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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

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**CLINICAL FEATURES AND OUTCOMES OF PATIENTS TREATED WITH
THERAPEUTIC PLASMA EXCHANGE IN INTENSIVE CARE UNIT OF THE
INTERNAL MEDICINE DEPARTMENT**

Diploma thesis

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List of abbreviations

a – acquired

aHUS – acquired Hemolytic uremic syndrome

AKI – acute kidney injury

c – congenital

Ca – Calcium

CNS – Central nervous system

cTn – cardiac Troponin

CVC – central venous catheter

FFP – Fresh frozen plasma

GVHD – graft-versus-host disease

HIV – Human immunodeficiency virus

HUS – Hemolytic uremic syndrome

i – idiopathic

ICU – Intensive care unit

LDH – Lactate dehydrogenase

MAHA - Microangiopathic hemolytic anemia

RBC – Red blood cell

STEC - Shiga toxin-producing enterohaemorrhagic E. coli

Tbv – total body volume

TMA – Thrombotic microangiopathy

TPE – Therapeutic plasma exchange

TTP – Thrombotic thrombocytopenic purpura

vWF – von Willebrand factor

1. INTRODUCTION

1.1. Therapeutic plasma exchange

Therapeutic plasma exchange (TPE), also known as plasmapheresis, is an extracorporeal technique that replaces patients' plasma to remove pathogenic molecules. Most common targets for removal are autoimmune antibodies, donor-specific antibodies, excessive paraproteins, cytokines, and endogenous and exogenous toxin (1). Many patients who require TPE are critically ill and admitted to the intensive care unit (ICU). It is an invasive procedure with often emergent indications, demanding its execution as soon as possible.

1.1.2. Mechanisms and principles of TPE

The mode of operation of the TPE consists of the extracorporeal removal, processing and return of blood plasma or its components. This can be achieved with two different modes of operation; either mechanical centrifugation or filtration with semipermeable membranes. In centrifugation, the components are separated by their different weights, the filtered plasma is discarded, and the erythrocytes are returned with donor plasma or colloids. In membrane plasma separation, the components are separated by size and the filtered, patient's own plasma is returned (2).

1.1.3. Technique

A large-lumen venous access is required to perform the TPE. This is usually performed as a central venous catheter via the right common jugular vein or the left subclavian vein. The exact procedure is as follows: First, 3-5ml of blood must be taken from the central venous catheter (CVC) and discarded. Blood is then taken for a laboratory chemical test. The calcium and potassium values as well as the fibrinogen values are of particular importance. The catheter is then flushed with heparinized NaCl solution to prevent thrombus formation. In the next step, a double lumen catheter connects the patient and the machine. The machine calculates the total body volume (tbv) and the effective plasma volume (tbv x (1- hematocrit)). The volume of the replacement product, in the case of Thrombotic thrombocytopenia purpura (TTP) and Hemolytic uremic syndrome (HUS) usually fresh frozen plasma (FFP) and or albumin, is calculated using the formula 40-60ml/kg. Once the process has been started, the machine separates the plasma and feeds the red blood cells (RBC) with the replacement fluid to the patient. Once the TPE has been completed, the Calcium (Ca), Potassium and Fibrinogen values are taken from the patient again (3).

During the process of extra corporal TPE a sufficient anticoagulation of the blood is crucial to prevent clotting inside the machine. This is ensured by the use of different types of

anticoagulants, from the which the most common are citrate and heparin. Today citrate is the most common one, as it has some advantages over heparin. Firstly, it has a shorter half-life (30-60 min), is generally safer to use and has a better reversibility by adding Ca. It can be used safely in patients with liver cirrhosis and acute kidney failure. The effect of citrate is predominantly evident “in vitro”, which reduces the risk of bleedings in the patient. On the contrary citrate binds to Ca and therefore depletes the free Ca, potentially leading to hypocalcemia. As a consequence, it is important to evaluate the patients Ca levels before inducing TPE and be prepared to supplement the patient with Ca or potassium salts afterwards. The second commonly used drug for anticoagulation is heparin. It’s a relatively cheap and well-known drug with a short half-time (23min-2.48h). The disadvantage is its ability of “in-vivo” anticoagulation. This bears the potential of significantly bleedings. Furthermore, it can cause a heparin-induced thrombocytopenia (4).

1.1.4. Indications for TPE treatment

TPE is used as a therapy for a variety of diseases and syndromes. Apart from TTP, other mentionable diseases would be hypertriglyceridemia, systemic vasculitis, and hyperviscosity syndrome. In the first mentioned, TPE decreases the levels of triglycerides, removes proteases and inflammatory mediators and decreases the hyperviscosity. Systemic or cryoglobulinemia-related vasculitis can be treated by TPE as it effectively removes the cryoglobulins. Another major disease treated with TPE is the hyperviscosity syndrome. There the procedure is very effective for a short time control of the symptoms and can be helpful by visual symptoms. Additionally it reduces the blood-viscosity by 20-30% in daily usage (5). A detailed and complete list would go beyond the scope of this paper, so the following presented in **Table 1.** is only a rough overview of potential diseases that can be treated with TPE.

Table 1. Overview of potential diseases and the direct benefits of TPE

Diseases	Mechanism of treatment
Neurological diseases	
Myasthenia Gravis	in acute crises, the acetylcholine-Ab is removed
Chronic inflammatory demyelinating polyneuropathy	reduces autoimmunity and disability
Lambert-Eaton syndrome	extraction of calcium channel antibodies promotion of neurological recovery during acute exacerbations.
Multiple Sclerosis	early use in acute cases improves outcome.
Neuromyelitis Optica	
Hematologic and Autoimmune	
Catastrophic anti-phospholipid syndrome	removes the Ab as part of a triple therapy
TTP	removes the ADAMTS13 autoantibodies
ANCA-Vasculitis	possible last option to save the patient's life
Hyperviscosity syndrome:	removal of paraproteins to reduce viscosity
Systemic Lupus Erythematosus	in severe hemolysis or alveolar hemorrhage
Cryoglobulinemic vasculitis	removal of cryoglobulins. standard therapy before the introduction of complement inhibitors
HUS	
Further indications	
Toxic epidermal necrolysis	removal of pro-inflammatory mediators removal of toxins to bridge the waiting time until transplantation
Acute liver failure	
Hypertriglyceridemic pancreatitis	reduction of the triglyceride level

Source: Hussein G, Liu B, Yadav SK, Warsame M, Jamil R, Surani SR et al. Plasmapheresis in the ICU. *Medicina (Kaunas)*. 2023;59:2152. [05.04.2024].

1.1.5. Use of TPE in the ICU of Internal medicine department

ICU on the Division for Urgent and Intensive Medicine with Clinical Pharmacology and Toxicology of the University Hospital of Split is a relatively young department. It was established in the year 2014. and is located on Križine. Since the beginning, the head of department is prof. Vedran Kovačić. The whole ward has a total capacity of 32 beds divided into 8 intensive care beds, 21 post ICU beds, 9 clinical toxicology beds, and one additional day bed for toxicology patients. Most commonly TPE in this ICU is used for patients with hematological indications like TTP, HUS or hyperviscosity syndrome, also for systemic vasculitis or severe hypertriglyceridemia complicated with pancreatitis. Patients with neurological indications are treated with TPE elsewhere.

1.1.6. Complications and contraindications of TPE

A number of complications can occur during or after TPE. The most common is an allergic reaction to the FFP. This is traditionally treated with the admission of corticosteroids (6). Other often occurring adverse effects are hypocalcemia or hypomagnesemia, triggered by the citrate used as anticoagulation. Furthermore, more general adverse effects are hypothermia, transfusion reactions, which are treated symptomatically, fluid and electrolyte imbalance, bleeding diatheses caused by hypofibrinogenemia and thrombocytopenia, hypotension, and nausea and vomiting (2).

Absolute contraindications are the absence of a central venous catheter or suitable large-lumen peripheral access, a hemodynamic or septic patient, as well as known allergies to FFP or heparin. Relative contraindications are hypocalcemia or the use of an angiotensin-converting enzyme inhibitor in the last 24 hours (7).

1.2. Thrombotic thrombocytopenia purpura (TTP)

Thrombotic microangiopathies (TMA) group of disorders in which small blood vessels are occluded by platelet-rich thrombi. The consequence is thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and ultimately end-organ damage. TTP and HUS are primary forms of thrombotic microangiopathies, and they occur spontaneously with no associated underlying cause. Secondary types of TMA occur in the context of pregnancy, autoimmune disease, malignancy, bone marrow transplantation or use of certain medications. They require different treatment than primary cause it should be aimed at correcting the underlying cause (8).

