SEMMELWEIS EGYETEM
DOKTORI ISKOLA

Ph.D. értekezések

2736.

DR. DEME DÁNIEL

Alapkutatások klinikai alkalmazása
című program

Programvezető: Dr. Vásárhelyi Barna, egyetemi tanár
Témavezető: Dr. Dr. Telekes András, címzetes egyetemi tanár

Prognostic importance of peripheral blood biomarker combinations in advanced cancer

Doctoral Dissertation

Dániel Deme, MD

Clinical Medicine Doctoral School
Semmelweis University

Supervisor: András Telekes, MD, Ph.D., honorary university professor

Official reviewers: László Csaba Mangel, MD, Ph.D., Prof.
Anna Horváth, MD, Ph.D.

Head of the Complex Examination Committee:
Miklós Tóth, MD, D.Sc

Members of the Complex Examination Committee:
Áron Cseh, MD, Ph.D.
Kinga Lakatos, MD, Ph.D.

Budapest
2022

Table of Contents

List of abbreviations

AC = adenocarcinoma

ALC = absolute lymphocyte count

AMC = absolute monocyte count

ANC = absolute neutrophil count

BC = breast cancer

CA = cancer antigen

CAR = C-reactive protein to albumin ratio

CBC = complete blood count

CI = confidence interval

CRC = colorectal cancer

CRP = C-reactive protein

D-dimer = cross-linked fibrin degradation products

D-dimer-d-LDH = D-dimer to LDH ratio

D-dimer-d-NLR = D-dimer to NLR ratio

D-dimer-d-PLR = D-dimer to PLR ratio

DNA = deoxyribonucleic acid

ECOG = Eastern Cooperative Oncology Group

GC = gastric cancer

GPS = Glasgow Prognostic Score

HNSCC = head and neck squamous cell carcinoma

HR = hazard ratio

IL = interleukin

LDH = lactate dehydrogenase

LDHxD-dimer = LDH and D-dimer scalar

LDH-d-D-dimer = LDH to D-dimer ratio

LDH-d-NLR = LDH to NLR ratio

LDH-d-PLR = LDH to PLR ratio

LMR = lymphocyte to monocyte rate

mGPS = modified GPS

NLR = neutrophyl to lymphocyte ratio

2NLRdLDH = NLR to LDH ratio

NLRdPLR = NLR to PLR ratio

NLRxD-dimer = NRL and D-dimer scalar

NLRxLDH = NLR and LDH scalar

NLR-d-Dimer = NLR to D-dimer ratio

NSCLC = non small cell lung cancer

NST = non specified type

OC = ovarian cancer

ORV = out of range value

OS = overall survival

PC = pancreatic cancer

PCA = prostate adenocarcinoma

PLR = platelet to lymphocyte ratio

PLRdLDH = PLR to LDH ratio

PLRdNLR = PLR to NLR ratio

PLR-d-Dimer = PLR to D-dimer ratio

PLRxD-dimer = PLR and D-dimer scalar

PLRxLDH = PLR and LDH scalar

PLRxNLR = PLR and NLR scalar

SCC = squamous cell carcinoma

SCLC = small cell lung cancer

SEER = Surveillance, Epidemiology, and End Results

TCC = transitional cell carcinoma

TNF = tumornecrosis factor

ULN = upper limit of normal

VEGF = vascular endothelial growth factor

1. Introduction

According to the definition by the National Institute of Health Biomarker Definitions Working Group biomarker is „a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [1]. In malignant diseases, biomarkers can be the results of (1) changes in malignant tissue compared to normal tissue, (2) changes in one type of malignancy that distinguish it from another, or (3) changes within a type of malignancy that distinguish one behavior from the other [2]. A prognostic biomarker provides information about the patients overall outcome, regardless of therapy [3]. The association between short overall survival (OS) and altered baseline values of elevated C-reactive protein (CRP) levels, decreased albumin levels, elevated cross-linked fibrin degradation product (D-dimer) levels, lactate dehydrogenase (LDH) levels, high CRP to albumin ratio (CAR), high absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) ratio (NLR) and low ALC to absolute monocyte count (AMC) ratio (LMR) have been reported.

