Liver and thyroid dysfunction as non-cardiac risk factors in heart transplantation and veno-arterial extracorporeal membrane oxygenation

PhD thesis

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1. INTRODUCTION

Our research group has been investigating non-cardiac risk factors in patients underwent mechanical circulatory support or heart transplantation. The unique profile of the Cardiovascular Centre of Semmelweis University, which hosts our research, played a major role in the selection of patient groups.

There is a huge literature on the long-term outcome of patients with severe heart failure. Their survival-enhancing drug therapies are based on the results of large randomized trials. In addition to the ongoing development of cardiac surgical therapeutic options, risk factors for patient outcome may change and new risk factors may be identified. Understanding these is essential to ensure proper patient selection, care, and correction of changeable risk factors.

1.1. End stage heart failure and end organ damage

In heart transplanted patients, it has described, that the extent and reversibility of end organ damage prior to transplantation determine mortality. The most common end organ damage occurs in the kidney, but liver and thyroid dysfunction associated with heart failure is not negligible either.

1.1.1. Liver dysfunction and the Model for End-stage Liver Disease scoring system

To some extent, liver dysfunction occurs in 10-30% of heart failure patients. Elevated venous pressure results in intrahepatic biliary congestion, which leads to damage to the bile ducts and to their fibrotic transformation. In congestive liver injury, synthetic function of the liver is impaired.

Critical circulatory insufficiency, low cardiac output, or hypoxia leads to ischemic hepatic impairment. Extensive liver cell death mainly affects the centrilobular part of the acins and is characterized by significant increase in transaminase level.

The model for end-stage liver disease (MELD) score was established for risk assessment in patients with hepatic insufficiency. The original MELD score includes the international normalized ratio (INR), serum creatinine, and total bilirubin. As a result, the MELD score is a comprehensive risk assessment score that includes synthetic

capacity and functionality of the liver as well as renal function. In the last decade, more and more studies have demonstrated the usefulness of MELD in patients with end-stage heart failure. Due to the common use of vitamin K antagonist drugs for anticoagulation in heart failure population, there has been a need for a new score systems, excluding INR. In the modified MELD (modMELD) INR was replaced by albumin, and the INR excluded MELD (MELD XI) score, which included only total bilirubin and creatinine, were obtained. The MELD score with serum sodium level (MELD Na) can be calculated from the original MELD score taking into account serum sodium levels. Studies examining the predictive value of different MELD scores have reported encouraging results in subpopulations of heart failure patient, especially in patients underwent heart transplantation or veno-arterial extracorporeal membrane oxygenation (VA ECMO) treatment.

1.1.2. Neuroendocrine and thyroid disorders

End-stage heart failure triggers a number of abnormal neuroendocrine responses. Beside activation of sympathetic nervous system, renin-angiotensin-aldosterone system, it can increase serum cortisol level and induces significant changes in thyroid function. In severe cardiogenic shock, activation of the hypothalamic-pituitary axis and regulation of hormone release are essential for an adequate stress response.

The thyroid gland is responsible for the synthesis and secretion of triiodothyronine (T3), thyroxine (T4) and reverse triiodothyronine (rT3), i.e. thyroid hormones. Thyroid hormone synthesis is regulated by a complex process via hypothalamus-hypophysis-thyroid gland axis.. The hypothalamus synthesizes thyrotropin-releasing hormone (TRH), which controls the production and release of thyroid stimulating hormone (TSH) in the anterior lobe of the pituitary gland. Based on observations, decrease in the amount of circulating free T3 occurs within a few hours after the insult, which is not followed by an increase in TSH level. In the initial acute phase, despite of decrease in T3 levels, TRH, TSH, and T4 level remain unchanged. If the stress persists for a longer period of time, we are talking about a chronic phase. T3 levels remain low, but even TSH and T4 levels fall below normal and the sensitivity of

hormone receptors decreases. In summary, the process can become maladaptive and dangerous.