The clinical presentation can vary widely, which makes a detailed history and physical examination coupled with laboratory tests even more important. Landmark laboratory findings include thrombocytopenia, schistocytes in the blood smear, elevated lactate dehydrogenase (LDH), decreased haptoglobin and normal coagulation values. While thrombocytopenia is caused by platelet aggregation and thrombus formation, microangiopathic hemolytic anemia is characterized by fragmentation of red blood cells. With the exception of pneumococcal hemolytic uremic syndrome, the Coombs test is usually negative (9).

1.2.1. Etiology

Thrombotic thrombocytopenia purpura results from the decrease or complete loss of the a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13

(ADAMTS13) enzyme. This enzyme has the function of inhibiting the von Willebrand factor (vWF) by inactivating the large multimers of the vWF (10, 11).

TTP is either congenital (c) or acquired (a), with acquired TTP (aTTP) being more common. aTTP is caused by autoantibodies and can be triggered by a variety of events. The most common causes are antiplatelet drugs, immunosuppressive agents, HIV, estrogen-containing oral contraceptives and pregnancy. Congenital TTP (cTTP) is the result of a mutation of the ADAMTS13 enzyme (12).

The sole deficiency of ADAMTS13 is not sufficient enough to trigger a clinically relevant TTP. A symptomatic onset of cTTP always requires a trigger, e.g. an infection or pregnancy (13). Another large group of triggers is the manifestation of cancer in the form of tumors. The most common form is mucin producing adenocarcinoma, with a disseminated disease, or with a confined bone marrow invasion. In the group of the adenocarcinomas the most common forms are gastric carcinoma, breast carcinoma, prostate carcinoma, and lung cancers. Furthermore, other malignancies like pancreatic adenocarcinoma or Lymphomas can be the cause of TTP (14).

1.2.2. Epidemiology

TTP is a rare disease that occurs predominantly after the age of 40 and affects women in a ratio of 2:1. The mortality rate of untreated TTP is 90%, but this can be reduced to 10-15% with the right therapy (12). Data for incidence of TTP in Croatia is showed in the study of a Croatian hematological association where the followed patients from September 2022 to February 2024 in 11 Croatian hematology centers and recorded 64 patients with TTP (15).

1.2.3. Pathology

TTP is characterized by a decrease in ADAMTS13 protease activity to less than 10%. Due to the ADAMTS13 deficiency, enlarged vWF multimers accumulate on the endothelial surface and cause platelet aggregation, which leads to thrombus formation. The resulting microthromboses lead to ischemia and damage to end organs. The most common affected organ systems are the kidneys and the central nervous system (CNS). The blood count shows thrombocytopenia, triggered by the increased thrombus requirement, and hemolytic anemia, triggered by the mechanical destruction of the erythrocytes in the constricted vessels. This changes the morphology of the erythrocytes and schistocytes develop (12).

Histopathological, platelet microthrombosis is seen in arterioles and capillaries with swelling of the endothelial cells and the subendothelial space. Larger vessels are not affected

in a TTP (16). ADAMTS13 is mostly synthesized in the liver. Its main function is the cleavage of the vWF. The plasma concentration is 0,7-1,4 µg/ml. A deficiency >10% in the plasma is causing idiopathic TTP (iTTP). In other TMAs the ADAMTS13 activity usually remains normal or only slightly reduced (>20%) (17).

1.2.4. Clinical presentation

In a TTP, the end-organ involvement usually manifests itself as neurological symptoms. These include headaches, confusion, strokes, dizziness, focal neurological deficits or seizures. At the onset, TTP is characterized by fatigue, dyspnea, petechiae or bleeding, and other frequently affected organs are the heart and the mesenteric vessels. The kidneys are less frequently affected compared to other forms of TMA. The occurrence of cardiac and neurological symptoms is an indication of a serious disease (9, 12).

To prove and monitor end-organ involvement these days the biomarker circulating cardiac troponin (cTn) can be used to not only show damage to cardiomyocytes, but also to other organs. It plays a role in detecting heart insufficiency, pulmonary embolism, kidney damages, sepsis, tachycardia or toxic damages (10).

The frequency of the respective symptoms is classified according to the Oklahoma Register. Gastrointestinal symptoms are the most common (69%), followed by weakness (63%), bleeding or purpura (54%), major neurological findings such as coma, seizures, strokes (41%), minor neurological findings such as headache or confusion (26%), fever and chills (10%), and the classic pentad, consisting of hemolytic anemia, thrombocytopenia, fever, acute kidney injury (AKI), and severe neurological findings at less than 5% (11). During TPE the troponin levels are reduced slightly (18).

1.2.5. Laboratory

If TTP is suspected, prompt action is required to give the patient a realistic chance of survival. The rarity of this disease further increases the difficulty of a targeted treatment, so it is important to recognize a TTP as soon as possible. Final confirmation is provided by laboratory evidence of an ADAMTS13 value <10%. However, this value is only determined in specialized centers or laboratories, which can lead to a delay of several days in the final diagnosis. Several scores have been developed to bridge this time disadvantage, with the PLASMIC score proving to be the most practicable (14). To be able to use the Plasmic Score, schistocytes must first be detected. One point is awarded to the score for each fulfilled

characteristic. A total of seven points can be achieved, with a value >5 indicating a high probability of TTP. The seven characteristics are as follows;

1. Platelet count <30,000/microL,
2. Signs of hemolysis (reticulocyte count <2.5%,
3. Undetectable haptoglobin or indirect bilirubin > 2 mg/dl),
4. MCV <90 fl,
5. INR < 1.5,
6. Creatinine < 2.0 mg/dl,
7. No cancer disease, and no organ or stem cell transplantation (19).

1.2.6. Treatment of TTP

The first line treatment for TTP is TPE with FFP. The aim of this treatment is the complete removal of autoantibodies and the replacement of the ADAMTS13 protease. TPE should be continued for at least two days and a clinical response should be achieved. The clinical response is as follows; Platelet count >150 x 10⁹/L, LDH < 1.5x upper normal limit, and no evidence of new or exacerbated end-organ ischemia (9).

1.3. Hemolytic uremic syndrome

1.3.1. Etiology

Hemolytic uremic syndrome (HUS) is divided into typical HUS and atypical HUS (aHUS). Typical HUS is predominantly caused by Shiga toxin-producing enterohaemorrhagic *E. coli* (STEC), while aHUS is caused by a genetic mutation in alternative complement activation (20). The typical HUS (90%), triggered by STEC, is usually transmitted through contaminated food or as a smear infection. Two to three days after infection, bloody diarrhea occurs and after three to ten days the actual HUS begins. This is accompanied by vomiting, fever and abdominal pain (21). aHUS (5-10%), as a consequence of a mutation in the alternative complement system, is initially characterized by non-specific symptoms, e.g. fatigue, pallor or somnolence. It often develops into AKI with oliguria, uremia and systemic fluid overload. This leads to a high risk of developing chronic kidney disease stage 3/4 or end-stage renal disease. Unfortunately, in comparison to typical HUS, complete recovery of kidney function is hardly possible without therapy. This is also reflected in the fact that approx. 50% of patients require dialysis and there is a high probability of extrarenal, cardiac or neurological manifestations. The resulting complications can include heart failure, pulmonary hypertension, seizures, coma or blindness. In addition, the relapse rate after treatment is also significantly higher (21).

The secondary HUS always follows a trigger. This can be, for example, a vitamin B12 metabolic disorder, HIV, influenza viruses, autoimmune diseases such as Systemic Lupus Erythematosus or malignant hypertension. One particular trigger is *Streptococcus Pneumoniae*,

which is responsible for 5-10% of all pediatric HUS cases. This form of HUS is the only one with a positive Coombs test (21).

1.3.2. Epidemiology

The group most frequently affected by HUS and aHUS are children <10y, with <5y being affected even more frequently. STEC-HUS is the most common cause of renal replacement therapy in the pediatric group. The much rarer, but with higher morbidity and mortality aHUS mostly affects children <5y and is mainly caused in winter by *Streptococcus Pneumoniae* (21).

1.3.3. Pathology

The typical pathway of HUS starts with the consumption of STEC-contaminated food, such as products associated with cattle. The bacterium invades the intestinal mucosa and begins to release the Shiga toxin. This binds to the Gb3 receptor and inhibits protein synthesis, which leads to apoptosis. At the same time, inflammatory cytokines are released, and the complement system is activated by the inhibition of factor H. After the toxin enters the bloodstream, it also binds to the Gb3 receptor, with the highest prevalence in the glomerular microvasculature. Due to its cytotoxicity, this process leads to a disturbance of hemostasis, cytokine release and complement activation leading to endothelial damage. Eventually this leads to the TMA-pathology (22).

In the case of aHUS, the complement system is activated in the same way as in HUS. However, the regulatory factor H, with its function of stabilizing C3 and inactivating C3b, plays a major role (22).

