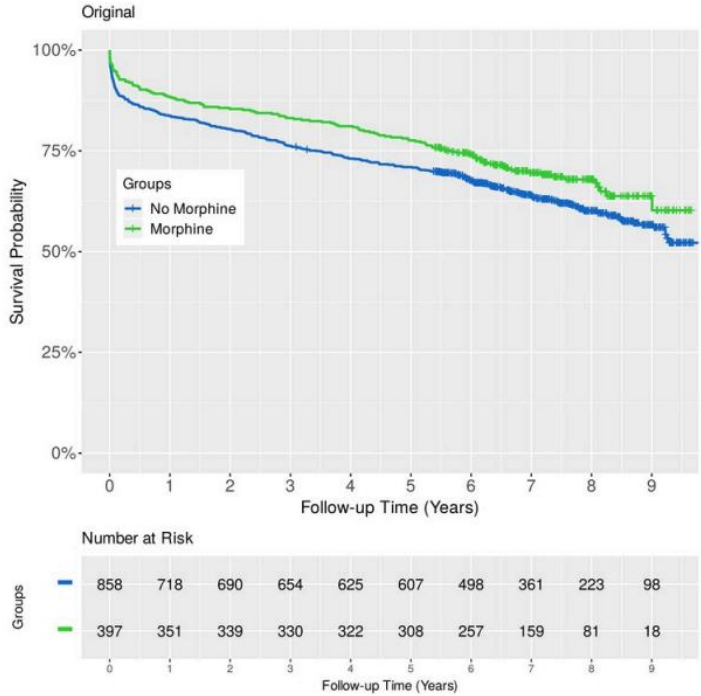

Figure 5/A.: Comparison of Kaplan-Meier survival curves. Analysis of the crude data revealed a statistically significant absolute mortality risk difference between the control and treated groups (p=0.0229, log-rank test).

To estimate the average treatment effect for the treated (ATT) we used 1 to 1 propensity score matching. There was no absolute risk difference detectable between the Kaplan-Meier survival curves of the matched control and treated groups (p = 0.3046). Likewise, the relative change in the hazard of death was not statistically significant when analysed by Cox regression (HR: 0.98, 95% CI: 0.76 to 1.26, p = 0.8574)

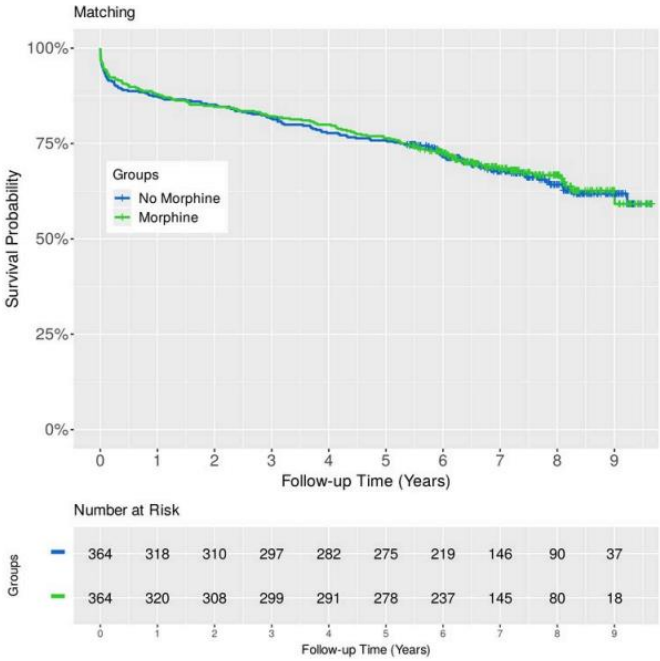

Figure 5/B.: Comparison of Kaplan-Meier survival curves - after propensity score matching. The difference observed in the original dataset is not detectable after adjusting for confounding using propensity score matching (p = 0.3046, log-rank test stratified on matched pairs).

We assessed the average treatment effect (ATE) by inverse probability of treatment weighting. As to absolute mortality risk difference, the Kaplan-Meier curves of the treated and untreated arms were almost identical ($p = 0.8518$). In addition, the hazard ratio was 1.01, 95% CI: 0.80 to 1.28, $p = 0.9010$.