Amiodarone, one of the most commonly used antiarrhythmic drugs, is known to cause thyroid dysfunction in patients with heart failure. Both hypothyroidism and thyrotoxicosis may occur as side effects of the treatment. Thyroid disease in the past medical history is known to increase these side effects.

Altered thyroid function may emerge from previous studies as an independent predictor of mortality in critically ill patients. The phenomenon has already been studied in heart failure and cardiac surgery patient populations, however, little information available in patient underwent heart transplantation.

1.2. Therapeutic options

1.2.1. Device therapy for heart failure

In patients with heart failure, mechanical circulatory support should be considered when symptoms persists despite optimal medical therapy. In case of refracter cardiogenic shock in patients with advanced heart failure, the use of short-term mechanical circulatory support is warranted. The primary goal is to restore cardiac output and improve the perfusion of vital organs. Before starting a mechanical assist device, it is important to set up a therapeutic plan, which can be followed even if the heart function does not improve.

VA ECMO is a mobile and simplified cardiopulmonary bypass machine. The system consists of an arterial and venous limb, a membrane oxygenator, a centrifugal pump, a cooling-heating module, a gas mixing unit and a display monitor. In each case, VA ECMO is a bridge to recovery or a bridge to decision about the next therapeutic option. In practice, it can be long-term circulatory support or heart transplantation. The most common clinical indications for VA ECMO are acute cardiogenic shock, postcardiotomy heart failure or decompensation of advanced chronic heart failure.

1.2.2. Heart transplantation

Heart transplantation is a treatment option in all patients treated with advanced heart failure, indication present in cases, where all medical, interventional and surgical treatment fails. A risk assessment based donor organ allocation has key importance. The short- and long-term outcome of heart transplantation and the patient's quality of life are determined by the occurrence of complications associated these procedures. Early complications can develop during the first 30 postoperative days. Late complications may occur after this period.

Early complications:

- Primary graft dysfunction (PGD)
- Infection
- Hyperacute rejection

Late complications:

- Malignancy
- Acute rejection
- Allograft vasculopathy (CAV)

2. OBJECTIVES

The main objective of this thesis was tailored around two main topics, hepatic dysfunction and thyroid dysfunction:

1. Is liver dysfunction assessed using MELD scores associated with survival in patients with advanced heart failure requiring VA ECMO treatment?

2. Is there any link between MELD score calculated prior to VA ECMO and absolute or in-hospital mortality? Can it be used to supplement the SAVE score?

3. What is the prognostic value of MELD score in different indication groups of patients treated with VA ECMO?

4. Is thyroid dysfunction characterized by decreased free thyroid hormone levels during the perioperative period associated with postoperative complications and survival in heart transplanted patients?

5. Does amiodarone play a role in perioperative low thyroid hormone levels?

6. Is decreased free T3 levels measured during the perioperative period associated with the onset of PGD and 30-day mortality?

7. Is decreased free T4 levels measured during the perioperative period associated with the onset of PGD and 30-day mortality?

3. METHODS

3.1. General characteristics

Our studies, which provide the topic of the dissertation, were performed by retrospective analysis of consecutive data collected prospectively. Our research work was hosted by the Cardiovascular Centre of Semmelweis University and the Department of Anesthesiology and Intensive Therapy of Semmelweis University.

Our investigations were carried out with the permission of the Semmelweis University Regional, Institutional Scientific and Research Ethics Committee (1091, Budapest, Üllői út 93.). Number and dates of permissions for our study: 141/2018; Budapest, August 3, 2018 and 65/2017; Budapest, April 6, 2017.

3.2. Patient population

Data from adult patients who underwent VA ECMO treatment between January 2012 and August 2018 were analysed and data from adult patients who underwent heart transplantation during the period January 2015 to December 2018 were used.