1.3.4. Clinical presentation

HUS is generally characterized by ischemic organ damage, neurological symptoms, renal insufficiency or, if the gastrointestinal tract is involved, hemorrhagic colitis.

STEC-HUS often shows a prodromal phase with vomiting, abdominal pain and diarrhea, which can also be bloody. After about a week, hemolytic anemia, thrombocytopenia and acute renal failure develop. HUS caused by *Streptococcus pneumoniae* is characterized by afebrile pneumonia and/or meningitis or sepsis (23).

1.3.5. Laboratory

The first indication of a TMA in the blood count is increased LDH, increased indirect bilirubin and increased plasma hemoglobin, as well as decreased haptoglobin. The detection of

schistocytes in the blood smear is characteristic. As mentioned above, a positive Coombs test is only to be expected in the case of *Streptococcus pneumoniae* HUS. If pancreatic involvement is present, the amylase and lipase levels will also be elevated. Microbiological testing for *Shigella* dysenteries and *Streptococcus pneumoniae* should be performed. A low complement value may or may not be specific for aHUS, as it can also be low in other forms of HUS (24).

1.3.6. Treatment of HUS

With the introduction of complement-inhibiting drugs, TPE has become less important in the treatment of aHUS. Today Eculizumab, a C5 antibody, is used to inhibit complement-mediated TMAs and shows a positive effect in the improvement of the renal function. (25).

In the acute phase, if a TMA is generally suspected, TPE is started as quickly as possible in order to bridge the waiting time for ADAMTS13 determination and minimize the risk of an untreated TTP (26). The past has shown that therapy with TPE alone does not provide satisfactory results. On the contrary, it led to a high rate (children: 36-48%, adults: 64-67%) of terminal renal failure or death after 3-5 years (27).

1.4. Additional drug treatment

1.4.4. Corticosteroids

Corticosteroids are used as standard additional therapy due to their immunosuppressive and anti-inflammatory effects. Prednisone or an equivalent is usually administered at a dose of 1-1.5mg/kg/day. A further advantage of this therapy is a positive effect on ADAMTS13 activity and a simultaneous reduction in anti-ADAMTS13-Ab. In addition, adequate corticosteroid therapy reduces possible side effects of TPE. However, due to the strong immunosuppressive effect, the possibility of a new infection occurring must always be kept in mind (28).

Other major adverse effects are presented in table 2.

Table 2. Adverse effects of corticosteroids on different systems

Adverse effects of corticosteroids			
Musculoskeletal	Glucocorticoid-induced osteoporosis leading to bone fractures	Steroid-induced myopathy causing painless muscle weakness	Osteonecrosis of the hip or knee joints
Metabolic and Endocrine	Development of cushingoid features	suppression of hypothalamic-pituitary-adrenal axis	Impaired growth and delayed puberty in children
Cardiovascular Adverse Effects	Fluid retention and edema	Hypertension, especially with higher doses	premature atherosclerosis with long-term use
Dermatologic	Skin thinning and atrophy	Formation of striae (stretch marks)	Impaired wound healing
Ophthalmologic	Development of cataracts, often bilateral	increased intraocular pressure, potentially leading to glaucoma	Central serous chorioretinopathy causing blurred central vision
Gastrointestinal	Gastritis or gastric ulcer formation	Increased risk of gastrointestinal bleeding	Hepatic steatosis
Neuropsychiatric	Mood disturbances	Sleep disturbances	Acute behavioral changes in children

Source: Corticosteroid Adverse Effects [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [updated 2023 Jul 3; cited 2024 May 1] Available from: <https://www.ncbi.nlm.nih.gov/books/NBK531462/>.

1.4.5. Monoclonal Antibodies

Rituximab is a monoclonal antibody that is directed against the CD20 antigen located on the lymphocytes. It has been used in TTP therapy since 2002. The effect of the drug is an increase in ADAMTS13 activity, B-cell depletion and thus a decrease in anti-ADAMTS13 antibodies. It can be used in the acute phase of a new TTP, as well as in exacerbated and refractory TTPs, and to achieve clinical remission (28). The regimen to use Rituximab remains similar to the known malignancy protocol with the dosage of 375 mg/m²/week-4 doses (30).

Caplacizumab is a new drug in the treatment of TTP. The anti-vWF nanobody reduces the adhesion between the vWF monomers and the platelets. Various studies, HERCULES and TITAN, have shown that a combined therapy of TPE and Caplacizumab generally shortens the duration of TPE, reduces the time to normalization of the platelet count and reduces the likelihood of relapse. The duration of treatment should begin before the start of TPE and continue for no less than 30 days after completion of TPE (9, 31).

2. OBJECTIVES

2.1. Objectives of the study

The main aims of the presented study were:

1. To assess the clinical characteristics of patients treated with TPE in the internal ICU.
2. To assess indications and laboratory parameters of patients treated with TPE.
3. To assess clinical features of the subgroup of patients with TTP

Hypotheses of the study:

1. There are significant gender differences in clinical features and outcomes in patients treated with TPE.
2. There are significant differences in laboratory parameters and apheresis specific parameters of the TPE treatments in ceased and survived patients.
3. There is a significant influence of length of hospital stay, total TPE volume and ADAMTS13 activity on laboratory parameters and other clinical features.

3. SUBJECTS AND METHODS

3.1. Study design

We conducted an observational retrospective cross-sectional study to investigate the clinical characteristics and epidemiological patterns of TMA leading to plasmapheresis. The study took place in the eight-bed medical ICU of the Internal Medicine Department. This ICU is dedicated primarily for adult medical patients and refers critical patients for various conditions. It is part of a Division of Emergency and Intensive Medicine with Clinical Pharmacology and Toxicology, University Hospital of Split. The study protocol was approved by the Ethics Committee at the University Hospital of Split with ethics code of 520-03/24-01/159; date of approval 09.07.2024.

3.2. Study population

The study population consisted of all adult patients who were treated with TPE in the ICU of the Division for Urgent and Intensive Medicine with Clinical Pharmacology and Toxicology, Internal medicine department of the University Hospital of Split, Croatia, during a ten-year period, from 12th May 2014 to 26th January 2024. There were no exclusion criteria except older than 18 years since we have included patients with different indications for TPE.

Initially to establish who were patients treated with TPE we have assessed the data from the Department of hemodialysis since they provide the apheresis machines and staff for TPE treatment. Through their TPE protocols we have assessed names of the patients and TPE specific parameters like number of TPE treatments, doses of TPE, fluids and anticoagulation drugs, complications and outcomes of patients. From that list of patients treated with TPE we have then collected specific patient medical charts from the archive (from 2019.) and the central electronic hospital records. Through medical charts of each patients, we have assessed their medical history, demographic characteristics, vital signs, laboratory tests, drugs, symptoms, and outcomes. From 2015. we also included the reports from the Research laboratory, Semmelweis University Budapest about the ADAMS13 activity and its inhibitors.

3.3. Statistical analysis

Descriptive statistics calculations and data were presented as number (percentages) for qualitative variables, and for quantitative variables are expressed as arithmetic mean \pm standard deviation if normally distributed, or median (interquartile range) if non-normally distributed. Kolmogorov-Smirnov test was used for estimation of the normality of quantitative variables distribution. Qualitative data between groups were compared with Chi-square and Fisher's exact tests, as appropriate. Quantitative data were compared using unpaired Student's -t test or

one-way ANOVA. Mann–Whitney test and Kruskal-Wallis tests were employed to analyze and compare quantitative variables with non-normal distribution. Correlations between quantitative data were calculated as significance of Pearson correlation coefficient for normally distributed variables or Spearman's rho coefficient for variables with a non-normal distribution. *P* values < 0.05 were considered significant. Statistical analysis was performed with SPSS software for Windows (IBM SPSS Statistics for Windows, version 26.0, Armonk, NY, USA).

4. RESULTS

During the 10-year observation study period in internal medical ICU 48 adult patients were treated with TPE with mean age of 50.12±15.86 years. Average length of hospital stay was 21.97±15.68 days and average number of TPE treatments for all study patients was 8.98±9.12 with average plasma exchange volume of 29001.65±30021.18 ml. Other specific apheresis parameters, laboratory parameters and parameters regarding ADAMTS 13 activity for all study patients are shown in **Table 3**.