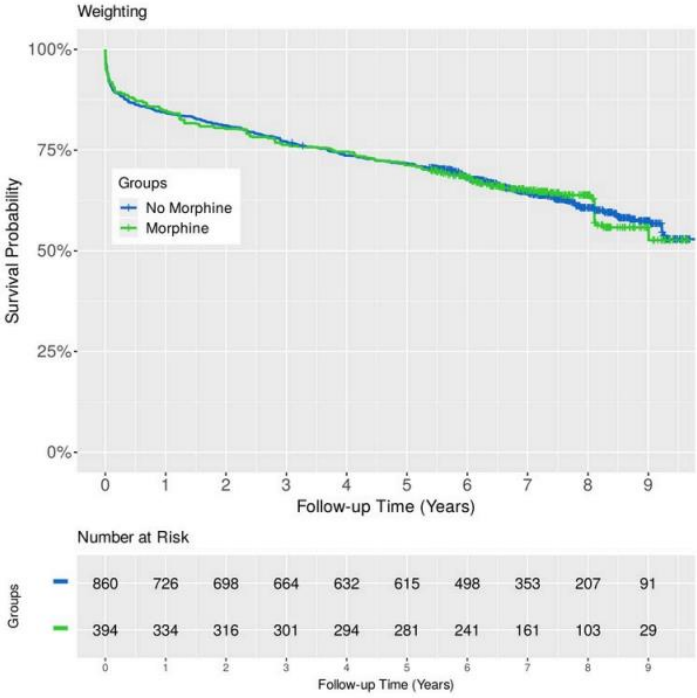

Figure 5/C.: Comparison of Kaplan-Meier survival curves - after inverse probability of treatment weighting. The difference observed in the original dataset is not detectable after adjusting for confounding using inverse probability of treatment weighting ($p = 0.8518$, design-based log-rank test).

The relative change in the hazard of death was estimated using univariable Cox regression in the original, matched, and weighted samples. Analysis of the crude data showed a statistically significant relative mortality difference favouring treatment with morphine. However, after reducing the bias with propensity score matching or inverse probability of treatment weighting, there is no significant difference detectable.

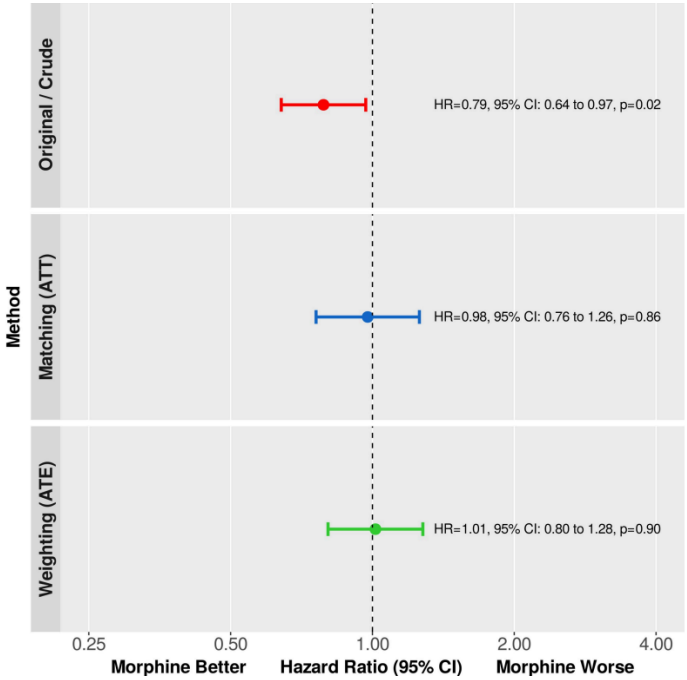

Figure 6. Relative change in hazard of 30-day mortality. After reducing the bias with propensity score-based methods, there is no significant difference between the treated and control groups.

5. Conclusions

Our results suggest that admission venous lactate level and the GRACE 2.0 score may be independent and additive predictors of 30-day all-cause mortality of STEMI patients treated with primary PCI. Therefore, using lactate level as an additional predictor may improve risk predictions. Further, preferably multi-centre randomised trials are warranted to confirm the findings of the present study.

