SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Clinical investigation of certain factors determining the outcome of treatment critically ill patients

by István László, MD

Supervisor: Béla Fülesdi, MD, Professor, Doctor of the Hungarian Academy of Sciences

UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF NEUROSCIENCES

DEBRECEN, 2024

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Members of the Examination Committee:	Prof. József Balla MD, PhD, DSc, MHAS
	Prof. János Gál MD, PhD

The Examination takes place at the Library, Department of Anaesthesiology and Intensive Care, Faculty of Medicine, University of Debrecen, on 3 Sept 2024, from 11 a.m.

Head of the **Defense Committee**:	Prof. Norbert Németh MD, PhD, DSc
Reviewers:	Prof. Barna Babik MD, PhD
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Members of the Defense Committee:	Prof. József Balla MD, PhD, DSc, MHAS
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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on 3 Sept 2024, from 1 p.m.

1. Introduction

Supportive care in intensive care units aims to prevent death, further deterioration and complications, and ultimately to improve patients' recovery and quality of life after ICU and hospital discharge. Objective measurement of the achievement these objectives is essential for assessing and improving the quality of ICU activity. Taking into account the above objectives, the outcome of the management of critically ill patients can be assessed from several perspectives. The main groups of different outcome markers are:

- Mortality (e.g. ICU, intrahospital, 30/60/90 etc. days, disease-specific)
- Incidence of adverse events, complications ("events of interest", e.g. various infections)
- Measures of resource utilization and cost ("resource utilization and cost", e.g. ICU bed utilization, number of ventilation days, number of renal replacement therapy days, length of ICU stay, ICU readmission rate, etc.)
- Patient-specific markers of quality of life, functional (somatic, cognitive and mental) status following ICU or hospitalisation

Of the above, in common practice, ICU outcomes are mostly characterised by mortality data, since mortality is an important (from the point of view of both providers and patients), numerically expressed, specific endpoint that can be easily retrieved and tracked in hospital databases. However, this figure shows a wide variation (10-50%) in the different publications. In the year 2022, a total of 823 patients were treated in the Central Intensive Care Unit of the Department of Anaesthesiology and Intensive Care at the University of Debrecen, our own institute; 150 of these patients died during their ICU stay (total ICU mortality 18.22%) and 34 patients died shortly after ICU discharge, during their same hospital stay (total in-hospital mortality 22.3%).

When evaluating the data, it is important to determine which factors influence the outcome and mortality of critically ill patients. Based on international literature references, the most important are:

- Medical condition indicating ICU admission
- Chronic comorbidities
- Patient age
- Therapeutic interventions related to the current condition
- Age of the patient

- Human factor (at the level of the idividual, the team and the system involved in care)

The factors listed here are in fact interrelated, mutually influencing broad categories, which can be broken down into a number of additional factors - some of these can be influenced, others cannot. It is the sum of these factors that ultimately determines the success of an individual patient's ICU treatment and the quality of life after. It would be an impossible task within the scope of a thesis to examine all influencing factors in a complex way. We have therefore set ourselves the goal of studying some of the most important challenges in the life of our clinic in recent years. The topics of this thesis are the haematopoietic stress response in COVID-19 patients, CIP ("critical illness" polyneuropathy) associated with sepsis and the transport of ICU patients.

2. Objectives

1. Our first objective was to study whether there is a correlation between the haemopoietic stress response and the critical condition of the patients and the fatal outcome of the disease in all patients with COVID-19 treated at the University of Debrecen Clinical Centre, Nagyerdei Campus, between 1 February 2021 and 31 March 2021.
2. In a second analysis (in the same patient group), we also sought to answer the question of whether a parameter of the haemopoietic stress response is a predictor of prognosis in patients requiring intensive care.
3. In our second study, we prospectively followed the dynamics of the development of CIP (critical illness polyneuropathy) in septic patients during the first 5 days after ICU admission and looked for correlations between changes in electrophysiological symptoms, severity of clinical symptoms and patient outcome.
4. The third part of my thesis is a summary of the anaesthesiologist's role during the transport of the patient from the operating theatre to the ICU, in response to an international invitation, with the aim of reviewing the protocol of our practice in this field.

3. Patients and methods

3.1 Study of the haematopoietic stress response in patients with COVID-19

This study is a retrospective descriptive analysis of prospectively collected data from patients with COVID-19 admitted to the COVID Centre of the University of Debrecen Clinical Centre between 1 February 2021 and 31 March 2021.

During this period, 258 COVID-19 positive cases with mild symptoms not requiring intensive care occurred and 104 patients were treated in the ICU. Patients who presented for admission with mild symptoms but required ICU treatment later in their illness were also considered as ICU patients for the analysis.

Drug therapy was initiated according to our local protocol, which was based on the then current international guidelines: in the early stage of infection (stage 1), therapy was based on acetylsalicylic acid, low molecular weight heparin and antiviral drugs (remdesivir, favipiravir or bamlanivimab). In stage 2 (characterised by pulmonary or other organ manifestations), corticosteroid therapy or immunosuppression (O2 requirement, severe symptoms, stage 2/b) was considered in addition to the above. In stage 3 (hyperinflammatory phase), drug therapy was based on immunosuppressive agents (tocilizumab or baricitinib), corticosteroids and cytokine adsorbent therapy. Admission to the ICU was decided by the ICU physicians based on the SAPS (Simplified Acute Physiology Score) criteria. The ventilation strategy was based on an internal protocol adopted from a position paper of the German Society of Pulmonary Medicine (DGP).

Prospectively collected clinical and laboratory data were extracted from patients' electronic medical records. In our present analysis, only parameters related to inflammation, coagulation and haemopoietic stress were included. For the sake of clarity, the most pathological (highest) value of the parameters measured during hospitalisation was included in all cases in the analysis, as it was our concept that this best reflected the most severe form of pathological lesion induced by COVID -19 infection.

Laboratory methods

- Haemoglobin was measured using a cyanide-free photometric method where cells were lysed by the addition of sodium lauryl sulphate (SLS). This converts hemoglobin to a sulfated derivative and the light absorbance is measured at 564 nm. For analysis,

a Siemens Advia 2120i (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) hematology analyzer was used.

- WBC (white blood cell count), IG (immature granulocyte count): after pre-treatment, cells are passed one by one through a laser beam for hydrodynamic focusing. Light scattered forward and sideways and myeloperoxidase activity are detected and converted into electrical pulses. White blood cells are displayed on bivariate scatter plots, resulting in absolute numbers and subclasses of white blood cells. A Siemens Advia 2120i (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) hematology analyzer was used for analysis.
- PLT (platelet count), MPV (mean platelet volume), PDW (platelet distribution width), Htc (HemaToCrit), RDW (red blood cell distribution width): Siemens Advia 2120i analyzers (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) flow cytometry-based method was used to determine platelet and red blood cell counts (PLT and RBC); PLTs and RBCs were plotted on bivariate scatter plots and histograms. The change in impedance is proportional to cell volume, resulting in a measure of cell count and volume. MPV, PDW and RDW were determined from PLT and RBC histograms. Htc was a calculated parameter.
- NRBC (Nucleated Red Blood Cell Count): measurements were based on flow cytometry method (Sysmex XN Sysmex America, Inc. Lincolnshire, IL, USA)
- CRP (C-Reactive Protein): measured from venous blood by photometric immunoturbidimetry using the Roche Cobas 8000 modular series (Roche Diagnostics, Mannheim, Germany).
- Procalcitonin (PCT): PCT was measured by a two-step sandwich immunoassay using streptavidin microparticles and an electrochemiluminescence detection system (Roche Cobas 8000; Roche Diagnostics, Mannheim, Germany).
- D-dimer was determined by latex-stained turbidimetric immunoassay (Instrumentation Laboratory, Bedford, Massachusetts, USA).

Statistical analysis

The data were first subjected to a normality test. Data with a normal distribution were compared using the corresponding t-tests, while data with a non-normal distribution were

compared using the Mann-Whitney test. The categorical data were analysed using a chi-square test. Pearson's analysis was used to examine the correlation between mean platelet volume and platelet count. Results of statistical analyses were considered statistically significant at $p<0.05$.