Table 3. Demographics and clinical features of all study patients

	Mean±	Std. Deviation	Minimum	Maximum
Age (years)	50.12±	15.86	21.00	77.00
Length of hospital stay (days)	21.97±	15.68	2	61
Number of TPE	8.98±	9.12	1.00	48.00
Total TPE volume (mmol)	29001.65±	30021.18	3020.00	118320.00
Volume of FFP used in TPE (ml)	31394.42±	31559.03	1360.00	0
Volume of HA solution used in TPE (ml)	9542.31±	5517.81	3300.00	21000.00
RBC (x10 ¹² /L)	2.76±	0.86	0.82	4.85
Hemoglobin (mmol/L)	83.62±	23.70	34.00	135.00
Thrombocytes (x10 ⁹ /L)	28.81±	25.78	7.00	126.00
Reticulocytes (per 1000 RBC)	91.11±	127.42	12.00	650.00
PT (11-13,5s)	0.94±	0.25	0.28	1.47
aPTT (30-40s)	24.05±	3.65	14.70	33.40
Fibrinogen (mmol/L)	3.59±	1.43	1.30	6.40
Glucose (mmol/L)	8.09±	2.71	4.30	14.00
Urea (mmol/L)	16.20±	17.87	5.10	90.90
Creatinine (mmol/L)	182.69±	262.14	44.00	1235.00
Bilirubine (µmol/L)	53.10±	35.50	11.00	161.70
AST (U/L)	70.67±	38.41	24.00	182.00
ALT (U/L)	44.37±	35.72	3.00	195.00
GGT (U/L)	66.41±	100.80	13.00	502.00
LDH (U/L)	1526.57±	850.08	400.00	4261.00
ALP (U/L)	150.94±	261.84	41.00	1183.00
Serum proteins (g/L)	61.86±	7.75	48.00	75.00
Serum albumin (g/L)	37.33±	7.01	27.00	60.40
CRP (mg/L)	34.68±	40.19	2.70	163.60
PCT (ng/L)	1.20±	1.89	0.07	6.44
Troponin (ng/ml)	95.21±	90.77	1.50	245.90
NT-proBNP (ng/L)	7553.13±	13085.53	119.00	39000.00
Potassium (mmol/L)	3.76±	0.44	3.10	4.50
Calcium (mmol/L)	2.16±	0.22	1.71	2.66
ADAMTS 13 activity (67-150%)	21.87±	29.77	0.00	84.00

ADAMTS 13 activity inhibitors	8.33± 12.57	0.00	36.00
C3 (0.9-1.8 g/L)	1.05± 0.33	0.46	1.77
C4 (0.15-0.55 g/L)	0.23± 0.11	0.07	0.47

Legend: TPE: therapeutic plasma exchange; FFP: fresh frozen plasma, HA: human albumin; RBC: Red blood cells; PT: Prothrombin Time Test, aPTT: Partial Thromboplastin Time, AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, GGT: Gamma-glutamyl Transferase, LDH: Lactate dehydrogenase, ALP: Alkaline Phosphatase, CRP: C-reactive Protein, PCT: Procalcitonin, NT-proBNP: N-terminal pro b-type natriuretic peptide. Data is presented as arithmetic mean± standard deviation.

From 48 patients treated with TPE 31 (64.58%) patients were diagnosed with TTP, 5 (10.42%) patients had hyperviscosity syndrome, 5 (10.42%) patients had systemic vasculitis and 5 (10.42%) patients had severe hypertriglyceridemia. All indications for TPE are shown in **Table 4**.

Table 4. Indications for TPE treatment

	Frequency	Percent
TTP	31	64.58
Atypical HUS	1	2.08
Severe hypertriglyceridemia	5	10.42
Hyperviscosity syndrome	5	10.42
Systemic vasculitis	5	10.42
AIHA	1	2.08

Legend: TTP: Thrombotic Thrombocytopenic Purpura, Atypical HUS: Atypical Hemolytic Uremic Syndrome, AIHA: Autoimmune Hemolytic Anemia

Most common clinical symptoms reported by the patients were malaise and weakness in 17 (26.56%) patients, followed by 14 patients (21.88%) which presented with neurological symptoms. 8 (12.5%) patients initially presented with jaundice and 6 (9.38%) patients had bleeding into skin of different sizes. Other clinical signs and symptoms in order of their frequency in the patients included in the study is shown in **Table 5**.

Table 5. Sum of all signs and symptoms of patients on admission to the ICU.

	Frequency	Percent
Malaise and weakness	17	26.56
Neurological symptoms	14	21.88
Jaundice	8	12.50
Bleeding into the skin	6	9.38
Subfebrile temperature	5	7.81
Diarrhea	4	6.25
Hematuria	4	6.25
Fever	3	4.69
GI and gynecological bleeding	3	4.69

Legend: GI: Gastrointestinal

In total we have observed 4 (12%) serious complications that appeared during of after the TPE: generalized epileptic seizures on two occasions, respiratory insufficiency on one occasion, and one acute kidney injury which required dialysis. Also, a total of 7 (6.85%) allergic reactions to FFP were recorded.

From all study patients 19 (39.6%) were men and 29 (60.4%) women and their differences are presented in the **Table 6**. Statistically significant differences were observed concerning levels of urea (31.13 ± 26.98 vs. 9.49 ± 3.31 , $p=0.001$) and creatinine (409.89 ± 392.20 vs. 80.45 ± 32.35 , $p<0,001$) which were significantly higher in male patients. Similarly, PCT (2.78 ± 2.54 vs. 0.29 ± 0.27 , $p=0.013$) was also significantly higher in male patients. In the contrary serum albumin values (34.26 ± 5.58 vs. 39.17 ± 7.29 , $p=0.049$) were significantly higher in females. There weren't statistically significant differences among number of TPE treatments or volumes of plasma or human albumin solutions used for TPE.

Table 6. Differences between male and female (Student's t-test for independent samples, one-tailed).

	Males (N=19)		Females (N=29)		<i>P</i>
	Mean±	Std. Deviation	Mean±	Std. Deviation	
Age (years)	47.88±	16.41	51.58±	15.63	0.231
Lenght of hospital stay (days)	21.70±	18.29	22.10±	14.73	0.474
Number of TPE	6.47±	6.17	10.62±	10.40	0.062
Total TPE volume (ml)	24242.94±	27492.23	32518.96±	31899.62	0.198
Volume of FFP used in TPE (ml)	27029.23±	30841.45	34231.80±	32483.22	0.265
Volume of HA solution used in TPE (ml)	8678.57±	4261.54	10550.00±	7001.07	0.283
Leucocytes (x 10*9/L)	9.81±	4.64	11.06±	4.73	0.256
RBC (x 10*12/L)	2.72±	0.43	2.77±	1.00	0.445
Hemoglobin (mmol/L)	83.44±	13.08	83.70±	27.49	0.490
Thrombocytes (x 10*9/L)	28.00±	18.81	29.15±	28.67	0.456
Reticulocytes (per 1000 RBC)	68.00±	69.23	99.20±	142.96	0.294
Fibrinogen (mmol/L)	4.03±	1.53	3.42±	1.40	0.190
Glucose (mmol/L)	8.32±	1.54	8.02±	3.01	0.418
Urea (mmol/L)	31.13±	26.98	9.49±	3.31	0.001
Creatinine (mmol/L)	409.89±	392.20	80.45±	32.35	<0.001
Bilirubine (µmol/L)	49.33±	34.44	54.71±	36.66	0.355
AST (U/L)	74.00±	38.25	69.24±	39.32	0.381
ALT (U/L)	45.00±	32.07	44.10±	37.93	0.475
GGT (U/L)	52.13±	42.32	71.86±	116.12	0.323
LDH (U/L)	1710.56±	898.54	1447.71±	838.52	0.224
ALP (U/L)	78.20±	22.45	178.92±	306.44	0.241
Serum proteins (g/L)	59.13±	7.38	63.43±	7.77	0.109
Serum albumin (g/L)	34.26±	5.58	39.17±	7.29	0.049
CRP (mg/L)	34.10±	24.29	34.93±	45.90	0.480
PCT (ng/L)	2.78±	2.54	0.29±	0.27	0.013
Troponin (ng/ml)	97.08±	54.31	94.17±	109.13	0.478
NT-proBNP (ng/ml)	15732.67±	20524.24	2645.40±	2957.42	0.094
Potassium (mmol/L)	3.99±	0.39	3.65±	0.43	0.027
Calcium (mmol/L)	2.23±	0.31	2.13±	0.17	0.174
ADAMTS 13 activity (67-150%)	15.00±	20.57	25.30±	33.92	0.274
ADAMTS 13 activity inhibitors	6.67±	11.55	9.17±	14.03	0.400
Complement classical (48-103 CH50/ml)	46.50±	27.45	63.20±	21.59	0.124
Complement alternative (70-125%)	68.75±	44.57	83.38±	32.24	0.263
C3 (0.9-1.8 g/L)	1.10±	0.39	1.02±	0.31	0.338
C4 (0.15-0.55 g/L)	0.23±	0.09	0.23±	0.12	0.487

Legend: TPE: therapeutic plasma exchange; FFP: fresh frozen plasma; HA: human albumin; RBC: Red blood cells; AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, GGT: Gamma-glutamyl Transferase, LDH: Lactate dehydrogenase, ALP: Alkaline Phosphatase, CRP: C-reactive protein, PCT: Procalcitonin, NT-proBNP: N-terminal pro b-type natriuretic peptide. P for significant differences is bolded. Data is presented as arithmetic mean± standard deviation.