Furthermore, despite previous findings indicating that periprocedural intravenous morphine administration may delay and reduce the effect of oral platelet P2Y12 receptor inhibitors in vitro which may be associated with larger infarct size, our findings show that intravenous morphine may have no impact on predischarge left ventricular ejection fraction and – more importantly – on all-cause mortality in STEMI patients treated with primary PCI. Thus, it may safely be used to relieve symptoms even in the era of primary percutaneous coronary intervention when reliable platelet $P2Y_{12}$ receptor inhibition is of crucial importance.

6. Bibliography of the Candidate[1]

6.1. Bibliography related to the present thesis

1. Hizoh I, **Domokos D**, Banhegyi G, Becker D, Merkely B, Ruzsa Z. Mortality prediction algorithms for patients undergoing primary percutaneous coronary intervention. J Thorac Dis. 2020;12(4):1706-20.
(IF: 2.895)

*Hungarian edition: **Domokos D**, Szabo A, Banhegyi G, Becker D, Edes IF, Ruzsa Z, et al. Primer perkután koronáriaintervencióval kezelt STEMI-betegek rizikóbecslő algoritmusai. Cardiologia Hungarica. 2020(50):272-82.*

2. **Domokos D**, Szabo A, Banhegyi G, Major L, Kiss RG, Becker D, et al. Impact of periprocedural morphine use on mortality in STEMI patients treated with primary PCI. PLoS One. 2021;16(1):e0245433.
(IF: 3.752)

3. **Szabo D**, Szabo A, Magyar L, Banhegyi G, Kugler S, Pinter A, et al. Admission lactate level and the GRACE 2.0 score are independent and additive predictors of 30-day mortality of STEMI patients treated with primary PCI-Results of a real-world registry. PLoS One. 2022;17(11):e0277785.
(IF: 3.752)

[1] Listed under the birth name (Dominika Domokos) in publications submitted before the year 2021.

6.2. Bibliography not related to the present thesis

1. Pólos M*, Domokos D*, Şulea CM, Benke K, Csikós G, Nagy A, et al. Needle in the heart: a rare case of cardiac tamponade caused by a migrated foreign body and mimicking ST segment elevation myocardial infarction. BMC Cardiovasc Disord. 2021;21(1):143. (IF: 2.174)
**joint first authors*

2. Szabó A, Tóth K, Nagy Á, Domokos D, Czobor N, Eke C, et al. The effect of cognitive dysfunction on mid- and long-term mortality after vascular surgery. BMC Geriatr. 2021;21(1):46. (IF: 4.070)

3. Skoda R, Bárczi G, Vágó H, Nemes A, Szabó L, Fülöp G, et al. Prognosis of the non-ST elevation myocardial infarction complicated with early ventricular fibrillation at higher age. Geroscience. 2021;43(5):2561-71. (IF: 7.581)

4. Tóth K, Szabó A, Nagy Á, Szabó D, Szécsi B, Eke C, et al. Preoperative nutritional state is associated with mid- and long-term mortality after cardiac surgery. Ann Palliat Med. 2021;10(11):11333-47. (IF: 1.925)

5. Domokos D, Szabo A, Banhegyi G, Polgar B, Bari Z, Bogyi P, et al. Needle aspiration for treating iatrogenic pneumothorax after cardiac electronic device implantation: a pilot study. J Interv Card Electrophysiol. 2020;57(2):295-301. (IF: 1.900)

6. Erath JW, Vamos M, Domokos D, Benz AP, Bari Z, Bogyi P, et al. Effects of implantation of quadripolar left ventricular leads on CRT response. J Interv Card Electrophysiol. 2019;55(1):73-81. (IF: 1.277)

7. Hizoh I, Banhegyi G, Domokos D, Gulyas Z, Major L, Kiss RG. Impact of Selective Aspiration Thrombectomy on Mortality in Patients With ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2018;121(7):796-804. (IF: 2.843)

8. Hizoh I, Gulyas Z, Domokos D, Banhegyi G, Majoros Z, Major L, et al. A novel risk model including vascular access site for predicting 30-day mortality after primary PCI: The ALPHA score. Cardiovasc Revasc Med. 2017;18(1):33-9.

9. Varga T, Mogyoródi B, Bagó AG, Cservenák M, Domokos D, Renner E, et al. Paralemniscal TIP39 is induced in rat dams and may participate in maternal functions. Brain Struct Funct. 2012;217(2):323-35. (IF: 7.837)