1.1. Prognostic importance of plasma C-reactive protein (CRP) levels

CRP is an acute phase protein, which belongs to pentraxins, consisting of five coiled chains (approximately 23 kDa) around a central pole with non covalent binding. CRP was first described in 1930. Tissue injury, infection or other inflammatory stimuli can increase rapid (in hours) CRP production in the liver cells by mainly interleukin (IL) -6. IL-1β and tumornecrosis factor (TNF) may contribute in the formation and excretion of CRP in the liver. Extrahepatic CRP production is present in smooth muscle cells around arterial plaques, macrophages, monocytes, lymphocytes, neurons and in the kidney [4]. CRP may bind to autologue (e.g. modified plasma lipoproteins, damaged cell membranes, various phospholipids, small nuclear ribonucleoprotein particules, apoptotic cells) and extrinsic ligands (e.g. glicans, phospholipids, capsular or somatic parts of bacteria, fungi or parasites, plant derived compounds) [5]. Nowadays CRP is regarded as a biomarker of acute and chronic inflammation. Chronic inflammation has a documented role in the pathogenesis and growth of malignant diseases [6-7]. Progression and survival of malignant diseases correlate with CRP-elevation [8-9]. The

lowest value of poor prognostic threshold of CRP (> 0.44 mg/L) was identified in a prospective study. Different prognostic thresholds were published for CRP e.g.: > 1.04 mg/L; > 1.78 mg/L; > 2 mg/L; > 3 mg/L; > 4 mg/L; > 4.5 mg/L; > 5 mg/L; > 6.9 mg/L; > 9.8 mg/L; > 17 mg/L; > 35 mg/L; > 60 mg/L; and > 82 mg/L [6].

1.2. Prognostic importance of albumin levels

In the 16th century Paracelsus precipitated albumin from urine using vinegar, and albumin was first crystallized in 1894 [10]. It was published in 1954, that malignant disease acts as plasma protein trap, and the malignant cells utilize the degradation products of proteins for the cell division [11]. In 1986 it was revealed, that the formation of albumin is determined by the osmotic colloid pressure [12]. Other factors also contribute to albumin synthesis e.g. the inflammatory and nutritional state of the human body and hormonal factors. Albumin provides approximately 60% of serum proteins; therefore, its main function is keeping osmotic pressure in normal range [13]. Furthermore in vitro and in vivo cell protective effects of albumin are known. It neutralizes carcinogens, e.g. nitrosamines and the aflatoxin, has strong antioxidant activity, stabilizes the duplication of deoxyribonucleic acid (DNA) and protects cells against radiation [14]. In patients with localized malignant diseases moderate hypalbuminaemia (in the range of 25 g/L to 35 g/L) or normal albumin level is often present. However, during disease progression, weight loss is accompanied by significant decrease of albumin level. Reduction of albumin level can be explained on the one hand by cachexia, and on the other hand large amount of cytokine production (IL-1, IL-6, IL-8, and TNF) [15-16]. Elevated levels of IL-1, -6, -8 and TNF increase the production of acute phase proteins, while inhibits albumin production [17-19]. TNF improves the permeability of the vessel wall, through which albumin leaves the circulation, thus it contributes to hypoalbuminaemia [20]. Other process of transmigration through the vessel wall to the intercellular space is caveola formation. During this physiological process, albumin binds to caveolin-1 receptor of endothelial cells, which results in shell (caveola) formation [21]. Thus in patients with malignant diseases decrease of serum albumin level is attributed to several factors, e.g. reduced albumin production due to liver injury; reduced amino acid intake; acute or chronic inflammatory conditions.