3.2 Assessment of the severity and clinical course of critical illness associated polyneuropathy (CIP) in septic patients

Our second study was an observational, prospective case series study, which was performed at the 18-bed Central Intensive Care Unit of the Department of Anaesthesiology and Intensive Care at the University of Debrecen Clinical Centre. In this study, we followed the dynamics of polyneuropathy in septic patients by neurophysiological studies. The study protocol was approved by the Research Ethics Committee of the University. In all cases, written informed consent was obtained either from the patients or from their relatives with the right to make a statement. At enrolment, patients fulfilling clinical criteria for sepsis and with at least APACHE II (Acute Phisiology And Chronic Health Evaluation) 12 or more severe were selected for the study, regardless of the number of multiple organ involvement. Exclusion factors were: established central nervous system disease and neuromuscular disease prior to sepsis. All our patients received standard surgical or drug treatment according to their clinical needs. Medication included goal directed fluid resuscitation, vasoactive agents, targeted antibiotic treatment based on cultures. During the organ support treatments, mechanical ventilation and renal replacement therapy were used according to the clinical picture and in accordance with the rules of the profession. Muscle relaxants were used only during surgical anaesthesia, if necessary, and no neuromuscular blocking agent was used for intensive care unit ventilation. APACHE II, SAPS II (Simplified Acute Physiology Score) and SOFA (Sequential Organ Failure Assessment) scores were followed daily to monitor patient severity.

Neurophysiological tests

For all patients, an orienting neurological examination and bilateral sensory and motor nerve conduction velocity studies of the median nerve and ulnar nerve were performed within 48 hours of ICU admission. The tests were then performed in all patients on four consecutive days. In cases where surgical intervention (and consequent neuromuscular blockade) was

required, the day of examination was postponed and residual neuromuscular blockade was excluded by repetitive ulnar nerve stimulation prior to electroneurographic examination. After the first 5-day period, electroneurographic (ENG) examinations were repeated weekly.

For measurements, we used a bedside electroneurographic device, the 2-channel Keypoint Electroneurograph (Alpine Biomed Aps, Skovlunde, Denmark). For stimulation and recording muscle responses, we used skin surface electrodes, widely used in clinical practice. To determine motor nerve conduction velocities, median nerve stimulation was performed at the elbow flexion and the volar surface of the wrist. Motor stimulation of the ulnar nerve was performed according to the ulnar nerve sulcus of the elbow. To determine the conduction velocity of the sensory nerves, the stimulation was delivered to the base of the fingers and the orthodromic recording was performed at the wrist. During motor stimulation, increasing intensities of stimulation were used to determine the stimulus strength at which the best compound muscle action potential (CMAP) was obtained. Similarly, for sensory stimulation, the optimal stimulus strength at which the best sensory nerve action potential (SNAP) was obtained was determined, also using increasing intensities of stimulation. In accordance with clinical practice, the temperature of the skin areas under test was kept above 32 °C to ensure adequate recording conditions. If significant electrolyte abnormalities were detected, ENG studies were performed only after their normalisation. In all cases, an attempt was made to study the peroneal and sural nerves, in accordance with the guidelines of the polyneurpathy study protocol. However, these studies (especially for the nervus peroneus) resulted in such a significant number of non-valuable registrations for both CMAP and SNAP that they were not used in the further evaluation.

The consecutive electroneurographic measurements were always performed by the same investigator (Dr. Réka Nemes).

The control group of the studies were the results of the tests performed in healthy subjects (n=21) at the Electrophysiology Laboratory of the Neurological Clinic of the University of Debrecen Clinical Centre; gender and age matching between the two groups was performed. Based on these data, the lower limit of nerve conduction velocities for the median nerve and ulnar nerve was set at 5 m/s. We adopted a lower limit of 5 mV for CMAP and 5 μV for SNAP for both median and ulnar nerves.

Our primary goal was to use parameters suitable for the general characterization of nerve functions during the evaluation. Accordingly, we calculated motor (MNCI: motor nerve

conduction index) and sensory (SNCI: sensory nerve conduction index) conduction indices for both motor and sensory nerves, as proposed by Witt et al. The indices were calculated as follows: the amplitude measured in a given patient was divided by the amplitude of the control group, averaged and then multiplied by 100 to obtain a percentage value relative to the control group, which corresponded to the conduction index of the nerve for both motor and sensory nerves. These indices were then used later to characterise the condition of the nerves in follow-up studies and also to correlate with clinical factors.

In each patient, we also correlated the severity score characterising the severity of the critical condition with the patients' current CMAP and SNAP values, as well as with the index values characterising nerve function calculated from the above.

Motor and sensory neural functions were assessed separately. The rationale for this was that previous studies have shown that motor nerve involvement may be more pronounced in critically ill patients, and we therefore thought that in this group of patients, where we study neuromuscular dysfunction in critically ill patients, this would better characterise the onset and course of the process. In three of our patients, we were only able to perform four examinations during the 5-day follow-up period because two of our patients died, and 1 patient was transferred to another care site for further treatment.

Statistical analysis

Median and interquartile ranges were used in the interpretation of the data according to the results of the preliminary normality tests. Mann-Whitney U test was used to compare electrophysiological parameters. Spearman's test was used to analyse the correlation between electrophysiological indices and disease severity scores. In all cases, a value of $p<0.05$ was accepted as the limit of statistical significance.

4. Results

4.1 Study of the haematopoietic stress response in patients with COVID-19

A total of 206 hospitalised COVID-19-positive cases were studied: 96 women and 110 men. Of the total patient population, 95 patients required intensive care during hospitalisation. The overall mortality in the total patient population was 37%. No differences in age and sex were found between patients who died and survived. The prevalence of comorbidities was similar

in the survived and the dead groups. There was one exception: chronic kidney disease, which was more common in patients with fatal outcomes. Mortality was also higher in patients who had at least 3 comorbidities in addition to COVID-19 infection. Although the % lung involvement was significantly higher in the fatal group, this difference did not reach the threshold of statistical significance. The data are presented in Table 1.

Parameter	**Dead (n=76)**	**Survived (n=130)**	**P-value**
Age (yeas)	67 (59.5-74)	65 (52-71)	P=0.56
Female / Male	35/41	61/69	P=0.87
Obesity (Yes / No)	22/54	36/94	P=0-84
Hypertension (Yes / No)	62/14	97/33	P=0.25
Diabetes (Yes / No)	19/57	44/86	P=0.14
Cardiovascular disease (Yes / No)	43/33	63/67	P=0.26
Pulmonary disease (Yes / No)	20/56	39/91	P=0.57
Central nervous system disease (Yes / No)	17/59	36/94	P=0.39
Kidney disease (Yes / No)	9/67	2/128	P<0.01
Malignancy (Yes / No)	8/68	14/116	P=0.95
Autoimmune disease (Yes / No)	11/65	12/118	P=0.24
>3 comorbidities (Yes / No)	41/76	40/130	P=0.03
Pregnancy (Yes / No)	0/76	2/130	P=0.28
Lung involvement on CT at referral (%)	50 (20-70)	30 (15-70)	P=0.084
Hgb (g/L)	116.5 (95.5-129.0)	127.5 (111.0-140.0)	P< 0.001

Table 1 - Clinical and laboratory characteristics of the entire COVID group. Grouping is based on survival versus fatal outcome. Median values and IQRs of 25-75% are given.

Htc (%)	0.35 (0.28-0.39)	0.37 (0.34-0.41)	P< 0.01
WBC (G/L)	13.8 (8.8-20.1)	11.1 (7.4-15.3)	P< 0.01
PLT (G/L)	202.5 (132.5-326.5)	272.0 (193.0-351.0)	P< 0.01
CRP (mg/L)	77.5 (21.6-168.1)	20.8 (6.1-99.8)	P< 0.001
PCT (µg/L)	0.35 (0.1-1.3)	0.1 (0.1-0.3)	P< 0.001
D-dimer (mg FEU/L)	1.51 (0.89-3.6)	1.12 (0.5-3.2)	P< 0.05

Table 1 (continued) - Clinical and laboratory characteristics of the entire COVID group. Grouping is based on survival versus fatal outcome. Median values and IQRs of 25-75% are given.

Comparison of laboratory findings of the entire COVID patient population in the survival and fatal outcome groups

Haemoglobin, haematocrit and platelet counts were lower and white blood cell counts and D-dimer values were higher in patients with fatal outcome than in those who survived COVID-19 infection. Among inflammatory parameters, C-reactive protein and procalcitonin levels were also found to be higher in patients who died. Parameters indicative of haematopoietic stress in the whole population are presented in Figure 1, grouping separately the results of patients who survived and those who died due to COVID-19 infection.