3.3. Variables

We retrieved patients 'age, gender, body weight, height, and significant comorbidities. Blood group data of our patients were also reported according to the ABO and Rh blood group systems. Our database also includes medications taken on a regular basis by our patients. The results of the last available laboratory test before the procedure were taken as a preoperative value. In the case of patients undergoing VA ECMO treatment, the type of cannulation used for implantation was indicated, and the length of treatment was also recorded. In heart transplant patients, we used the results of the obligatory hemodynamic measurement with Swan-Ganz catheter prior to the inclusion in the transplant waiting list, and the underlying disease leading to transplantation was also recorded.

3.3.1. Survival After Veno-arterial Exctracorporeal membrane oxygenation score

We calculated the SAVE score for our patients who underwent VA ECMO treatment. The SAVE scoring system classifies patients into five risk groups, using the following 13 preoperative variables, such as: etiology of cardiogenic shock, age, body weight, hepatic failure, central nervous system dysfunction, acute or chronic renal failure, need for intubation before the treatment, pre-implantation circulatory arrest, diastolic blood pressure, pulse pressure and pre-implantation bicarbonate value.

3.3.2. United Network for Organ Sharing score

UNOS scores were calculated for patients who underwent heart transplantation. Recipient factors included in the model were age, BMI, mean pulmonary artery pressure, total bilirubin, serum creatinine, previous transplantation, previous malignancy, preoperative mechanical ventilation, and transplantation from a non-continuous-flow mechanical circulatory support device. The donor factors included in the model were are age, cold ischemic time, sex difference of donor and recipient, and diabetes.

3.3.3. Model for End-stage Liver Disease scores

MELD, modMELD, MELD XI, and MELD Na scores were calculated for all patients undergoing VA ECMO treatment based on the last available laboratory parameters before implantation.

3.3.4. Variables related to thyroid function

A history of hypothyroidism and hyperthyroidism was recorded in the heart transplant group. Treatment with l-thyroxine, methimazole or propylthiouracil and amiodarone in the pre- or post-transplant period is indicated. Serum levels of TSH, free T3, and free T4 were used to monitor thyroid function.

3.4. Endpoints

In the liver dysfunction part, our primary endpoint was overall mortality (death by any cause) and our secondary endpoint was in-hospital mortality. Mortality data were last updated on November 20, 2018.

In the thyroid dysfunction part, our primary endpoints were the onset of any form of PGD, and our secondary endpoints were 30-day mortality and vasoplegia syndrome.

3.5. Statistics

Statistical analysis was performed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). Mean and standard deviation were used to describe normally distributed variables, and Student's t-test was used to compare them. For non-normally distributed variables, median and interquartile range (IQR) were used and Mann-Whitney's U-test was used for comparison. Element numbers (n) and percentages (%) were used to describe categorical variables, and chi-square or Fischer's exact test was used for comparison. In all cases, two-tailed trials were performed and $p < 0.05$ was considered as significant difference. Propensity score (PS) and inverse probability weighting (IPW) values were calculated. Univariate and multivariate Cox regression analysis were used to examine independent perioperative factors associated with our endpoints. Factors that had a value of $p < 0.20$ during the univariate analysis were included in our multivariate models. We adjusted our final multivariate models for the factors determining the examined endpoint and those closely related to the examined factor.

4. RESULTS

4.1. The effects of liver dysfunction

Data from 135 patients treated with VA ECMO were analysed. The median age was 58 years (IQR: 48-64) and the median follow-up time was 952 days (IQR: 417-1555). Overall mortality was 71.1% (n = 96), 30-day mortality was 47.4% (n = 64), and in-hospital mortality was 62.2% (n = 84). The median duration of VA ECMO treatment was 6 days (IQR: 3-7) and the median survival was 31 days (IQR: 8-338).

Members of the surviving patient group were younger, less likely to have diabetes, and most received ECMO treatment with central cannulation. However, they had a higher SAVE score than the deceased. Among survivors, higher sodium and albumin levels were measured. The creatinine, bilirubin, and INR values of the deceased were significantly higher prior to implantation. There was no difference in enzyme activities related to liver function. There was no significant difference in the need for transfusion of the three basic blood products. There was also no difference in complications and implantation of a ventricular circulatory support device.