Enormous data of the literature and clinical experience support the fact, that prognosis is predicted by nutritional state of patients suffering from locally advanced and/or metastatic malignant diseases. It is known, that in case of stress (e.g. perioperative period, chemo- or chemoradiotherapy), malnutrition can be prevented by appropriate nutrition in patients with localized malignant diseases. Stable disease and stabilisation of catabolic process can be achieved by reaching adequate nutritional state resulting in regeneration of energy store (anabolic state) [22]. In advanced malignant disease baseline higher albumin value (generally > 35 g/L) predicts better prognosis [23]. The lowest poor prognostic threshold (< 28 g/L) was confirmed both in a prospective and in a retrospective study [24]. However in the normal range of albumin [upper limit of normal (ULN) 54 g/L] multiple prognostic thresholds were identified e.g.: < 36 g/L; < 37.1 g/L; < 37.4 g/L; and < 40 g/L [23].

1.3. Prognostic importance of cross-linked fibrin degradation product (D-dimer) levels

Cross-linked fibrin degradation product (D-dimer) was first described in 1973 [25-26], which is formed principally through cascade of blood coagulation and fibrinolysis. D-dimer elevation (≥ 0.5 μg/mL) indirectly indicates the increased activation of blood coagulation cascade (hypercoagulation), which is caused by the absolute or relative dominance of procoagulant factors. In the former case excess of procoagulant factors (e.g. tissue factor, cancer procoagulant, cancer-cell-derived blood coagulating activity-1) produced by malignant cells enhance blood coagulation. Along with these processes vascular endothelial growth factor (VEGF) produced by malignant cells stimulates blood coagulation. Permeability of vessels is enhanced by VEGF, thus larger amount of coagulant factors escape from the blood plasm directly to the enviroment of malignant cells [27]. D-dimer elevation is an indicator of the proliferation of malignant cells [28]. D-dimer can be elevated in malignant diseases without thrombosis, which is explained by procoagulant factors produced by malignant cells. Among patients with malignant diseases elevated D-dimer predicts shorter OS regardless thromboembolism [29]. Different poor prognostic thresholds of D-dimer were confirmed both above and below the ULN value (≥ 0.5 μg/mL) e.g.: > 2.000 μg/mL; > 1.500 μg/mL; > 1.465 μg/mL; > 1.330 μg/mL; > 1.000 μg/mL; > 0.860

μg/mL; > 0.850 μg/mL; > 0.800 μg/mL; > 0.760 μg/mL; > 0.710 μg/mL; > 0.59857 μg/mL; > 0.550 μg/mL; > 0.375 μg/mL; > 0.340 μg/mL; > 0.250 μg/mL; > 0.232 μg/mL; and > 0.03 μg/mL [30].

1.4. Prognostic importance of lactate dehydrogenase (LDH) levels

LDH was first described in muscle in 1919 [31]. LDH catalyses the reversible piruvate-lactate conversion in anaerob conditions. Particular LDH activity pattern is typical to normal tissues, which is determined by the function of the tissues and the extent of LDH elevation. Among relevant causes of LDH elevation are highlighted tissue injury, necrosis, hypoxia and haemolysis. Lactate formation is significantly increased by LDHA isoenzyme expressed by malignant cells. Increased LDH activity is directly proportional with lactate formation [32-34]. Lactate induces the proliferation of malignant cells [35], the angiogenesis [36-38], and inhibits the innate and adaptive immunresponses. Serum LDH elevation (> 480 U/L) correlates with shorter OS. Large metaanalyses have proven, that even in the range of normal laboratory values (< 480 U/L), baseline LDH elevation is associated with poor prognosis of malignant diseases. In a recent metaanalysis [39] the lowest threshold was e.g. 197.3 U/L. Other published poor prognostic thresholds for LDH are e.g.: > 160.5 U/L; > 225 U/L; > 240 U/L; > 245 U/L; > 250 U/L; > 252 U/L; > 313 U/L; > 469 U/L; > 800 U/L; and > 1000 U/L [40].