It can be seen that the fatal outcome group also had a higher proportion of nucleated red blood cells (NRBC) and a higher red blood cell distribution width (RBCDW). Similarly, the mean platelet volume (MPV) and platelet distribution width (PDW) were also significantly higher in COVID-19-infected patients who died. A significant negative correlation was found between mean platelet volume and platelet count in the whole population (Pearson correlation coefficient: -0.39; $p<0.001$), and this was also found in the group of patients not requiring intensive care (Pearson correlation coefficient: -0.42; $p<0.001$). A slight but statistically significant increase in the number of immature granulocytes (IG) was found in patients with fatal outcomes (Figure 2).

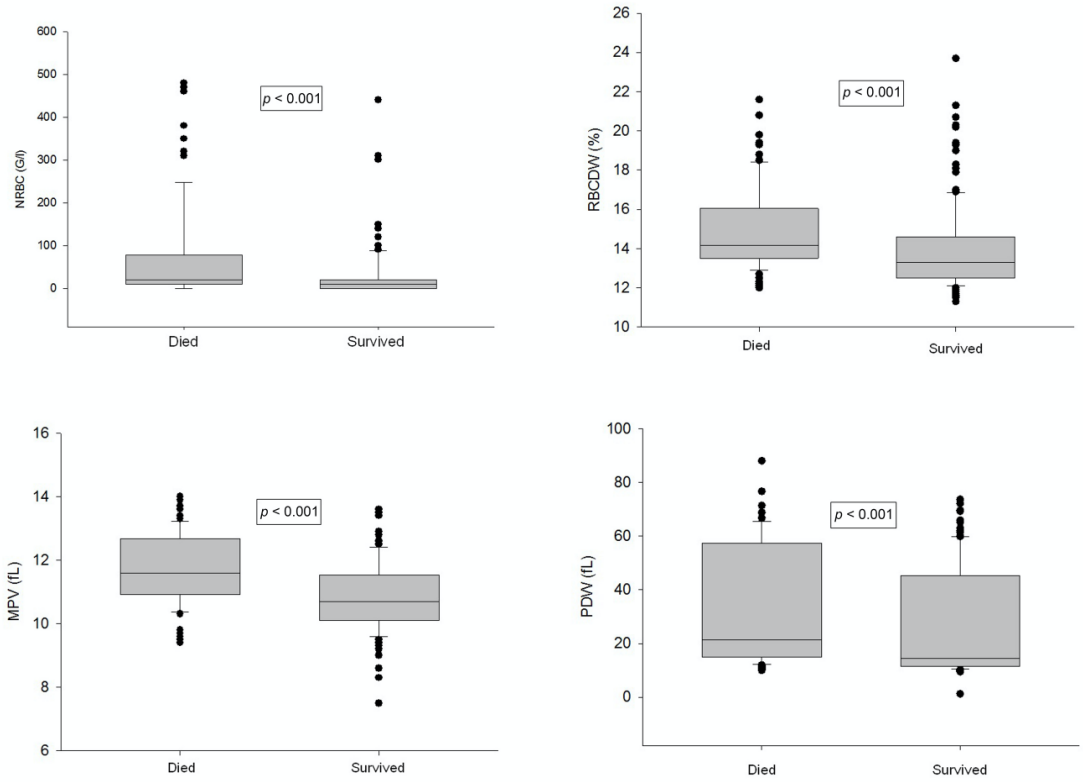

Figure 1 - Analysis of haematopoietic stress parameters (NRBC, RBCDW, MPV, PDW) in the whole patient population. Grouping was based on fatality vs survival.

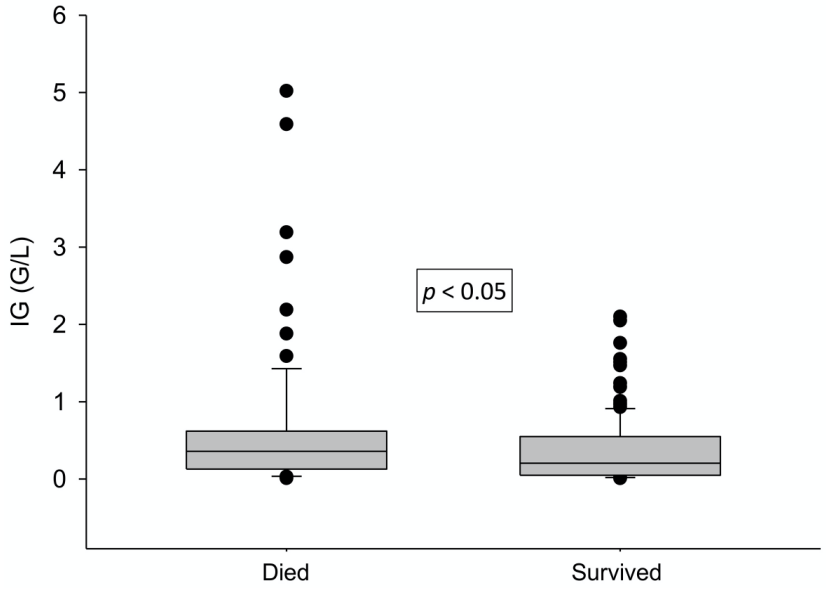

Figure 2 - The number of immature granulocytes (IG) in the total patient population. Grouping was based on fatal outcome vs survival.

In a subsequent analysis, we investigated whether there was a correlation between the severity of lung involvement and laboratory parameters indicative of haemopoietic stress. In the whole patient population, we could not detect a correlation between the % of lung areas affected by infection and the percentage of nucleated red blood cells (NRBC: r2= 0.03, p = 0. 69), mean platelet volume (MPV: r2= 0.05, p = 0.43), platelet distribution width (PDW: r2= 0.13, p = 0.07) and immature granulocyte count (IG: r2= 0.03, p = 0.7).

Comparison of clinical and laboratory parameters between COVID patients requiring and not requiring intensive therapy

When we grouped patients according to whether they required ICU treatment or not, we found statistically significant differences between the two groups in both the percentage of lung involvement and laboratory parameters in critically ill patients. In addition to the elevated laboratory parameters characteristic of inflammation in the critically ill patients, it was also evident that laboratory values characteristic of haemopoietic stress (NRBC, IG, MPV, PDW) were significantly elevated. Thus, the increase in haematopoietic stress was observed in parallel with the severity of the disease. The specific data are summarized in Table 2.

Parameter	**ICU (n=95)**	**Non-ICU (n=111)**	**P-value**
Age (years)	65 (57-70)	67 (53-76)	p=0.14
Female / Male	35/60	60/51	Chi^2=5.98, P=0.01
Lung involvement (%)	60 (20-80)	20 (15-50)	p<0.001
Hgb (g/L)	121 (98,2-134)	126 (110.2-140)	p=0.03
Htc (%)	0,36 (0,29-0,39)	0,37 (0,33-0,41)	p=0.06
WBC (G/L)	14,5 (10,7-20,1)	9,2 (6,3-12,7)	p<0.001

Table 2 - Clinical and laboratory characteristics of the total COVID population. Patients were grouped according to the need for intensive care unit treatment. Median values and IQR of 25-75%, and mean values and standard deviation were given, depending on the distribution of the data.

PCT (µg/L)	0,2 (0,1-0,9)	0,1 (0,1-0,3)	p<0.001
CRP (mg/L)	79,5 (19,5-149,1)	19,7 (4,3-84,4)	p<0.001
D-dimer (mg FEU/L)	2,1 (1,2-15,5)	0,9 (0,5-1,4)	p<0.001
NRBC (G/l)	20 (10-60)	10 (0-20)	p<0.001
RCDW (%)	13,8 (13,0-14,9)	13,7 (12,5-15,1)	p=0.6
IG (G/L)	0,42 (0,20-0,75)	0,16 (0,04-0,39)	p<0.001
MPV (fL)	11,4±1,2	10,9±1,2	p<0.01
PDW (fL)	19,9 (13,7-57,7)	14,5 (11,6-44,7)	p<0.001

Table 2 (continued) - Clinical and laboratory characteristics of the total COVID population. Patients were grouped according to the need for intensive care unit treatment. Median values and IQR of 25-75%, and mean values and standard deviation were given, depending on the distribution of the data.

Analysis of COVID-19 patients treated in the intensive care unit

Grouping of clinical and laboratory findings was also performed in the ICU-only population. In this analysis, the criterion for classification was whether the outcome of the patients was good (survival) or fatal. Routine laboratory parameters (Hgb, Htc, WBC, PLT, D-dimer) did not differ between the two groups. In fact, statistically significant differences could only be detected in routine inflammatory parameters (PCT, CRP) (Table 3).