In our study 6 (12,5%) patients ceased. All deaths were in the group of patients who were diagnosed as TTP (19,4%) and not a single death was recorded in other groups. This difference in the distribution of mortality according to diagnoses was statistically significant (Chi square= 17.084, P< 0,001).

Differences between ceased and survived patients are presented in **Table 7**. Patients that survived had longer length of hospital stay (25.78 ± 15.75 vs. 9.33 ± 6.86 , $p=0.010$), higher number or TPE treatments (10.29 ± 7.04 vs. 3.50 ± 2.59 , $p=0.014$), and according to that also higher amount of TPE plasma volume (38706.77 ± 33222.11 vs. 12238.33 ± 8518.37 , $p=0.033$). Ceased patients had higher levels of leucocytes (10.30 ± 4.81 vs. 12.23 ± 3.98 , $p=0.033$), higher levels of CRP (32.96 ± 43.75 vs. 41.55 ± 22.30 , $p=0.329$), and higher levels of creatinine (164.38 ± 265.86 vs. 270.60 ± 250.85 , $p=0.001$).

Table 7. Differences between ceased and survived patients (Student's t-test for independent samples, one-tailed).

	Survived		Ceased (N=6)		<i>P</i>
	Mean	Std. Deviation	Mean	Std. Deviation	
Age (years)	48.89±	15.85	53.50±	14.84	0.259
Length of hospital stay (days)	25.78±	15.75	9.33±	6.86	0.010
Number of TPE	10.29±	7.04	3.50±	2.59	0.014
Total TPE volume (ml)	42244.36±	33490.24	12238.33±	8518.37	0.021
Volume of FFP used in TPE (mmol)	38706.77±	33222.11	12238.33±	8518.37	0.033
Leucocytes (x 10 ⁹ /L)	10.30±	4.81	12.23±	3.98	0.033
RBC (x10 ¹² /L)	2.81±	0.92	2.56±	0.58	0.186
Hemoglobin (mmol/L)	85.39±	24.64	76.83±	20.09	0.265
Thrombocytes (x10 ⁹ /L)	30.09±	28.33	23.67±	11.18	0.383
Reticulocytes (per 1000 RBC)	96.27±	139.66	68.40±	48.34	0.297
PT (11-13.5s)	1.02±	0.18	0.61±	0.19	0.334
aPTT (30-40s)	23.43±	3.36	26.50±	4.04	<0.001
Fibrinogen (mmol/L)	3.79±	1.46	2.68±	0.91	0.032
Glucose (mmol/L)	7.96±	2.89	8.68±	1.96	0.081
Urea (mmol/L)	11.77±	8.86	37.48±	33.16	0.323
Creatinine (mmol/L)	164.38±	265.86	270.60±	250.85	0.001
Bilirubine (µmol/L)	50.93±	36.16	61.77±	34.39	0.210
AST (U/L)	68.13±	37.02	80.83±	45.80	0.257
ALT (U/L)	45.75±	38.30	38.83±	24.61	0.239
GGT (U/L)	56.83±	98.34	112.40±	111.01	0.340
LDH (U/L)	1451.92±	784.90	1825.17±	1106.17	0.135
ALP (U/L)	148.75±	277.50	168.50±	98.29	0.172
Serum proteins (g/L)	62.55±	7.80	55.00±	1.41	0.462
Serum albumin (g/L)	38.74±	6.65	30.25±	4.03	0.098
CRP (mg/L)	32.96±	43.75	41.55±	22.30	0.329
Potassium (mmol/L)	3.73±	0.43	3.83±	0.53	0.234
Calcium (mmol/L)	2.23±	0.19	1.89±	0.16	0.317

Legend: TPE: therapeutic plasma exchange; FFP: fresh frozen plasma; RBC: Red blood cells; PT: Prothrombin Time Test, aPTT: Partial Thromboplastin Time, AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, GGT: Gamma-glutamyl Transferase, LDH: Lactate dehydrogenase, ALP: Alkaline Phosphatase, CRP: C-reactive protein. P for significant differences is bolded. Data is presented as arithmetic mean± standard deviation.

Our results showed statistically significant and rapid rise of the number of thrombocytes in the first three days of treatment with TPE. (**Figure 1**).

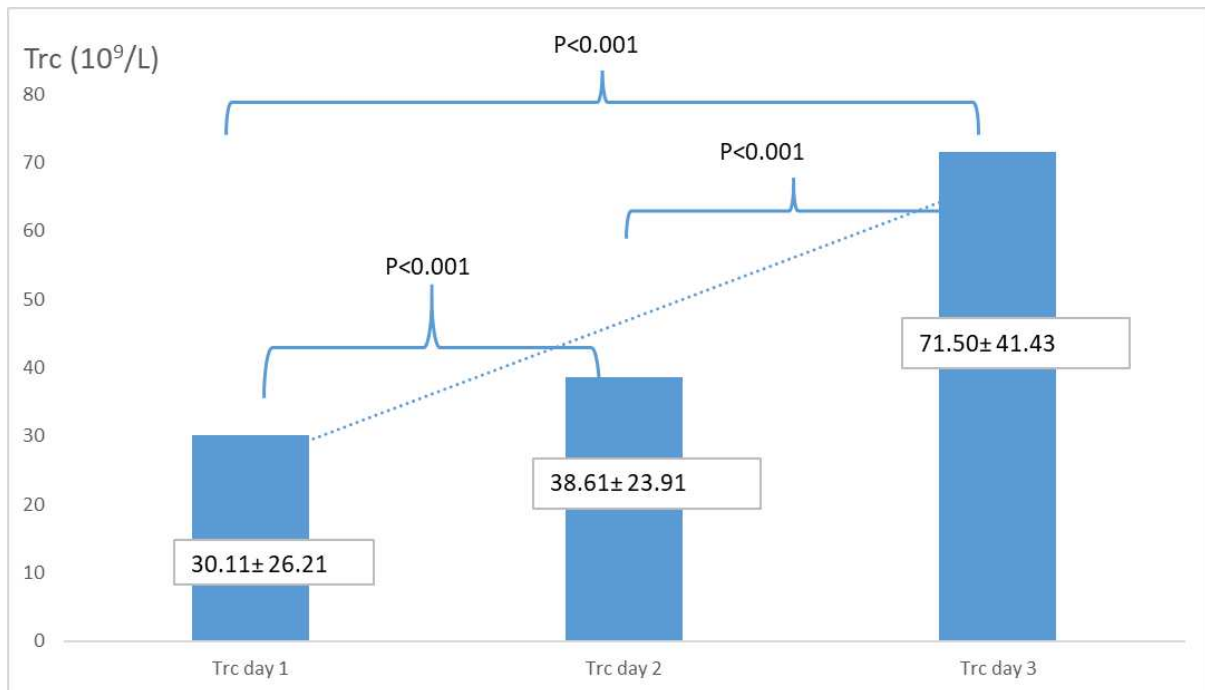


Figure 1. Increase of the average number of thrombocytes from the first to the third day of TPE treatment (Student's t-test for dependent samples, one-tailed). Legend: Trc: Thrombocytes

Also, levels of plasma LDH showed statistically significant decrease from the first to the third day of TPE treatment (**Figure 2**).