1.5. Prognostic importance of CRP to albumin ratio (CAR)

Prognostic role of CAR was first revealed in a study of ovarian cancer in 2017 [41]. Since then several studies have proven the poor prognostic role of elevated baseline CAR with different tresholds e.g. > 0.68; > 0.195; > 0.022; > 0.073; > 0.03; > 0.141; > 0.064; > 0.05; > 0.1; and > 0.18 [42-52].

1.6. Prognostic importance of absolute neutrophil to absolute lymphocyte ratio (NLR)

Leukocytes were discovered in 1843, and the method of differential blood cell counting was described in 1879 [53]. As a marker of systemic inflammation, NLR has been addressed as independent predictor of OS in cancer patients. In 2014 based on a meta-analysis NLR > 4 is associated with an adverse OS [54]. Since then several

metaanalyses have supported the evidence of the prognostic significance of elevated baseline NLR e.g.: 1.77 to 5; 2.6 to 5.25; > 3; > 3.2; > 4.03; > 5; > 5.3; 2 to 6; and > 6 [55-62].

1.7. Prognostic importance of absolute lymphocyte to absolute monocyte ratio (LMR)

It is known, that lymphocytes play important role in anticancer immunity [63-64]. The reduction of lymphocyte count predicts poor prognosis [65], and monocytes play important role in the progression of malignant diseases [66]. Furthermore in the microenvironment of the neoplastic tissue, circulating monocytes differentiate to macrophages [67]. M2 type macrophages facilitate the growth of the malignancy, the neovascularisation and metastasis formation [68], thus elevated monocyte count is associated with poor prognosis [69]. Consequently, low LMR value predicts poor prognosis. Different prognostic cut-offs of LMR are published e.g. < 4.44; < 5.00; < 4.00; < 1.67; < 3.17; < 2.22; < 3.45; < 3.84; < 3.85; < 3.95; < 4.20; and < 4.35 [70-74].

1.8. Prognostic importance of platelet to absolute lymphocyte ratio (PLR)

Platelets were discovered in 1842 [53]. Association between baseline elevated PLR and short OS was described in several malignancies with different thresholds e.g.: >146.2; ≥200; ≥180; >150; >220; >181.24 [75-86].

2. Objectives

The aims of this study were the following:

(1) to reveal an association among the well-known biomarkers, some of their combinations and the OS in real-life situation of consecutive patients suffering from advanced cancer;

(2) to select the three most significant single biomarkers and investigate their combinations regarding prognostic values;

(3) to form prognostic groups and stratify the patients determining the prognostic significance of these.

3. Methods

Ethical approval was waived by the Medical Research Council (No. IV/5406-1 /2021/EKU) for this retrospective analysis.

Blood samples of consecutive patients with advanced cancer treated in a single institution (Oncology Department of Szent Lázár County Hospital, Salgótarján, Hungary) were taken as part of the routine investigation before the initiation of the therapy of the given disease. Recurrent disease was defined as the previously resected malignant disease had locally or regionally (in lymphnodes) recurrency at the time of sampling. Metastatic disease was defined as unresectable multiple metastases were present at the time of sampling. Patients with all the following biomarkers available were eligible to the study: CRP, D-dimer, LDH, albumin, and complete blood count (CBC). Exclusion criteria consisted of suspected infection, hematological malignancy, the lack of at least one biomarker data point, rapid progression [i.e., from laboratory testing, Eastern Cooperative Oncology Group (ECOG) performance status progressed to 3 before the initiation of anticancer treatment], or death caused by something other than disease progression.