Parameter	**Died** **(n=49)**	**Survived** **(n=46)**	**P-value**
Age (years)	67 (59.0-72.2)	64 (53.2-67.0)	P< 0.05
Female / Male	15/34	20/26	Chi^2 = 6.49 P=0.01
Lung involvement (%)	50 (28.7-76.2)	70 (20-80)	P=0.63
Hgb (g/l)	120.0 (95.7-129.5)	124.5 (108.0-136.0)	P= 0.11

Table 3 - Comparison of clinical and laboratory characteristics of ICU patients. Median values and IQR of 25-75% are given.

Htc (%)	0.35 (0.28-0.39)	0.37 (0.33-0.39)	P= 0.16
WBC (G/L)	15.2 (10.2-20.0)	14.3 (11.6-20.1)	P= 0.76
PLT (G/L)	229.0 (128.7-365.2)	268.0 (193.0-367.0)	P= 0.189
CRP (mg/L)	90.8 (30.3-177.9)	52.1 (14.0-121.9)	P< 0.05
PCT (µg/L)	0.44 (0.1-1.5)	0.1 (0.1-0.5)	P< 0.05
D-dimer (mg FEU/L)	2.1 (1.4-14.2)	2.9 (1.1-16.3)	P=0.86

Table 3 (continued) - Comparison of clinical and laboratory characteristics of ICU patients. Median values and IQR of 25-75% are given.

Comparison of parameters indicative of haematopoietic stress in survivors and deceased patients requiring intensive care

The nuclear red blood cell count (NRBC) was not different in the survivor and fatal outcome groups, but the red blood cell distribution width (RBCDW) was found to be slightly higher in the deceased. The mean platelet volume (MPV) was also higher in the patients who died compared to those who survived, but no difference was found in platelet distribution width (PDW) (Figure 3).

In the whole ICU population, we found a strong negative correlation between mean platelet volume (MPV) and platelet count (PLT) (Pearson correlation coefficient: -0.37; $p<0.001$). Subgroup analysis revealed that this negative correlation was only present in deceased patients (correlation coefficient: -0. 37; $p<0.01$), but not for surviving patients (correlation coefficient: -0.27; $p=0.06$). The number of immature granulocytes (IG) did not differ between the two groups (Median: 0.40 CI: 0.17-0.69 vs. 0.46 CI: 0.20-0.77; $p=0.74$).

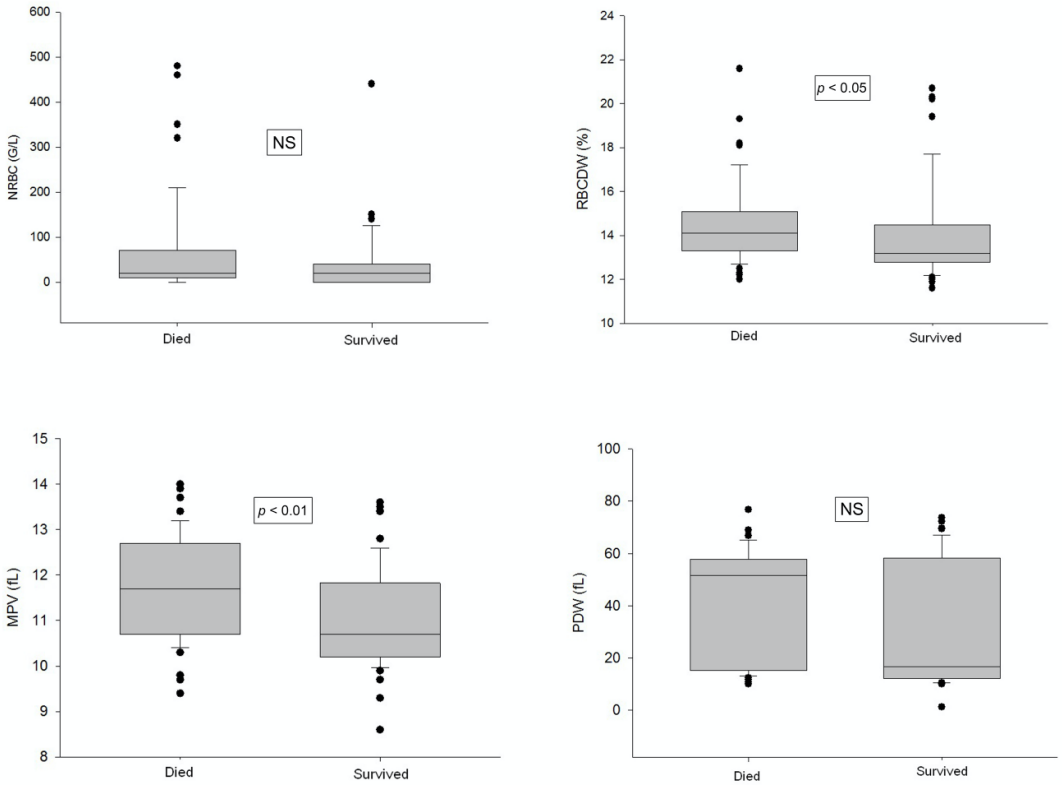

Figure 3 - Comparison of haematopoietic stress parameters (NRBC, RBCDW, MPV, PDV) in the group requiring intensive care unit treatment. Grouping was based on fatal outcome vs. survival (NS: not significant)

4.2 Assessment of the severity and clinical course of critical illness polyneuropathy (CIP) in septic patients

Twenty-one critically ill patients (APACHE II score ≥ 12 at referral) were included in the study. The mean age of patients was 63.52±16.9 years, male:female ratio was 15:6. At the time of referral, the APACHE II score was 15.38±6.19, the mean SAPS II score was 37.95±12.43, and the mean SOFA score was 7.14±3.28. The clinical characteristics of our patients are summarized in Table 4. At the time of ICU admission, all patients met the clinical criteria for sepsis and all patients had positive culture findings to justify an infectious origin. Clinical signs of septic shock were noted in 10 of the 21 patients. At the time of the first ENG examination, 13 of the 21 patients were ventilated and received analgo-sedation to ensure this. In these patients, muscle tone could not be assessed during clinical examination. In the remaining 8 patients where muscle tone could be assessed, a generalised decrease in muscle tone was found in 3 patients at the time of ICU admission, and in 5 patients muscle tone was normal at

this time. The intrinsic reflexes of the limbs (biceps, triceps, radius, ulna, patella and Achilles reflexes) were sluggish in 8 of 21 patients on clinical examination, of these 6 patients had decreased muscle tone on muscle tone examination, and in 2 patients a generalised decrease in muscle strength was observed on routine neurological examination.

Results of electroneurographic studies:

- During the first examination after admission, 18 of the 21 patients were observed to have at least 20% reduction in motor (MNCI) and sensory (SNCI) nerve conduction indices (see Table 4). We found no differences between the two sides in the measurements, so we then averaged the results of the two-sided registries and used these values in the comparative statistics. Both median and ulnar nerves compound muscle action potential (CMAP) were significantly lower than laboratory reference values in healthy subjects; median nerves: 2.3 mV (IQR: 1.5/3.425) vs 8.4 mV (IQR: 6.7/9.4), $p<0.001$; ulnar nerves: 2. 9 mV (IQR: 2.18/3.88) vs 7.4 mV (IQR: 6.3/8.4), $p<0.001$. The same was observed for sensory nerve action potential (SNAP); median nerve: 2.1 µV (IQR 1. 2/4.33) vs 5.5 µV (IQR 4.8/8), $p<0.001$; ulnar nerve: 2 µV (IQR 1.23/4) vs 5.2 µV (IQR 4.1/6.4), $p<0.001$. It was therefore found that the reduction in action potential amplitude affected both motor and sensory fibres of the nerves. Calculated median motor nerve conduction index (MNCI) was 61% (IQR 40.63/72.38) in the study patients compared to 153% (IQR 136.63/178.25) in control subjects ($p<0.001$). Similarly, the calculated value of the median sensory nerve conduction index (SNCI) was 44% (IQR 29.25/75.13) in our patients and 110% (IQR 92.63/140.99) in the control population ($p<0.001$). A comparative analysis of the values is shown in Figure 4. At the first examination, after referral, we found normal ENG test results in 3 of 21 patients (100-80% MNCI and SNCI), 8 patients with mild (80-50%) and 10 patients with severe (<50%) amplitude reduction of the indices (Table 4). While nerve conduction amplitude was reduced, conduction velocity values were normal in almost all cases.