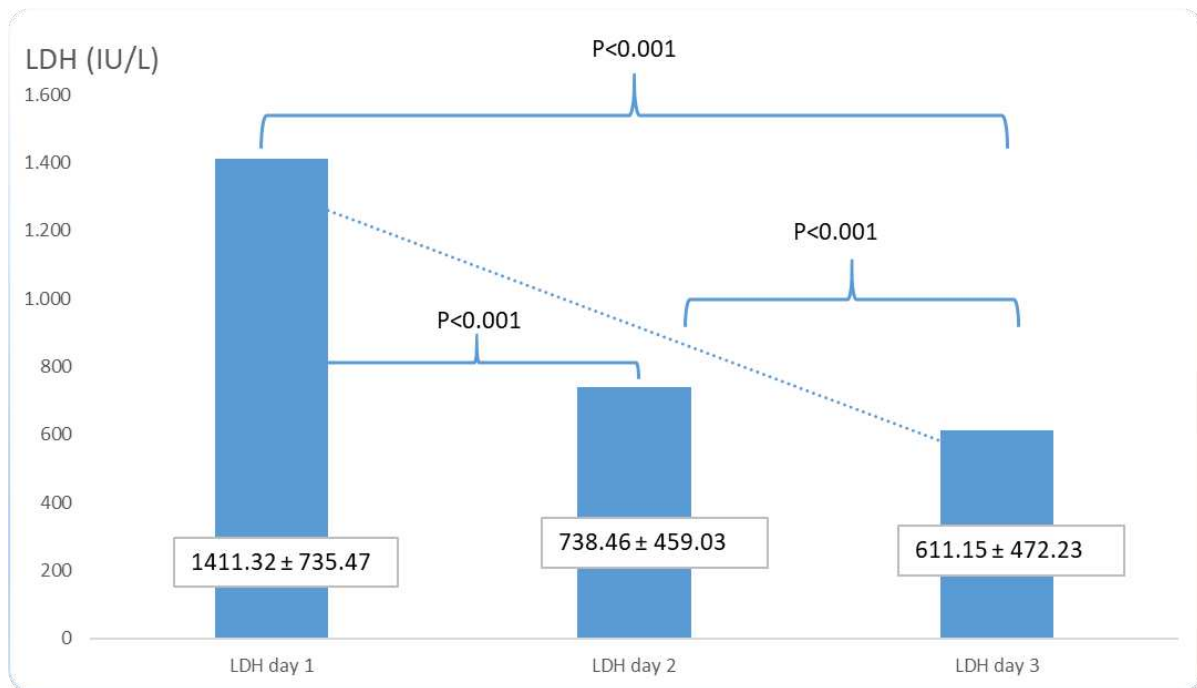


Figure 2. Decrease of the levels of plasma LDH from the first to the third day of TPE treatment (Student's t-test for dependent samples, one-tailed). Legend: LDH: Lactate dehydrogenase

Correlations between the length of hospital stay and total TPE volume with clinical and laboratory parameters for all patients are demonstrated in **Table 8**. The number of days of hospital stay positively correlated with the total TPE volume ($p=0.004$) and with the number of TPE treatments ($p<0.001$). Total TPE volume correlated positively with fibrinogen ($p=0.013$), troponin ($r=0.652$, $p=0.006$) and calcium ($p=0.005$). Duration of hospital stay correlated positively with fibrinogen ($p=0.009$) and calcium ($p=0.020$).

Table 8. Correlation analysis between length of hospital stay and total TPE volume with clinical and laboratory parameters in all patients, Pearson's correlation, one-tailed, significant correlations are bolded.

	Length of hospital stay		Total TPE volume	
	r	P	r	P
Age (years)	-0.125	0.255	-0.327	0.020
Length of hospital stay (days)	/	/	0.487	0.004
Number of TPE	0.518	0.002	0.923	<0.001
Total TPE volume (ml)	0.487	0.004	/	/
Leucocytes	-0.218	0.128	0.273	0.080
RBC (x10 ⁹ /L)	-0.034	0.431	0.103	0.301
Hemoglobin (mmol/L)	-0.007	0.485	0.113	0.287
Thrombocytes (x10 ⁹ /L)	0.078	0.344	0.041	0.417
Reticulocytes (per 1000 RBC)	0.275	0.087	0.003	0.494
PT (11-13.5s)	0.361	0.027	0.348	0.035
aPTT (30-40s)	-0.364	0.026	-0.429	0.011
Fibrinogen (mmol/L)	0.510	0.009	0.494	0.013
Glucose (mmol/L)	-0.077	0.370	-0.261	0.133
Urea (mmol/L)	-0.120	0.272	-0.262	0.093
Creatinine (mmol/L)	0.314	0.052	-0.049	0.405
Bilirubine (μmol/L)	-0.055	0.388	0.239	0.110
AST (U/L)	0.156	0.210	-0.043	0.415
ALT (U/L)	0.388	0.019	0.115	0.281
GGT (U/L)	-0.080	0.342	-0.160	0.212
LDH (U/L)	-0.063	0.374	-0.094	0.318
ALP (U/L)	0.030	0.453	-0.273	0.144
Serum proteins (g/L)	0.047	0.418	0.338	0.073
Serum albumins (g/L)	-0.105	0.313	0.285	0.099
CRP (mg/L)	-0.290	0.064	0.078	0.346
PCT (ng/L)	0.133	0.348	-0.285	0.198
Troponin (ng/L)	-0.021	0.473	0.652	0.006
NT-proBNP (ng/L)	-0.161	0.352	-0.118	0.390
Potassium (mmol/L)	0.023	0.453	-0.332	0.045
Calcium (mmol/L)	0.450	0.020	0.543	0.005

Legend: TPE: therapeutic plasma exchange, RBC: Red blood cells, PT: Prothrombin Time Test, aPTT: Partial Thromboplastin Time, AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, GGT: Gamma-glutamyl Transferase, LDH: Lactate dehydrogenase, ALP: Alkaline Phosphatase, CRP: C-reactive protein, PCT: Procalcitonin; NT-proBNP: N-terminal pro b-type natriuretic peptide. r: Pearson's correlation coefficient, P for significant differences is bolded. Data is presented as arithmetic mean± standard deviation.

In our patients we also assessed the ADAMTS13 activity and correlated it with specific apheresis parameters, laboratory parameters and ADAMTS 13 related factors. Our data showed that ADAMTS13 activity positively correlated with the number of RBC ($r= 0.480$, $p=0.041$), number of thrombocytes ($r=0.489$, $p=0.038$) and sC5b-9-levels ($r=0.735$, $p=0.005$). Furthermore, ADAMTS13 activity correlated negatively with total TPE volume ($r=-0.502$, $p=0.040$) and bilirubin ($r=-0.616$, $p=0.009$). Correlation between ADAMTS 13 activity with other laboratory parameters and ADAMTS 13 related factors for all study patients with TTP is demonstrated in **Table 9**.

Table 9. Correlation analysis between ADAMTS 13 activity and specific apheresis parameters, laboratory parameters and ADAMTS 13 related factors in patients with TTP (N=31), Pearson's correlation, one-tailed, significant correlations are bolded.

	ADAMTS 13 activity	
	r	P
Age (years)	0.219	0.226
Lenght of stay (days)	0.068	0.412
Number of TPE	-0.356	0.106
Total TPE volume (ml)	-0.502	0.040
Leucocytes (x10*9/L)	-0.258	0.186
RBC (x10*12/L)	0.480	0.041
Hemoglobin (mmol/L)	0.443	0.065
Thrombocytes (x10*9/L)	0.489	0.038
Reticulocytes (per 1000 RBC)	-0.297	0.151
Fibrinogen (mmol/L)	-0.388	0.151
Glucose (mmol/L)	-0.372	0.145
Urea (mmol/L)	0.227	0.218
Creatinine (mmol/L)	0.109	0.355
Bilirubine (mmol/L)	-0.616	0.009
AST (U/L)	-0.042	0.443
ALT (U/L)	-0.159	0.293
GGT (U/L)	-0.136	0.321
LDH (U/L)	0.320	0.132
ALP (U/L)	-0.402	0.162
Serum proteins (g/L)	-0.182	0.307
Serum albumin (g/L)	-0.090	0.402
CRP (mg/L)	-0.123	0.337
PCT (ng/L)	0.258	0.311
Troponin (ng/L)	-0.104	0.387
Potassium (mmol/L)	0.021	0.471

Calcium (mmol/L)	-0.450	0.082
ADAMTS 13 inhibitors	0.109	0.390
Complement classical (48-103 CH50/ml)	0.458	0.058
Complement alternative (70-125%)	0.262	0.218
C3 (0.9-1.8 g/L)	0.124	0.336
C4 (0.15-0.55 g/L)	0.009	0.488
Factor H (250-880 mg/L)	0.289	0.169
I antigen (70-130%)	0.085	0.397
B antigen (70-130%)	-0.013	0.483
Anti-H IgG (<110)	0.016	0.479
C1q Ag (60-180)	0.059	0.432
Anti-C1q IgG (<52)	0.220	0.271
sC5b-9 (110-252 ng/mL)	0.735	0.005

Legend: TPE: therapeutic plasma exchange; RBC: Red blood cells; AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, GGT: Gamma-glutamyl Transferase, LDH: Lactate dehydrogenase, ALP: Alkaline Phosphatase, CRP: C-reactive protein; PCT: Procalcitonin. r: Pearson's correlation coefficient, P for significant differences is bolded. Data is presented as arithmetic mean± standard deviation.

In the group of patients with TTP we have assessed correlation between total TPE volume exchange and troponin plasma concentration at admission time (**Figure 3**). Patients with initially higher levels of troponin had been treated with higher total TPE plasma volume.