CRP, LDH, and albumin were measured with commercially available Roche tests on Cobas c501 or Cobas 6000 analysers (Tokyo, Japan). D-dimer levels were measured by a chemiluminescent immunoassay (PATHFAST, Tokyo, Japan). CBC was determined with Cell-dyn 3700 (Abbott Park, IL, United States and Beckman Unicel DxH600, Miami, FL, United States). The CAR and the CBC derived parameters such as LMR, NLR, and PLR were calculated as the ratio of CRP and albumin, the lymphocyte count and the monocyte count, the ratio of the neutrophil count and the lymphocyte count, and the ratio of the platelet count and the lymphocyte count, respectively.

For the purpose of statistical analysis, the CRP value of 4.9 mg/L for <5 mg/L (lower level of detection), and the D-dimer value of 5.1 μg/mL for >5 μg/mL (higher level of detection) were used. All other biomarker values were handled with the measured numeric values. Cut-off determination was performed with the validated “Cutoff Finder” online tool. Statistical analysis was performed by R Studio Software. For each value a comparison was made between the median OS values below and over

the cut-off value by the log-rank test. The value with the largest gap and Chi-squared statistics was selected. Comparison of the prognostic groups with Cox proportional hazard regression was performed. Log-rank test was used to detect the differences between survival curves within the prognostic groups in the Kaplan-Meier analysis as well as to assess the significance of the Cox model. OS time was defined as the length of survival from the date of laboratory testing. Survival data measured in months were computed according to Surveillance, Epidemiology, and End Results (SEER) recommendations: days between the dates were divided by one twelfth of 365.24. For the median follow-up time calculation, we used a reverse Kaplan-Meier estimator [87].

The same method was applied for the analysis of biomarker-combinations (unpublished data).

4. Results

4.1. Patient characteristics

Between July 2016 and August 2019, blood samples of 88 consecutive patients with advanced malignant disease were analysed. No common infectious diseases were diagnosed. Data of 13 patients were excluded from the final analysis because of haematological malignancy (1), the lack of any of biomarker's data (2), death caused by rapid progression before the initiation of anticancer therapy (4) or by other cause of death, than disease progression (6). Thus the final retrospective analysis included the data of 75 patients. The shortest censored survival time was 24 months, i. e. the time has elapsed since July 2019. As of July 2021, 6 (8%) patients were still alive. Data of patient characteristics are described in Table 1 [87]. Further details of the patients are available in the Supplementeray Material [87].

4.2. Baseline biomarkers and survival

With a median follow-up of 47 months [95% confidence interval (CI): 37.2 – 49.3] the median OS was 12.1 months (95% CI: 7.8 – 18.3) (Fig. 1). Mean values of CRP, D-dimer, LDH, albumin, CAR, LMR, NLR and PLR were: 28.83 mg/L, 1.70 μg/mL, 482.12 U/L, 41.62 g/L, 0.8118, 3.41, 4.29, and 168.83, respectively.

4.3. Determination of cut-off values

The following cut-off values were determined for CRP 30.65 mg/L (Chi-squared = 20.85; $p < 0.001$), D-dimer 1.98 μg/mL (Chi-squared = 12.94; $p < 0.001$), LDH 410.50 U/L (Chi-squared = 10.45; $p < 0.001$), albumin 44.35 g/L (Chi-squared = 15.63; $p < 0.001$), CAR 1.4950 (Chi-squared = 23.54; $p < 0.001$), LMR 2.65 (Chi-squared = 3.45; $p = 0.063$), NLR 4.34 (Chi-squared = 10.50; $p < 0.001$) and PLR 168.20 (Chi-squared = 15.17; $p < 0.001$). Regardless to CAR, the three most significant biomarkers were the following: CRP (Eta-squared = 0.188; large power size), albumin (Eta-squared = 0.147; large power size) and PLR (Eta-squared = 0.153; large power size) (Table 2.) [87].

Application of CAR (unpublished data) and PLR, three biomarkers were significantly associated with OS in the following order: D-dimer, NLR and LDH.