	Sex (F/M)	Age (years)	Diagnosis	DM (+/-)	APACHE II	SAPS II	SOFA	SIRS, Sepsis, Septic shock	Respiratory mode	MNCI/SNCI	5 day follow-up	Weekly follow-up	Outcome (D/Di)
01.	M	63	SAP	+	15	29	4	Szeptikus sokk		50-80 %	↓	↓	D
02.	M	64	SAP	+	20	42	6	Szeptikus sokk	SIMV	50-80 %	↓		D
03.	F	38	Peritonitis	-	13	35	5	Szepszis	SIMV	50-80 %	↑		Di
04.	M	67	UTI	+	20	50	8	Szeptikus sokk	CPAP	<50 %	↑		Di
05.	M	84	SAP	+	16	45	6	Szepszis	CPAP	<50 %	→		D
06.	F	58	Peritonitis	-	13	32	6	Szeptikus sokk		<50 %	↑		D
07.	M	51	SAP	-	15	39	9	Szeptikus sokk	IPPV	<50 %	↓		D
08.	M	85	Cholecystitis	+	23	47	12	Szepszis		50-80 %	→	→	Di
09.	M	79	Peritonitis	-	17	68	9	Szepszis	CPAP	50-80 %	→	↑	Di
10.	M	36	SAP	-	12	17	4	Szepszis		80-100 %	→		Di
11.	M	26	Peritonitis	-	16	28	9	Szeptikus sokk		80-100 %	↓	↑	Di
12.	M	53	AAAR	-	18	45	9	Sokk	CPAP	50-80 %	↓	↓	D
13.	M	70	SAP	+	13	31	5	Szepszis	CPAP	<50 %	↓	↓	Di
14.	M	57	Pneumonia, ARDS	+	14	30	5	Szepszis	PRVC	<50 %	↓		Di
15.	M	49	Perineal abscess	-	12	30	10	Szeptikus sokk		80-100 %	↓		Di
16.	F	78	Peritonitis	+	20	58	8	Szeptikus sokk	CPAP	<50 %	↓		D
17.	F	85	Wound infection	+	20	48	6	Szepszis	CPAP	<50 %	→		Di
18.	F	83	Ileus, Peritonitis	-	19	51	6	Szeptikus sokk	CPAP	<50 %	↓		D
19.	F	71	Oesophageal perforation	-	12	40	10	Szepszis	SIMV	50-80 %	→	→	D
20.	F	71	Pyothorax	-	15	32	2	Szepszis		<50 %	→		D
21.	F	66	Peritonitis	-	24	46	7	Szepszis		50-80 %	↑	↑	Di

Table 4 (previous page) - Main clinical characteristics of the CIP patients included in our study; M: male, F: female, SAP: serious acute pancreatitis, UTI: urinary tract infection, AAAR: abdominal aortic aneurysm rupture, ARDS: acute respiratory distress syndrome, DM: diabetes mellitus, +: DM present, -: DM absent, SIMV: synchronized intermittent mandatory ventilation, CPAP: continuous positive airway pressure, IPPV: intermittent positive pressure ventilation, PRVC: pressure regulated volume controlled (ventilation), ↑: MNCI/SNCI increase, ↓: MNCI/SNCI decrease, →: MNCI/SNCI stagnation, D: death, Di: discharge from ICU

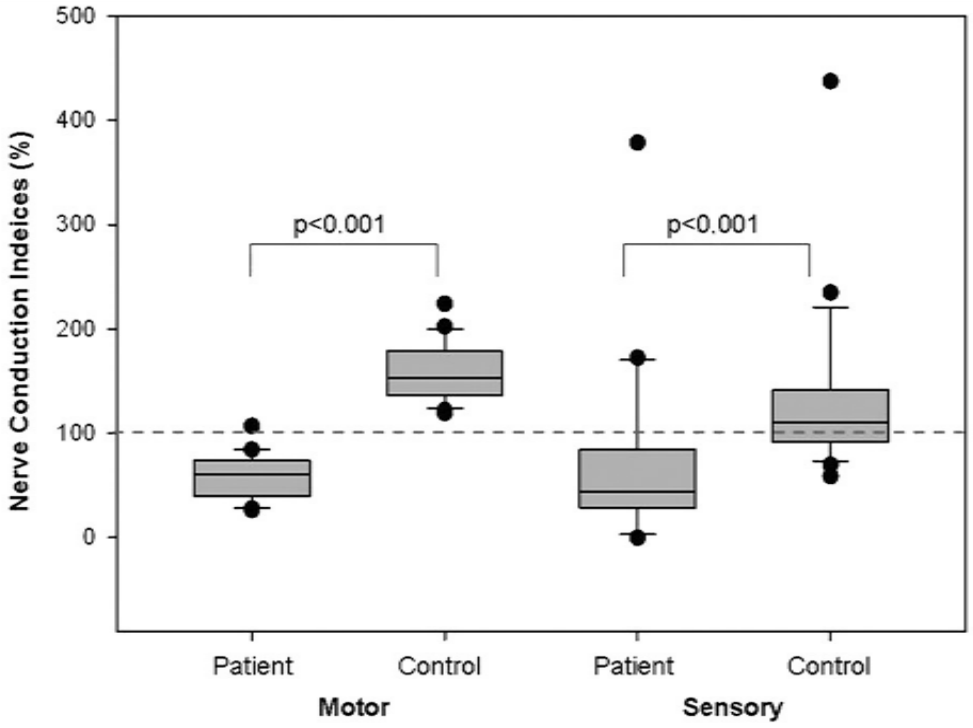

Figure 4 - Motor and sensory nerve conduction index scores compared to age-matched healthy controls in the first study. The dashed line indicates the laboratory reference values.

- Changes in the results of ENG tests during the first 5 days of treatment: during the first 5 days, an improvement in electroneurographic results was observed in 4 patients and no change in 7 patients. Almost half of the patients (10 patients) showed a worsening of electrophysiological findings during the first 5 days (Table 4).
- We were able to perform electrophysiological testing at one week in 8 patients. Of the remaining patients, 7 patients died, another 6 patients were discharged from the intensive care unit and for organisational reasons we were unable to perform the follow-up ENG study. Based on the available 1-week measurement results, we

observed improvement in 3 of the 8 patients, unchanged electrophysiological status in 2 patients and worsening in another 3 patients.

Correlation between electrophysiological findings recorded at admission and patient outcome: None of the patients in whom the ENG test at admission was normal died. In contrast, 4 of our 8 patients diagnosed with mild ENG abnormalities at the time of admission (4/8; 50%) and 6 of 10 patients with severe ENG abnormalities (6/10; 60%) had fatal outcomes. One of the patients with electrophysiological improvement during the 5-day follow-up period (1/4; 25%), 3 of the patients with unchanged ENG results (3/7; 43%), and 6 of the patients diagnosed with worsening electrophysiological results during the 5-day follow-up period (6/10; 60%) died during the follow-up period.

Correlation between clinical severity and nerve conduction velocity indices:
SAPS II and APACHE II scores showed significant negative correlations with both ulnar nerve and median nerve CMAP and SNAP amplitudes, and motor and sensory conduction indices, respectively. In other words, the more severe the clinical condition of the patient at admission, the more pronounced was the degree of detectable nerve damage. Among the general scoring systems, the correlation with SAPS II was found to be the strongest (Table 5).

	SAPS II		**APACHE II**		**SOFA**	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
N. medianus CMAP	-0,374	p<0,001	-0,237	p<0,05	-0,193	NS
N. ulnaris CMAP	-0,602	p<0,001	-0,462	p<0,001	-0,368	p<0,001
MNCI	-0,541	p<0,001	-0,388	p<0,001	-0,307	p<0,01
N. medianus SNAP	-0,462	p<0,001	-0,215	p<0,05	-0,141	NS
N. ulnaris SNAP	-0,445	p<0,001	-0,325	p<0,001	-0,149	NS
SNCI	-0,458	p<0,001	-0,285	p<0,01	-0,136	NS

Table 5 - Examination of the relationship between some parameters of electroneurography and different severity scores using Spearman correlation analysis.

The strongest correlation was found between the SAPS II score and the CMAP of the ulnar nerve (Spearman's r = -0.602) and the motor nerve conduction index (MNCI) (Spearman's r = -0.541) (Figure 5).