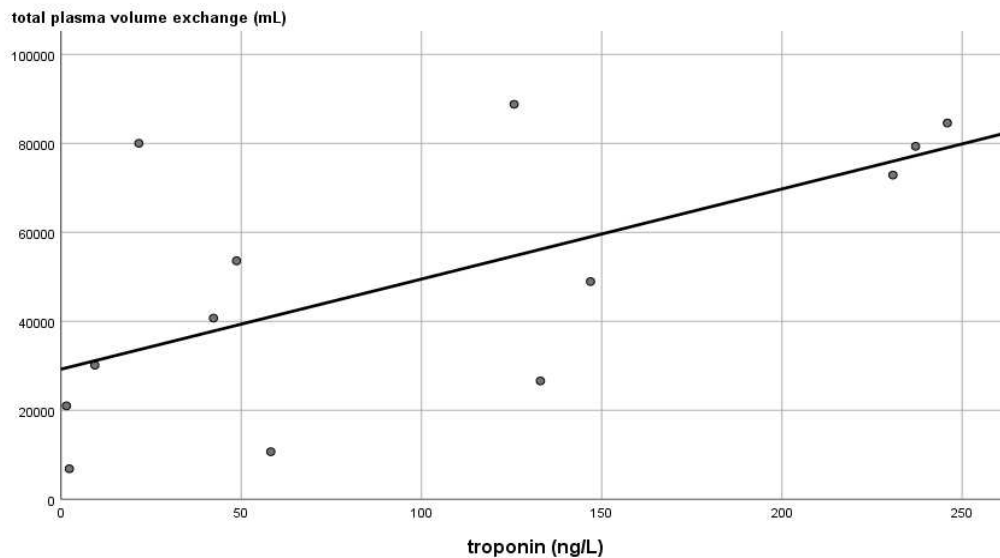


Figure 3. A regression graph with the equation of linear regression demonstrated a correlation between total plasma volume exchange of the patients with TTP (N=31) and troponin plasma concentration at admission time ($Y = 202.53X + 29243.45$), $r^2 = 0.409$; $P = 0.019$.

5. DISCUSSION

During the 10-year observation study period in the internal ICU, in total, 48 adult patients were treated with TPE (4.8 per year). The aim of the study was to get an overview of the characteristics of patients treated with TPE, including indications for TPE, clinical features, laboratory parameters and their outcome.

Most of the studies retrospectively investigate TPE treatment in general ICUs where they have collective data from all the departments including neurological diseases as the most common indication for TPE (32, 33). Our study solely focused at the TPE treatment in internal ICU where most the common cases were patients with haematological indications, especially with TTP.

In our study median age of the patients treated with TPE was 50.12 years, what is similar to other retrospective single centre studies with an average age of study patients from 45 to 56 years (32, 33). Mean length of hospital stay in our study was 21.97 days but varied from 2 to 61 days because of a variety of indications for TPE. Longest hospital stay in our study was observed in patients with refractory TTP who required a series of TPE treatments.

Our study showed that majority of patients treated with TPE was diagnosed with TTP 31 (64.58%) what is similar to results in other retrospective studies like Ring et al. which is also a single centre study. Difference is that their analysis included also other ICUs not only internal ICU and showed that 46,5% of the patients treated with TPE were diagnosed with TTP (32). TTP itself is more commonly acquired and caused by autoantibodies, which are triggered by some events. Most common are antiplatelet drugs, immunosuppressive agents or pregnancy (12). Another big risk factor are various types of cancer, for example mucin producing adenocarcinomas or disseminated diseases (34). In our study a total of 3 patients were diagnosed with cancer beforehand: one with pancreatic carcinoma, one with metastatic rectal carcinoma, and one with mamma carcinoma.

As mentioned earlier TTP was the most relevant indication for TPE treatment in the internal ICU, followed by 5 (10.42%) equally distributed cases of hyperviscosity syndrome, severe hypertriglyceridemia, systemic vasculitis and one case (2.08%) of atypical HUS. Similarly single centre study of Seker et al. showed that in the subgroup of haematological indications like hyperviscosity syndrome as an indication for TPE was present in 12.5% of all study patients and severe hypertriglyceridemia with pancreatitis in 15% of the patients (33).

There are no pathognomonic symptoms and signs for setting the indications for TPE treatment. Diagnosis usually takes time and hematological indications like TTP or HUS are the most time relevant diseases when it comes to immediate treatment (26). So, we have assessed most common symptoms and signs mentioned in medical records of our patients. Our results

demonstrated that the most common signs and symptom in our study patients were malaise and weakness presented in 26.56% patients. This is congruent with the Oklahoma registry where weakness as a sign is mentioned in 63% of all patients. In our study neurological symptoms were present in 21.88% while in Oklahoma register 41% patients presented with neurological symptoms (11). This can be explained by the fact that our study focused only on internal medicine ICU while patients with neurological diseases are treated with TPE elsewhere. High frequency of jaundice as a sign of hemolysis and symptoms that include bleeding either to the skin or into urinary or GI tract in our study population can be explained by the large number of patients with hematological indications for TPE.

Statistical analysis showed significant differences between men and women. In our study there were 19 (39.6%) men and 29 (60.4%) women. The shown data correlates with the general epidemiology as TTP predominantly occurs after the age of 40 and affects women in a ratio of 2:1 (12). The data showed statistically significantly elevated levels of urea and creatinine in male patients. This can be explained by the generally higher muscle mass in men (35). Also, procalcitonin was significantly higher in men. Although it might be a sign of higher vulnerability to infections in men but would need an own and more detailed analysis as the values of leucocytes and C-reactive protein in men and women didn't show significant differences. Furthermore, women had statistically significant higher levels of serum albumin than men. According to Herrmann et al. a lower serum albumin level can be a predictive value for increased mortality (36). Despite the fact, that the number of male patients compared to female patients was lower, there were no gender difference in deaths in our study. A total of 6 people died, of whom 3 were male and 3 were female.

As discussed earlier 6 patients ceased and all of them were in the group of patients diagnosed with TTP. This can be compared to a study from Fodil and Zafrani from 2021. in which they had a population of 1096 patients admitted to then ICU with a mortality of 15-20% (37). Also, studies showed overall hospital survival rate in patients treated with TPE that included 105 patients was 88.6% (32). When we compared the differences between survived and ceased patients, ones who survived had longer hospital stay, higher number of TPE treatments and as expected also higher amount of TPE plasma volume used in TPE treatments. Ceased patients had statistically significant higher levels of leucocytes and CRP suggesting presence of inflammation. Also, they present with higher levels of creatinine than in survived patients. Previous studies have shown that renal involvement in TMA is marker of a worse outcome (38). Moreover, the ceased patients presented with a higher but not statistically significant level of LDH than patients who survived. These results correlate with the work of

Zhu et al. where they concluded that elevated LDH levels are a predictor for higher mortality rates (39).

For the diagnosis of TTP, which was the most common in our study, treatment guidelines suggest daily plasma exchange (TPE) to continue for a minimum of 2 days after platelet count has been $>150 \times 10^9/L$ and should then be stopped (40). In the present study, we evaluated thrombocytes and LDH count trends in TTP patients. Previous studies have shown that patterns of thrombocytes response to TPE can be predictive for refractory TTP and misdiagnosed patients with TTP. Our results revealed statistically significant and quick elevation of thrombocytes count with concomitant rapid decline of LDH levels in first three days of TPE treatment suggesting TPE as very efficient treatment for TMAs (9). The average number of treatments with TPE in the group of patients with TTP was 12.26 treatments per patient. Compared to one study from the United States with an average of 13 TPE in TTP, our results are similar (41).

Prognosis and outcomes of patients in ICUs generally and especially ones with serious diagnosis that require specific treatment as TPE can often be very difficult to predict due to many variables. Analysis of our study patients revealed significant correlations of length of hospital stay and total TPE plasma volume with clinical and laboratory parameters. Duration of hospital stay correlated positively the total TPE plasma volume and the numbers of TPE treatments, but negatively correlated with aPTT. Possibly patients who stayed longer in the hospital were refractory to therapy, needed more TPE treatments and due to use of more anticoagulation drugs (mostly heparin) had longer aPTT. Also, total TPE plasma volume as expected correlated positively with the number of TPE treatments and correlated negatively with aPTT cause of use of more anticoagulation drugs.

In our study total TPE plasma volume showed significant positive correlation with initial troponin levels. Subsequent linear regression analysis also revealed that patients with initially higher levels of troponin had been treated with higher total TPE plasma volume. Previous studies also showed that serum levels of troponin at the admission to ICU indicate more severe clinical picture in patients with TTP and thus is expected to need more TPE treatments and TPE used plasma. TTP-induced cardiovascular manifestations may vary from asymptomatic (raised cardiac biomarkers) to sudden cardiac death, myocarditis, arrhythmias, heart failure, or myocardial infarction (42). An elevated troponin is an independent predictor of death or refractory to treatment and represents a prognostic indicator in TTP patients (43).