Table 1. Characteristics of the 75 patients [87]

Sex			
	Male	57.3% (43/75)	
	Female	42.6% (32/75)	
Average age			
	Male	62.97 ys	
	Female	66.65 ys	
Malignancy	**(n=75)**		**TNM stage**
	Locally advanced (20/75)		
		HNSCC (8/20)	
			Nasopharynx: cT4cN1cM0
			Hard palate: cT3cN2acM0
			Pharynx: cT2cN0cM0
			Hypopharynx: cT3cNxcM0, cT3cN0cM0, cT3cN1cM0, cT2cN2bcM0, cT2cN1cM0
		SCLC & hypopharyngeal SCC (1/20)	cT2cN2cM0;cT1cNxcM0
		SCLC (1/20)	cT3cN3cM0
		NSCLC SCC (2/20)	cT4cN2cM0, cT2cNxcM0
		NSCLC AC (3/20)	cT2cNxcM0, cT4cN1cM0, cT3cN2cM0
		GC AC (1/20)	cT3cN1cM0
		PC AC (1/20)	cT4cNxcM0
		CRC (2/20)	Transverse colon: cT4cN2cM0; Rectum: cT4cN1cM0
		OC AC (1/20)	cT3cN1cM0
	Recurrent (6/75)		
		HNSCC (2/6)	
			Tongue: cT2cN1cM0
			Pharynx: cT2cN2acM0

Malignancy (n=75) (Table 1. continued)		**TNM stage**
Recurrent (6/75)		
GC AC (1/6)	Abdominal lymphnode	pT3pN2cM0
BC (3/6)	Axillary lymphnode	cT1ccN1cM0
	Neck lymphnode	pTxcN3cM0
	Local	cT4cNxcM0
Metastatic (49/75)		
Parotid SCC (1/49)	Suprarenal met.	cT3cN2bcM1
Tongue SCC (1/49)	Pulmonary met.	cT1cN2acM1
Hypopharyngeal SCC (2/49)		
	Pulmonary met.	cT1cN1cM1
	Bone met.	cT1cN1cM1
NSCLC AC (5/49)		
	Pulmonary, cerebral met.	cT2cN2cM1
	Pleural carcinosis	cT1ccNxpM1
	Bone met.	cT3cN2cM1
		cT4cN2cM1
	Pulmonary, bone met.	pT2pN1pM1
NSCLC SCC (2/49)		
	Bone met.	cT4cN2cM1
	Pulmonary, bone met.	cT3cN1cM1
GC AC (3/49)		
	Hepatic met.	cT3cN3cM1
	Peritoneal carcinosis	cT3cNxcM1
		cT4cN3cM1
CRC AC coecal (4/49)		
	Hepatic met.	pT4pN1pM1
		pT3pN2pM1
	Hep. met., perit. carcinosis	cT4cNxcM1
		cT4cN1pM1
CRC AC transverse (1/49)	Hepatic met.	pT4pN1pM1
CRC AC sigmoid (1/49)	Peritoneal carcinosis	pT3pN2pM1

Malignancy (n=75) (Table 1. continued)		**TNM stage**
Metastatic (49/75)		
CRC AC rectal (8/49)		
	Hepatic met.	cT4cNxpM1
		pT2pN1pM1
		pT2pNxpM1
		cT4cN2pM1
	Hepatic, pulmonary met.	pT3pN1pM1
		pT3pN1pM1
		cT4cNxcM1
	Pulmonary met.	cT4cN1cM1
PC AC (8/49)		
	Pulmonary met.	cTxcN2cM1
	Bone met.	cTxcNxcM1
	Bone, cerebral met.	cT2cN2cM1
	Hepatic met.	cT2cNxpM1
		cT2cNxpM1
		cT2cN2pM1
		cT2cN2pM1
		cT2cN1pM1
Cholecyst AC (1/49)	Hepatic met.	pT2pN1pM1
PCA (3/49)		
	Hep., pulm., bone met.	pT1ccN1cM1
	Pulmonary, bone met.	pT2acNxcM1
	Bone met.	cT2acN1cM1
Bladder TCC (1/49)	Pulmonary met.	pT2bpN2cM1
BC NST (5/49)		
	Pulmonary, bone met.	pT4cpN3acM1
		pT1cpN2cM1
	Perit. carcin., bone met.	pT2pN2acM1
	Bone met.	pT1cpN2acM1
		cT4cN1cM1
BC neuroendocrine (1/49)		
	Mediastinal, bone met.	cT4cN1cM1
OC AC (2/49)		
	Pulmonary met.	cT1bcNxcM1
		cT3cN1cM1