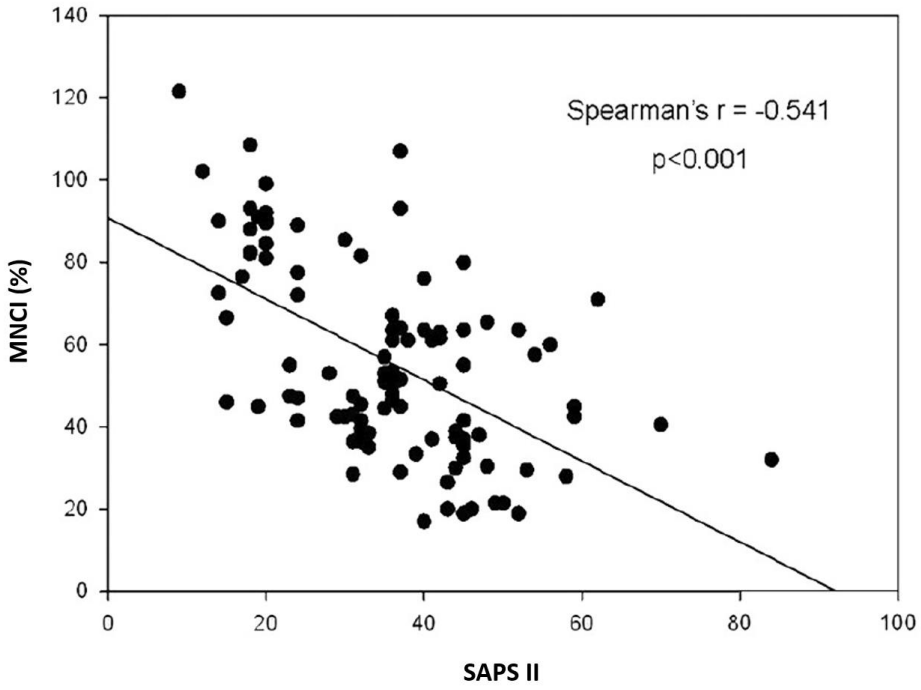

Figure 5 - Correlation between the Motor Neural Conduction Index (MNCI) and the SAPS II score.

5. Discussion

As mentioned in the introduction, the success of ICU treatment is determined by a complex combination of many factors. Including but not limited to, the most important influencing factors are summarised in Table 6.

It can be seen that the success of ICU treatment is a complex system that is determined not only by the medical condition requiring ICU treatment but also by the comorbidity of the patients, the therapeutic interventions, the complications that are inevitably associated with the treatment, and a number of human factors related to the individuals involved in the care, the team and the care system. The success of a patient's treatment can therefore be determined by the individualised optimalisation of these many care factors for that particular patient. In this thesis, we had the opportunity to study three of the factors that influence outcomes.

Medical condition indicating admission to intensive care unit	• Respiratory failure (e.g. pneumonia, ACPO – acute cardiogenic pulmonary oedema, AECOPD – acute exacerbation of chronic obstructive pulmonary disease, PE – pulmonary embolism, ARDS – acute respiratory distress syndrome) • Severe sepsis / septic shock / multi-organ disfunction os failure • Respiratory and circulatory arrest / PCAC (post-cardiac arrest care) • Severe cardiac event (e.g. AMI – acute myocardial infarction, arrhythmia, cardiogenic shock) • Hypertensive crisis conditions (e.g. aortic dissection, preeclampsia/eclampsia) • Acute, severe deterioration in neurological status (e.g. stroke, traumatic / non-traumatic intracranial haemorrhage, status epilepticus) • Polytrauma • Severe renal impairment, severe disturbances of fluid / electrolyte / acid-base balance • Liver failure • Severe/life-threatening poisoning • Severe endocrine-metabolic disorders (e.g. DKA – diabetic ketoacidosis) • Acute abdomen (e.g. severe acute pancreatitis, ileus, perforation, peritonitis, mesenteric thrombosis, AAAR – abdominal aortic aneurysm rupture) • Bleeding conditions (e.g. gastrointestinal bleeding, obstetric/gynaecological bleeding, respiratory bleeding) • Major/extended surgery, intraoperative surgical/anesthesia complication
Chronic comorbidities	• DM (diabetes mellitus) • COPD (chronic obstructive pulmonary disease) • HT (hypertension), IHD (ischaemic heart disease), heart failure • Chronic renal failure • Cirrhosis of the liver • Immune deficiency status / ISU (immunosupression) • Malignancy / oncotherapy • Cachexia / other deficiency states • Obesity • Abuses • Dementia
Age	• Older age

Table 6 - Key factors determining the outcome

Therapeutic interventions for the current condition	*Interventions before admission to intensive care* • Stabilisation • Transport *Intensive care* • Artificial airway management • Mechanical ventilatory support • Pharmaceutical/mechanical circulatory support • Extracorporeal (RRT – renal replacement therapy / ECMO – extracorporal membrane oxygenisation/ immunomodulation) treatments • Antimicrobial therapy • Artificial nutrition • Specialist care • Physiotherapy *Interventions following intensive care unit discharge* • General care • Somatic and psychological rehabilitation • Specialist care
Complications	• Mechanical complications associated with invasive devices • Drug side-effects • Nosocomial infections • VALI / VILI (ventilation associated / induced lung injury) • Blood glucose anomalies • Fluid/electrolyte/acid-base balance disorders • Haematopoietic disorders • Thromboembolic events • Bleeding (e.g. gastrointestinal bleeding, bleeding from surgical site) • Decubitus ulcers • CIP/CIM (critical illness polyneuropathy / myopathy) • Patient movement/transportation related complications
Human factor	*At individual caregiver level* • Physical condition (illness, hunger/thirst) • Mental state (rest, stress management, mind-altering drug) • Readiness/experience *At team level* • Number of people • Roles • Plan / common mental picture • Communication *At medical system level* • Infrastructure, physical/personnel conditions • Procedures / protocols • Quality assurance / audit • Ongoing training

Table 6 (continued) - Key factors determining the outcome

1) The COVID-19 epidemic has placed a significant burden on intensive care units. Optimizing resources at a 3rd progression level care facility included, in addition to patients requiring ventilation, the challenge that, in addition to operating the "needs-intensive wards" created for critical-condition COVID-19 patients, we also had to ensure the ability to meet the demand for acute surgical care both locally and in case of regional priority interventions (neurosurgery, thoracic surgery, cardiac surgery, paediatric surgery, burns surgery, care of high-risk pregnancies). In our first study, we investigated the ability of the haemopoietic stress response to predict outcome based on two months of patient flow data from a 58-bed COVID intensive care unit and its integrally linked general COVID department at the Nagyeredei Campus of the University. In doing so, we identified some factors that were associated with poor outcome in patients requiring intensive care.
2) In another study, we aimed to prospectively investigate critical illness polyneuropathy (CIP), one of the most common and challenging complications of septic patients in the ICU, and found that electrophysiological evidence of both sensory and motor nerve involvement can be detected in the early phase.
3) In our third study, we looked at the role of the human factor and the related organisational tasks in our own central operating block of 10 operating theatres. The focus of the study was on the role of the anaesthetist in stabilising the condition of critically ill patients undergoing surgery and ensuring safe intra-hospital transport from the operating theatre to the intensive care unit. In doing so, we have reviewed our current practice and formulated a set of procedures adapted to local conditions, which will form the basis for the future operation of our institute.

Our study of patients with COVID-19 clearly demonstrated stress activation of the bone marrow haematopoietic system in patients with adverse outcomes following COVID-19 infection. In the entire COVID-19 population (ICU and non-ICU patients), early granulocyte and platelet forms were observed in addition to early immature erythrocyte cell lines and showed a clear association with mortality.

An important initial feature of SARS-CoV-2 virus infection is severe damage to the airway epithelium, which results in the virus itself and the consequent release of factors into the systemic circulation. It is currently known that alveolar macrophages and alveolar epithelial cells play a crucial role in the excessive release of cytokines and consequently in the induction of the systemic immune response (SIRS). As knowledge has grown, it has become increasingly clear that, in addition to lung parenchymal damage and associated hypoxaemia, uncontrolled release of the systemic immune response and consequent activation of the coagulation system are fundamental determinants of the subsequent clinical outcome of COVID-19 infection. In addition to generating SIRS, the dramatic release of cytokines also enhances the production of acute phase proteins through activation of hepatocytes. Acute phase proteins are known to play a crucial role in the activation of bone marrow haemopoiesis during various inflammatory conditions.