We found significantly higher MELD scores among patients who died during the follow-up period according to all four scoring systems. Based on our univariate Cox regression analysis, pre-implantation variables were included in our multivariate models for both of our endpoints were: SAVE score, age, VA ECMO inserted with central cannulation; albumin, INR, creatinine, sodium, total bilirubin, MELD, modMELD, MELD XI, and MELD Na. Table 1 contains the final models of our multivariate Cox regression analysis for absolute and in-hospital mortality. All models were adjusted for SAVE score, indication for VA ECMO implantation, central cannulation, and vitamin K antagonist anticoagulation.

Table 1.: Multivariable Cox regression analyses of Model for End-stage Liver Disease scores

HR: hazard ratio; 95% CI: 95% confidence interval; SAVE: survival after veno-arterial extracorporeal membrane oxygenation; VKA: vitamin-K antagonist; MELD: model for end-stage liver disease; modMELD: modified MELD; MELD XI: INR excluded MELD; MELD Na: MELD with sodium

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	In-hospital mortality			***Overall mortality***		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
SAVE	0.93	0.90-0.97	<0.001	0.94	0.91-0.97	<0.001
Indication	0.96	0.77-1.20	0.722	0.97	0.79-1.20	0.797
Central cannulation	0.85	0.54-1.46	0.502	0.77	0.50-1.18	0.229
VKA therapy	0.68	0.38-1.24	0.209	0.71	0.41-1.23	0.222
MELD	**1.04**	**1.00-1.07**	**0.040**	**1.04**	**1.01-1.07**	**0.015**

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	In-hospital mortality			***Overall mortality***		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
SAVE	0.93	0.90-0.97	<0.001	0.94	0.91-0.97	<0.001
Indication	0.96	0.77-1.20	0.711	0.97	0.79-1.20	0.780
Central cannulation	0.82	0.51-1.30	0.390	0.74	0.48-1.14	0.167
VKA therapy	0.83	0.48-1.44	0.508	0.87	0.53-1.44	0.594
modMELD	1.02	1.00-1.05	0.118	**1.03**	**1.00-1.05**	**0.032**

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	In-hospital mortality			*Overall mortality*		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
SAVE	0.93	0.89-0.96	<0.001	0.93	0.90-0.96	<0.001
Indication	0.97	0.77-1.21	0.753	0.98	0.80-1.20	0.838
Central cannulation	0.79	0.50-1.25	0.318	0.71	0.46-1.09	0.114
VKA therapy	0.83	0.48-1.44	0.506	0.88	0.53-1.46	0.608
MELD XI	1.02	0.99-1.05	0.280	1.02	0.99-1.05	0.151

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	In-hospital mortality			*Overall mortality*		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
SAVE	0.94	0.90-0.97	<0.001	0.94	0.91-0.97	<0.001
Indication	0.96	0.77-1.20	0.744	0.98	0.80-1.20	0.826
Central cannulation	0.93	0.58-1.49	0.757	0.83	0.53-1.29	0.410
VKA therapy	0.63	0.35-1.14	0.127	0.66	0.39-1.14	0.138
MELD Na	**1.05**	**1.02-1.09**	**0.003**	**1.05**	**1.02-1.09**	**0.001**

MELD, modMELD, and MELD Na scores showed an independent association with overall mortality. MELD and MELD Na scores were independently associated with in-hospital mortality as well.

4.2. The effects of thyroid dysfunction

Data from 151 adult heart transplanted patients were retrieved. The median age was 54 years (IQR: 45-59). Heart transplantation was required in the majority of cases for non-ischemic dilated cardiomyopathy (61.6%) and ischemic dilated cardiomyopathy (24.5%). PGD occurred in 29 (19.2%) patients after heart transplantation. In the first 30 days after surgery, 10 (6.6%) patients died. All but one patient was involved in PGD. The incidence of vasoplegia was 15.2%.