Since the year 2015. samples of blood of internal ICU patients who are diagnosed with TTP, underwent to Budapest Semmelweis University in the research laboratory of prof. Zoltán

Prohászka for complete analysis of ADAMTS 13 activity and its related factors. Only 15 patients in our study had a complete report about the ADAMTS13-activity. An ADAMTS13 activity of less than 10% is the laboratory cut of value for the diagnosis of TTP (12). Average ADAMTS 13 activity of our study patients was 21.87%. Yang et al. showed, that a reduced ADAMTS13 activity was associated with a higher mortality (44).

We have investigated correlations of ADAMTS 13 activity and clinical and laboratory markers of study patients who had a full ADAMTS 13 activity report. Our data showed that ADAMTS13 activity correlated positively with the number of red blood cells (RBC), initial level of thrombocytes and sC5b-9-levels. Diagnosis of TTP is often challenging because of the delay of having the results for ADAMTS 13 activity and its inhibitors, so studies investigated potential markers for recognition of severe or refractory disease. Soluble C5b-9 sC5b9, the terminal complement complex in previous studies has been shown as a potential biomarker for the development of TMA among patients with active graft-versus-host reaction (GVHD). Early raise of the sC5b-9 activation marker in GVHD patients was predictive for later development of transplant associated-TMA (45).

Furthermore, ADAMTS13 activity correlated negatively with total TPE plasma exchange volume and bilirubin. Small sample of patients with ADAMTS 13 activity report limits our conclusions. Previous studies showed similar negative correlation between unconjugated bilirubin and ADAMTS13 activity suggesting that unconjugated bilirubin lowers plasma ADAMTS13 activity (46).

TPE-associated complications rates vary significantly, ranging from 1–2% up to 39% (47). In our study we have observed 4 serious complications. Two patients had generalized epileptic seizures, one had respiratory insufficiency, and one had acute kidney injury that required dialysis. Furthermore, a total of 7 allergic reactions towards the used plasma were recorded. Apter et al. discovered an average between 3-12% of cases where FFP was used in the treatment of TTP lead to adverse reactions (48).

The presented study had some limitations, mostly due its retrospective design and data from a single center. Additionally, there was a general lack of follow-up data. During the data collection we struggled with the availability of patients' data, as during our study period the hospital information system was transformed from paper charts into an electronical form and this electronical form was updated again during this 10 years.

6. CONCLUSION

This retrospective study assessed the use of TPE in ICU of Internal medicine department. The most common indication was TTP. The treatment with TPE is an effective therapy for patients with TTP and shows a rapid increase of thrombocytes and simultaneously a rapid decrease of the LDH-level.

We identified several associations: prolonged length of hospital stay correlated positively with the number of TPE, elevated troponin at admission correlated with increased total TPE volume, and ADAMTS13-activity correlated positively with the level of RBC, the initial thrombocytes, and sC5b-9-level.

Overall, this study once more highlights the importance of TPE as treatment for TTP, especially in the surrounding of the ICU. It also shows the necessity of a continuous monitoring of the clinical and laboratory parameters, to improve the outcome and avoid complications as much as possible.

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8. ENGLISH SUMMARY

Objectives: The objective of study was to assess the clinical characteristics, laboratory parameters and specific apheresis parameters of patients treated with therapeutic plasma exchange (TPE) in the internal intensive care unit (ICU).

Subjects and Methods: An observational retrospective study was conducted during ten-year period. Subjects were patients treated with TPE in ICU of the Internal medicine department

Results: In total 48 patients were treated in ICU with TPE with median age of 51.12 years and 29 (60.4%) of them were women. Most common indications for TPE were Thrombotic thrombocytopenic purpura (TTP) in 31 (64,58%) patients, followed by 5 (10.42%) patients with hyperviscosity syndrome, 5 (10.42%) patients with systemic vasculitis and 5 (10.42%) patients had severe hypertriglyceridemia. Symptomatology included malaise and weakness in 17 (26.56%) patients, followed by 14 (21.88%) patients with neurological symptoms, 8 (12,5%) patients with jaundice and 6 (9,38%) patients had bleeding into skin. Gender differences revealed that females had higher levels of serum albumin (39.17 ± 7.29 vs. 34.26 ± 5.58 , $p=0.049$), while male showed higher levels of urea (31.13 ± 26.98 vs. 9.49 ± 3.31 , $p=0.001$), creatinine (409.89 ± 392.20 vs. 80.45 ± 32.35 , $p<0.001$), and procalcitonin (2.78 ± 2.54 vs. 0.29 ± 0.27 , $p=0.013$). A total of 6 (12.5%) patients ceased and all were diagnosed with TTP. Patients who survived had longer hospital stay (25.78 ± 15.75 days vs. 9.33 ± 6.86 , $p=0.010$), higher number of TPE treatments (10.29 ± 7.04 vs. 3.50 ± 2.59 , $p=0.014$), and higher amount of total TPE used plasma (42244.36 ± 33490.24 vs. 12238.33 ± 8518.37 , $p=0.021$). The ceased patients had significantly higher levels of leucocytes (12.23 ± 3.98 vs. 10.30 ± 4.81 , $p=0.033$) and creatinine (270.60 ± 250.85 vs. 164.38 ± 265.86 , $p=0.001$). Length of hospital stay correlated positively with number of TPE treatments ($p=0.004$) and total TPE plasma volume ($p=0.004$). Patients with initially higher levels of troponin had been treated with higher total TPE plasma volume.

Conclusion: Most common indication for TPE in internal ICU was TTP with higher prevalence in female patients. All ceased patients were diagnosed with TTP. Initially higher levels of troponin were associated with use of higher plasma volumes in TPE treatments.

9. CROATIAN SUMMARY

Naslov rada: Kliničke osobitosti i ishodi liječenja bolesnika liječenih terapijskom izmjenom plazme u internističkoj intenzivnoj jedinici.

Cilj istraživanja: Cilj ovog istraživanja je bio procijeniti kliničke karakteristike, laboratorijske pokazatelje i parametre postupka afereze kod bolesnika liječenih terapijskom izmjenom plazme (TIP) u internističkom JIL-u (Jedinici intenzivnog liječenja).

Ispitanici i metode: Opservacijska retrospektivna studija provedena je tijekom desetogodišnjeg razdoblja. Ispitanici su bili odrasli bolesnici liječeni s TIP-om u internističkom JIL-u.

Rezultati: Ukupno 48 bolesnika je liječeno u internističkom JIL-u sa TIP-om prosječne dobi 51.12 godina od čega je bilo 29 (60.4%) žena. Najčešće indikacije za liječenje TIP-om bile su TTP kod 31 (64,58%) bolesnika, 5 (10.42%) bolesnika je imalo hiperviskozni sindrom, 5 (10.42%) sistemski vaskulitis i 5 (10.42%) tešku hipertrigliceridemiju. Najviše se bolesnika prezentiralo slabošću i malaksalošću, njih 17 (26.56%), potom slijedi 14 (21.88%) bolesnika sa neurološkim simptomima, 8 (12,5%) sa žuticom i 6 (9,38%) sa krvarenjem u kožu. Žene su imale više razine serumskog albumina (39.17 ± 7.29 vs. 34.26 ± 5.58 , $p=0.049$), dok su muškarci imali značajno više vrijednosti ureje (31.13 ± 26.98 vs. 9.49 ± 3.31 , $p=0.001$), kreatinina (409.89 ± 392.20 vs. 80.45 ± 32.35 , $p < 0.001$) i prokalcitonina (2.78 ± 2.54 vs. 0.29 ± 0.27 , $p=0.013$). Ukupno 6 (12.5%) bolesnika je preminulo i svi su pripadali skupini bolesnika s TTP-om. Bolesnici koji su preživjeli su imali značajno duže vrijeme boravka u bolnici (25.78 ± 15.75 dana vs. 9.33 ± 6.86 , $p=0.010$), veći broj TIP postupaka (10.29 ± 7.04 vs. 3.50 ± 2.59 , $p=0.014$.) i veću količinu plazme korištene u TIP postupcima (42244.36 ± 33490.24 vs. 12238.33 ± 8518.37 , $p=0.021$.). Preminuli bolesnici su imali značajno povišene vrijednosti leukocita (12.23 ± 3.98 vs. 10.30 ± 4.81 , $p=0.033$.) i kreatinina (270.60 ± 250.85 vs. 164.38 ± 265.86 , $p=0.001$.). Duljina boravka u bolnici je pozitivno korelirala sa brojem postupaka TIP ($p=0.004$) i ukupnim volumenom izmijenjene plazme ($p=0.004$). Bolesnici sa višim početnim vrijednostima troponina su liječeni sa ukupno većom količinom plazme.

Zaključak: Najčešća indikacija za liječenje terapijskom izmjenom plazme u internističkom JIL-u je TTP sa značajno višom prevalencijom kod žena. Svi umrli bolesnici su imali dijagnozu TTP-a. Vrijednosti troponina su bile povezane sa dozom ukupnog volumena plazme korištenog u postupcima TIP-a.