The nucleated red blood cells (NRBCs) are not detectable in peripheral blood in healthy individuals. They are in fact erythrocyte precursor cells that filter through the bone marrow fenestrations during maturation and thus do not normally appear in the blood. Their appearance is due either to markedly increased erythropoiesis or to impairment of filtration mechanisms. In clinical practice, peripheral blood nucleated erythrocytes occur in severe arterial hypoxia, severe systemic infection, or in conditions characteristic of massive haemorrhage. Some authors have reported a clear association between the appearance of nucleated erythrocytes and ICU outcome: the appearance of nucleated erythrocytes is a sign of worse prognosis in both surgical and internal medicine critical conditions. In another study, 220 NRBC/µL was found to be a cut-off value in patients with ARDS to distinguish between fatal and non-fatal outcomes. At the time of our study, little data were available on NRBC in relation to SARS-CoV-2 infection. Linssen and colleagues attempted to establish and validate a haemocytometric scoring system for the dynamics and prognosis of infection. One element of this was NRBC, and their reported data series suggests that there is a significant difference in the number of NRBCs between critically and non-critically ill COVID-patients.

Similarly, we found elevated NRBC in the entire population of patients hospitalised for SARS-CoV-2 infection and it should also be noted that in patients who died following infection, NRBC was almost double the NRBC of survivors (median and IQR: 20. 0/10.0-80.0/ vs. 10.0/0.0-20.0/). We also observed that when critically ill patients were classified according to survival, no statistically significant difference was found between those who died and those who

survived (median and IQR: 20. 0/10.0-70.0/ vs. 20.0/0.0-40.0). However, the fact that the red blood cell distribution width (RBCDW) was significantly higher in patients who died in the ICU than in patients who survived ICU treatment (median and IQR: 14.1/13.3- 15.0/ vs. 13.2/12.8-14.4) suggests that erythropoiesis is also significantly activated with increasing severity of illness. Previous clinical studies have confirmed that the erythrocyte distribution width is a strong predictor of ICU mortality, whether we consider immediate ICU mortality or in-hospital mortality after ICU treatment: a value of 14.5% or above is a very sensitive predictor of fatal outcome. Similar to our study, Gowda and colleagues have demonstrated a correlation between red blood cell distribution width and mortality in COVID-19 patients.

We have also demonstrated activation of the granulocyte lineage of the haematopoietic system in patients treated for coronavirus infection. The number of immature granulocyte forms (IGs) was significantly different in the intensive care and non-intensive care groups. Our observation differs slightly from the results of Linssen and colleagues, who failed to detect a significant further increase in the number of immature granulocyte forms in patients with coronavirus infection not requiring ICU treatment. Our study is similar to this study in that we were able to detect the appearance of immature granulocyte forms in the entire patient population of patients with SARS-CoV-2 infection. We demonstrated a difference in the number of immature granulocytes between patients requiring intensive care and patients not requiring intensive care (ICU patients had higher numbers of immature granulocytes), but we could not detect a correlation between ICU survival and the number of immature cell forms. Considering that granulocytes play a major role in the production of inflammatory cytokines and in the generation of the cytokine storm, our results suggest that granulocyte activation in the bone marrow occurs early in the course of infection and continues with the same intensity throughout the course of the disease.

Thrombotic events are one of the most common complications of SARS-CoV-2 infection and a major determinant of fatal outcome. Studies to date have shown that several factors may be responsible for platelet activation following infection: direct binding of the pathogenic microorganism to the platelet surface and damage to the endothelium, with consequent release of von Willebrand factor, have been described. However, it should also be remembered that the systemic inflammatory response alone leads to activation of the coagulation cascade and the production of thrombin also activates platelets. The direct platelet-activating effect of respiratory viruses has been described previously in patients with

viral pneumonia. It is well known that platelet count (PLT) is reduced in respiratory viral infections (including coronavirus infection) and that reduced platelet count is a predictor of poor outcome. We have been able to confirm these previous observations in our own patient data: in the entire SARS-CoV-2 infection cohort, we ourselves found lower platelet counts in patients who had a fatal outcome compared to those who survived the infection. Higher mean platelet volume (MPV), indicative of the presence of circulating, large, mostly reticular platelets, is one of the most sensitive markers of platelet activation, as previously observed. Previous studies have already demonstrated differences in MPV in COVID-19 patients with mild to moderate symptoms. Higher MPV values may be predictive of disease progression and fatal outcome. Similar to this previous study, we also found higher MPV values in patients with fatal outcome and this was true for our whole patient population (ICU + non-ICU) as well as for our ICU-only patients. A previous reference in the literature in ICU patients referred to the MPV/PLT ratio in critically ill patients as a very specific marker of platelet activation, and we investigated this as well. We found that both in our total COVID-19 patient population and in its ICU-only patient group, a statistically very high correlation between the two parameters was detected: the lower the platelet count, the higher the MPV values measured. Another characteristic parameter of the appearance of early platelet forms, platelet distribution width (PDW), was found to be a similarly useful predictive parameter: in the total patient population, it was significantly higher in patients who died than in those who survived the disease. The same association was not found in the subgroup of ICU patients. It should be noted that already in previous literature reports, PDW was considered as a confirmatory factor for the presence of SARS-CoV-2 infection (mild form) when its value exceeded 12.7 fL, and its prognostic function was also demonstrated - when its elevation exceeded 17%, the probability of death increased 6.3-fold. Comparing these observations with our results, we can say that in our own overall SARS-CoV-2 population, PDW was found to be 21.4% (14.9-57.5%) in patients who died and 14.4% (11.6-45.1%) in patients who survived. Although the differences did not reach the limit of statistical significance in our ICU subgroup (51.5 /15.2-57.6/ % in deceased vs. 16.7 /12.3-57.8/ % in survivors, $p = 0.09$), the results still show a trend towards platelet activation being a significant determinant of outcome in COVID-19 patients. This is supported by a recently published study that achieved a 50% reduction in mortality in patients with SARS-CoV-2 infection with a single 81 mg aspirin dose.

Thus, our assays have clearly demonstrated activation of the bone marrow haematopoietic system in SARS-CoV-2 patients for all cell lines. We have also described some parameters that showed a clear association with mortality in both the overall and the intensive care population. Our limited number of cases and our single-centre study do not allow us to define pathogenicity cut-off values for these laboratory values.

In our study of polyneuropathy in critically ill patients, we found that electrophysiological abnormalities can be detected the day after admission. In our opinion, it is important to point out that in our patient group, 85% of patients showed evidence of electrophysiological abnormalities in order to improve patient outcome and to aim for early rehabilitation. In many cases, the sedation used in the management of a critical condition may mask the loss of function and is only detected later in a more severe form. This high rate has been confirmed by previous studies.

The pathophysiological background of neuromuscular abnormalities in critically ill patients is not yet fully understood, but is likely to be a multifactorial process. In addition to individual predisposition (alcoholism, diabetes mellitus, autoimmune or rheumatological processes as underlying disease), bioenergetic disturbances, microvascular lesions, inflammation and alterations in cellular metabolism are thought to be involved. Muscle biopsy studies early in the process have also confirmed that the initial period is not so much histological as functional changes, with at most mild signs of muscle necrosis, despite the fact that sensory nerve conduction amplitudes are already significantly reduced.

In line with this, in a significant proportion of our patients, electrophysiological signs of critical neuropathy were already detectable after referral. Among them, 4 patients showed improvement in both motor and sensory amplitudes during the 5-day follow-up period (including 1 patient with complete normalization). In patients who were allowed weekly follow-up, we observed improvement in electrophysiological status in 3 additional patients. These data suggest that in some cases, the initial functional nerve conduction abnormalities may undergo a spontaneous improvement process. Our observations are confirmed by the report of Ahlbeck and colleagues, who followed their patients for one month and found that neuromuscular abnormalities associated with critical status showed fluctuations during the follow-up period. They also confirmed that cases that started as neuropathies and did not

spontaneously recover showed a tendency to develop myopathy associated with critical status.

Regarding the relationship between CIP-CIM and outcome, two previous studies have shown a link between the development of neuropathy associated with critical illness and higher mortality. Khan and colleagues went even further and demonstrated that septic patients who had an abnormal post-admission ENG examination had significantly higher mortality. In our study, the predictor of mortality was only partly the electrophysiological difference detected on admission, but rather the electrophysiological trend in the first week: patients who showed improvement had a better prognosis than those who showed electrophysiological deterioration. It was also confirmed that the development of CIP-CIM limits or slows down rehabilitation after improvement of the septic pathology, which may be another explanation for the poor outcome. We can therefore say that the outcome depends on the severity of the initial electrophysiological impairment and its dynamics during the first week (worsening or improving trend). It should be noted, although our case numbers are too small to draw a far-reaching conclusion, that younger patients were more likely to have improved electrophysiology and a better prognosis in the early phase.