Patients with PGD had significantly higher BMI, UNOS recipient, donor, and pooled scores, and more required mechanical circulatory support prior to transplantation, and the cold ischemic time of implanted donor hearts was longer compared to the control group. From the study population 29 patients had been diagnosed with thyroid disease before surgery, 20 of whom were diagnosed with hypothyroidism and 9 with hyperthyroidism. Prior to transplantation, 24 recipients and 45 donors received some form of l-thyroxine treatment. Patients with PGD had a higher incidence of low T4 levels and a combination of low T3 and T4. No significant differences were found for other perioperative variables related to thyroid function. There was no significant difference in the incidence of our endpoints between patients with normal and low free T3 levels. Patients with low free T4 levels had a higher incidence of PGD, vasoplegia compared with the group with normal free T4 levels.

After our univariate analysis, we further examined low free T4 and collectively low T3 and T4 levels using multivariate models. After adjustment to the combined UNOS score, we found an independent association between low free T4 levels and PGD (HR: 5.23; 95% CI: 2.26–12.08; $p < 0.001$) and 30-day mortality (HR: 7.23, 95% CI: 2.07-25.23, $p = 0.002$). The combined low T3 and T4 levels and PGD (HR: 3.91; 95% CI: 1.50-10.19; $p = 0.005$) and 30-day mortality (HR: 6.03; 95% CI: 1.66-21.95; $p = 0.006$) we were able to show a close univariate relationship. We also adjusted our multivariate models for anamnestic thyroid disease, pre-implantation thyroid hormone treatment, chronically administered amiodarone treatment, and IPW values of preoperative variables. Low free T4 and collectively low free T3 and T4 levels showed an independent association with PGD. No independent association was found with the 30-day mortality. The results are shown in Table 2.

Table 2: Multivariate Cox regression analysis for low free T4 and low free T3 and T4 levels

HR: hazard ratio; 95% CI: 95% confidence interval; PGD: primary graft dysfunction; UNOS: United Network for Organ Sharing; IPW: inverse probability weighting; T3: triiodothyronine; T4: thyroxine

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	30-day mortality			***PGD***		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
UNOS	1.48	1.16-1.89	<0.001	1.30	1.13-1.50	<0.001
Hypothyroidism	-	-	-	0.51	0.09-2.95	0.450
Hyperthyroidism	-	-	-	0.61	0.11-3.34	0.571
Recipient L-thyroxine supplementation	-	-	-	1.07	0.21-5.41	0.931
Donor L-thyroxine supplementation	0.75	0.14-3.98	0.733	2.04	0.84-4.94	0.113
Amiodarone	1.59	0.42-6.02	0.496	1.30	0.55-3.06	0.550
IPW	1.19	0.74-1.93	0.471	0.97	0.78-1.21	0.794
Low T_4	5.49	0.72-42.09	0.101	**6.49**	**2.26-18.60**	**0.001**

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	30-day mortality			***PGD***		
	HR	***95% CI***	***p***	***HR***	***95% CI***	***p***
UNOS	1.43	1.14-1.80	0.002	1.30	1.14-1.49	<0.001
Hypothyroidism	-	-	-	0.30	0.05-1.96	0.209
Hyperthyroidism	-	-	-	0.69	0.14-3.47	0.654
Recipient L-thyroxine supplementation	-	-	-	1.61	0.31-8.40	0.570
Donor L-thyroxine supplementation	0.84	0.15-4.77	0.840	2.31	0.98-5.43	0.056
Amiodarone	1.62	0.41-6.48	0.494	1.34	0.58-3.13	0.498
IPW	1.40	0.89-2.20	0.147	1.03	0.86-1.24	0.721
Low T_3 and T_4	2.99	0.49-18.32	0.237	**4.87**	**1.52-15.58**	**0.008**

5. CONCLUSIONS

The applicability of the four MELD scores was examined in the risk assessment prior to VA ECMO treatment in different indications. Pre-existing organ dysfunctions play a key role in mortality. In particular, modMELD and MELD Na scores help to assess renal and hepatic dysfunction and are thus sensitive predictors of absolute mortality associated with VA ECMO treatment. By calculating MELD, modMELD, and MELD Na scores prior to VA ECMO treatment in different diagnoses, we can obtain a simple, easily accessible, and reproducible tool that can be used to improve risk assessment and consider further treatment options.