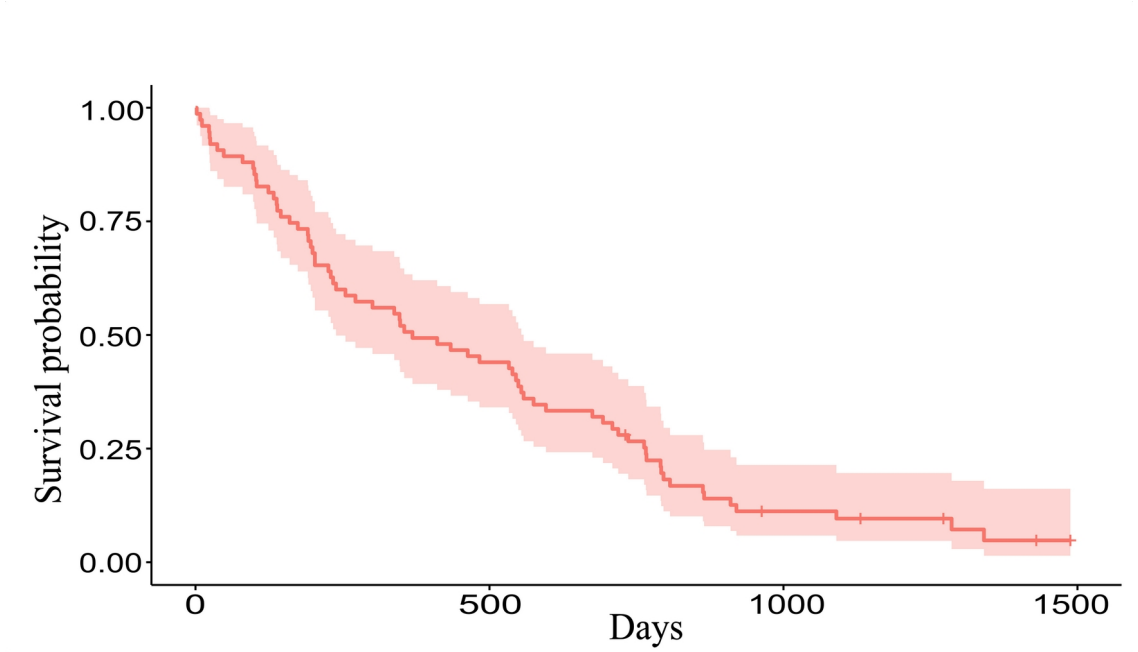

Fig. 1. The Kaplan-Meier plot of 75 patients [87]

69 patients died, 6 patients are still alive (censored data). Median OS is 369 days (12.12 months), range 2-1488 days (0.06-48.89 months).

On examination the combinations of PLR, D-dimer, NLR and LDH, the most significant combinations were found to be PLR and D-dimer scalar (PLRxD-dimer) (Chi-sqared = 28.19; $p < 0.001$) and NLR (Chi-squared = 10.50; $p < 0.001$). Cut-offs for PLRxD-dimer (unpublished data) and for NLR [87-88] were 150.3 and 4.34.