Previous studies and the present study have shown that the severity of the critical condition and the duration of multi-organ involvement are independent risk factors for CIP. In a previous prospective observational study, APACHE II and III severity scores were found to be good predictors of neuromuscular lesions associated with critical status. In our own study, we were unable to demonstrate an association between clinical severity score at admission and electrophysiological abnormalities at admission. We also did not observe that electrophysiological abnormalities at admission predicted a trend towards electrophysiological deterioration during the first 1 week. Rather, we observed an inverse correlation between daily SAPS II and APACHE II scores and motor and sensory nerve conduction indices, i.e., the more severe the patients' condition, the more severe the electrophysiological abnormality at follow-up. This suggests that the change in peripheral nerve function (improvement or worsening) is most closely related to the change in overall condition. This also emphasises the need for early, effective sepsis treatment.

Based on our studies, we can say that electrophysiological abnormalities reflect the response of the whole body during the systemic inflammatory reaction. The early electrophysiological abnormalities, especially their progressive nature in the first days, may point to severe

damage to peripheral nerves by sepsis and the risk of myopathy associated with criticality. Our observation that effective treatment of the septic process early in the course of sepsis results in spontaneous improvement of early neuropathic abnormalities is another contribution to the importance of timely, complex and effective treatment of sepsis.

6. Independent findings

1. We are among the first in the international literature to study the stress response of the haematopoietic system in patients with SARS-CoV-2 infection.
2. We found that the haemopoietic stress response is more pronounced in critically ill coronavirus-infected patients.
3. We found that a greater number of nucleated red blood cells in the peripheral blood cell count is a sign of poor prognosis.
4. We also demonstrated activation of the granulocyte lineage of the haematopoietic system in patients treated for coronavirus infection. The number of immature granulocyte forms was significantly different in the intensive care and non-intensive care groups.
5. In the overall SARS-CoV-2 infection group, lower platelet counts were found in patients with fatal outcomes compared to those who survived the infection. In parallel, we found higher mean platelet volume values in patients who had a fatal outcome and this was true for our whole patient population (ICU + non ICU) as well as for ICU-only patients.
6. In our prospective electrophysiology study in critically ill patients, we demonstrated that electrophysiological signs of critical neuropathy were already detectable after referral. We found a correlation between the severity of neuropathy and the severity scores for critical status.
7. We confirmed that electrophysiological progression during the first week after admission is a predictor of poor outcome in critically ill patients.
8. Our summary on perioperative transport of critically ill patients contributed to the renewal of our own institutional protocol in this field.

7. Summary

Assessing the outcome of critically ill patients is very important for evaluating and improving the quality of ICU activity. However, this is not an easy task, because the fate of patients is determined by a number of interrelated and interacting factors. In this thesis, we aimed to study the haemopoietic stress response in COVID-19 patients, the CIP (critical illness polyneuropathy) associated with sepsis and the transport of ICU patients.

By investigating the relationship between COVID-19 and the haematopoietic stress response, we have clearly demonstrated the activation of the bone marrow haematopoietic system in COVID-19 patients for all cell lines. The results suggest that there is a correlation between elevated levels of parameters indicative of the haematopoietic stress response and the severity of the patients' condition and fatal outcome. In the context of the prognostic function of these markers, we found that NRBC (nucleated red blood cell count) was higher in fatal cases (for the whole patient population) and in critically ill patients requiring intensive care. RBCDW (red blood cell distribution width) was higher in fatal cases (both in the total patient population and in patients requiring intensive therapy). The MPV (mean platelet volume) was higher in fatal cases (both in the total patient population and in patients requiring intensive therapy) and in critically ill patients requiring intensive care. MPV/PLT (platelet) ratio was higher in fatal cases (both in the total patient population and in patients requiring intensive therapy). PDW (platelet distribution width) was higher in fatal cases (both in the total patient population and in patients requiring intensive therapy) and in critically ill patients requiring intensive therapy. IG (immature granulocyte count) was higher in fatal cases (for the total patient population) and in critically ill patients requiring intensive care.

In the study of CIP in septic patients, we found that a significant proportion of patients treated for sepsis in the ICU have electrophysiological abnormalities suggestive of CIP at the time of admission. The results of follow-up studies suggest that, with respect to the initial ENG abnormalities, a spontaneous improvement process is initiated in some cases. With regard to the association between CIP and outcome, we found that in our study the predictor of mortality was only partly the electrophysiological abnormality detected on admission, but rather the electrophysiological trend during the first week: patients who showed improvement had a better prognosis than those who showed electrophysiological deterioration. With regard to the association between severity of condition and CIP, it was observed that there was an inverse correlation between daily SAPS II and APACHE II scores and motor and sensory nerve conduction indices, i.e. the more severe the patients' condition, the more severe the electrophysiological abnormality during the follow-up period. This suggests that changes in peripheral nerve function (improvement or worsening) are most closely related to changes in overall condition.

The third part of the thesis is based on an internationally commissioned summary, summarising the role of the anaesthetist in the perioperative transport of critically ill patients. Our publication contributed to the renewal of our own institutional protocol in this field.

8. Abbreviations

AAAR – abdominal aorta aneurysm rupture

ACPO – acute cardiogenic pulmonary oedema

AECOPD – acute exacerbation of chronic obstructive pulmonary disease

AMI – acute myocardial infarction

APACHE II – acute physiology and chronic health evaluation score (2nd version)

ARDS – acute respiratory distress syndrome

CAUTI / CA-UTI – catheter associated urinary tract infection

CIM – critical illness myopathy

CIP – critical illness polneuropathy

CLABSI – central line associated blood stream infection

CMAP – compound muscle action potential

COPD – chronic obstructive pulmonary disease

COVID-19 – coronavirus disease of 2019

CPAP – continuous positive airway pressure

CRBI – catheter related bloodstream infection

CRP – C-reactive peptid

DGP – Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin / German Society for Pneumology and Respiratory Medicine

DKA – diabetic ketoacidosis

DM – diabetes mellitus

ECMO – extracorporal membrane oxygenisation

ENG – electroneurography

Hgb – haemoglobin

HT – hypertension

Htc – haematocrit

ICU – Intensive Care Unit

IG – immature granulocyte (count)

IHD – ischaemic heart disease

IPPV – intermittent positive pressure ventilation

IQR – interquartile ratio

ISU – immunsupression

MNCI – motor nerve conduction index

MPV – mean platelet volume

NRBC – nucleated red blood cell (count)

NS – non-significant

O2 – oxigen (molecule)

PCAC – post-cardiac arrest care

PCT – procalcitonin

PDW – platelet distribution width

PE – pulmonary embolisation

PLT – pletelet (count)

PRVC – pressure regulated volume controlled (ventilation)

RBC – red blood cell (count)

RBCDW / RDW – red (blood cell) distribution width

RRT – renal replacement therapy

SAP – serious acute pancreatitis

SAPS II – simplified acute physiology score (2nd version)

SARS – severe acute respiratory syndrome

SARS-CoV-2 – type 2 coronavirus causing severe acute respiratory syndrome

SIMV – syncronised intermittent mandatory ventilation

SIRS – systemic inflammatory response syndrome

SLS – sodium lauryl sulphate

SNAP – sensory nerve action potential

SNCI – sensory nerve conduction index

SOFA – sequential organ failure assessment (score)

UTI – urinary tract infection

VALI – ventialtor-associated lung injury

VAP – ventialtor-associated pneumonia

VILI – ventialtor-induced lung injury

WBC – white blood cell (count)

9. References

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Subject: PhD Publication List

Candidate: István László
Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

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Total IF of journals (all publications): 17,172
Total IF of journals (publications related to the dissertation): 2,776

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

25 March, 2024

10. Acknowledgements

First of all, I would like to thank the head of our department, my mentor Prof. Dr. Béla Fülesdi for his support and advice, without whose steadfast help this work would never have been completed.

Thanks to Prof. Dr. János Kappelmayer, Head of the Institute of Laboratory Medicine at the University of Debrecen, and his colleague Dr. Katalin Tisza, who collected and analysed the various laboratory data for our articles.

I am also grateful to my colleague Dr. Réka Nemes, whose scientific work provided the basis for the part of my dissertation on the "critical illness" polyneuropathy in septic patients.

Thanks to my colleague Dr. Norbert Balázsfalvi, who was my persistent helper in collecting data on COVID patients.

Thanks to all the staff of the COVID Centre, the Institute of Laboratory Medicine and the Central Intensive Care Unit of the Department of Anaesthesiology and Intensive Care at the University of Debrecen Clinical Centre, who made the studies possible through their persistent work.

Last but not least, I am grateful to my family for their patience and support.