The association between low free thyroid hormone levels and adverse outcomes after heart transplantation were investigated. Low free T3 levels alone were not associated with the onset of PGD, whereas low free T4 levels were. The appearance of low free T4 levels may highlight a point in the progression of advanced heart failure where the possibility of hormone replacement arises.

Based on our results is important to look beyond traditional cardiac risk factors in patients who have undergone heart transplantation or VA ECMO support, because there might be new factors affecting our patient's long term survival. The liver and thyroid dysfunction, we have been investigating, might be two of these, but the accurate understanding requires further prospective, multi-centre studies.

6. LIST OF OWN PUBLICATIONS

6.1. Publications related to the thesis

Nagy Á; Holndonner-Kirst E; Eke Cs; Kertai MD; Fazekas L; Benke K; Pólos M; Szabolcs Z; Hartyánszky I; Gál J; Merkely B; Székely A. (2020) Model for end-stage liver disease scores in veno-arterial extracorporeal membrane oxygenation. Int J Artif Organs, 43: (10) 684-691.

Nagy Á; Holndonner-Kirst E; Eke Cs; Szécsi B; Szabó A; Plamondon M; Fazekas L; Pólos M; Benke K; Szabolcs Z; Hartyánszky I; Merkely B; Gál J; Székely A. (2020) Perioperative Low Tetraiodothyronine Levels and Adverse Outcomes After Heart Transplantation: A Retrospective, Observational Study. J Cardiothorac Vasc Anesth, 34: (10) 2648-2654.

Holndonner-Kirst E; Nagy Á; Czobor NR; Fazekas L; Lex DJ; Sax B; Hartyánszky I; Merkely B; Gál J; Székely A. (2018) Higher Transaminase Levels in the Postoperative Period After Orthotopic Heart Transplantation Are Associated With Worse Survival. J Cardiothorac Vasc Anesth, 32: (4) 1711-1718.

Holndonner-Kirst E; Nagy Á; Czobor NR; Fazekas L; Dohán O; Kertai MD; Lex DJ; Sax B; Hartyánszky I; ***Merkely B; Gál J; Székely A. (2019) The Impact of l-Thyroxine Treatment of Donors and Recipients on Postoperative Outcomes After Heart Transplantation. J Cardiothorac Vasc Anesth, 33: (6) 1629-1635.***

6.2. Publications not related to the thesis

Pólos M; Benke K; Ágg B; Stengl R; Szabó A; Nagy Á; Ruskó B; Hedberg J; Radovits T; Susánszky É; Merkely B; Székely A; Szabolcs Z. (2020) Psychological factors affecting Marfan syndrome patients with or without cardiac surgery. Ann Palliat Med, 9: (6) 52-52.

Nagy Á; Kim JH; Jeong ME; H MH; Putzu A; Belletti A; Biondi-Zoccai G; Landoni G. (2019) Non-vitamin K oral anticoagulants for coronary or peripheral artery disease: a systematic review and meta-analysis of mortality and major bleeding. Minerva Cardioangiol, 67: (6) 477-486.

Belletti A; Nagy Á; Sartorelli M; Mucchetti M; Putzu, A; Sartini C; Morselli F; De Domenico P; Zangrillo A; Landoni G, Lembo R. (2020) Effect of Continuous Epinephrine Infusion on Survival in Critically Ill Patients. Crit Care Med, 48: (3) 398-405.

Kim JH; Nagy Á; Putzu A; Belletti A; Biondi-Zoccai G; Likhvantsev VV; Yavorovskiy AG; Landoni G.(2020) Therapeutic Hypothermia in Critically Ill Patients: A Systematic Review and Meta-Analysis of High Quality Randomized Trials. Crit Care Med, 48: (7) 1047-1054.