Table 2. Comparison of the median OS based on the cut-off value for each significant biomarker [87]

	CRP (mg/L)		**albumin (g/L)**		**PLR**	
Cut-off value	> 30.65	≤ 30.65	≤ 44.35	> 44.35	> 168.20	≤ 168.20
n=	16	59	47	28	28	47
Median OS (months)	4.89	17.71	8.94	21.54	6.67	18.20
Mann-Whitney test (Z statistic)	3.75		3.32		3.38	
p-value	<0.001		< 0.001		< 0.001	

Summary of the significant and non-significant biomarker-combinations are demonstrated in Table 3 and 4 (unpublished data).

Table 3. Biomarker-combinations with significant association of overall survival

Biomarker combination	Cut-off	Chi-squared	p-value
PLRxD-dimer (µg/mL)	150.3	28.19	< 0.001
LDHxD-dimer (U/L x µg/mL)	969.3	23.01	< 0.001
NLRxD-dimer (µg/mL)	5.035	15.44	< 0.001
PLRxNLR	471.3	13.06	< 0.001
NLRdPLR	0.03531	10.48	0.001
PLRdNLR	28.32	9.19	0.002
PLRdLDH (U/L)	0.5755	8.58	0.003
D-dimer-d-LDH (µg/mL / U/L)	0.0051	8.23	0.004
PLRxLDH (U/L)	50440	7.91	0.005
NLRdLDH (U/L)	0.012	7.62	0.006
LDH-d-D-dimer (U/L / µg/mL)	181.5	5.05	0.025
LDHdPLR (U/L)	0.739	4.57	0.032

---x--- = scalar; ---d--- = ratio;

Table 4. Biomarker-combinations with <u>NO</u> significant association of overall survival

Biomarker combination	Chi-squared	p-value
D-dimer-d-PLR (µg/mL)	3.78	0.052
D-dimer-d-NLR (µg/mL)	3.66	0.056
NLR-d-D-dimer (µg/mL)	3.11	0.077
PLR-d-Dimer (µg/mL)	2.41	0.120
LDHdNLR (U/L)	0.17	0.680
NLRxLDH (U/L)	0.06	0.800

---x--- = scalar; ---d--- = ratio;

4.4. The relationship between the prognostic cut-off values and survival

For each biomarkers (CRP, albumin and PLR) the results of the comparison of the median OS of the groups above and below the cut-off value are demonstrated on Fig. 2A-B-C and 3A-B-C-D. For CRP and PLR (Fig. 2A and 2C) longer survivals were found below, than above the cut-off values, and for albumin (Fig. 2B) longer survival was found above the cut-off value [87].

For the most significant biomarker-combinations (CAR, PLRxD-dimer, NLR and NLRdLDH) values under the cut-off were associated with longer overall survival (Table 5.), (Fig.3.) (unpublished data).

Table 5. Comparison of median survival based on each cut-off values of biomarker-combinations (unpublished data)

	CAR (mg/L / g/L)		**PLRxD-dimer (µg/mL)**		**NLR**		**NLRdLDH (U/L)**	
Cut-off value	>1.4950	≤1.4950	>150.30	≤150.30	>4.34	≤4.34	>0.012	≤0.012
n=	11	64	43	32	22	53	16	59
Median OS (months)	4.07	16.69	6.67	25.11	5.24	17.71	3.68	17.51
Mann-Whitney test (Z statistics)	3.68		4.82		3.32		3.09	
p-value	<0.001		<0.001		<0.001		0.002	

PLRxD-dimer = PLR and D-dimer scalar; NLRdLDH = NLR to LDH ratio

4.5. Classification of patients into risk groups

4.5.1. Application of three biomarkers (CRP, albumin, PLR)

With the combination of triplet biomarkers (CRP, albumin and PLR), prognostic groups were created independently from stage, histology and time to progression on first line therapy. Four prognostic groups were formed based on the cut-off values of each biomarker Group 1: No biomarker with out-of range value (ORV), defined by the cut-off value; Group 2: One ORV biomarker; Group 3: Two ORV biomarkers; Group 4: Three ORV biomarkers (Table 6) [87].

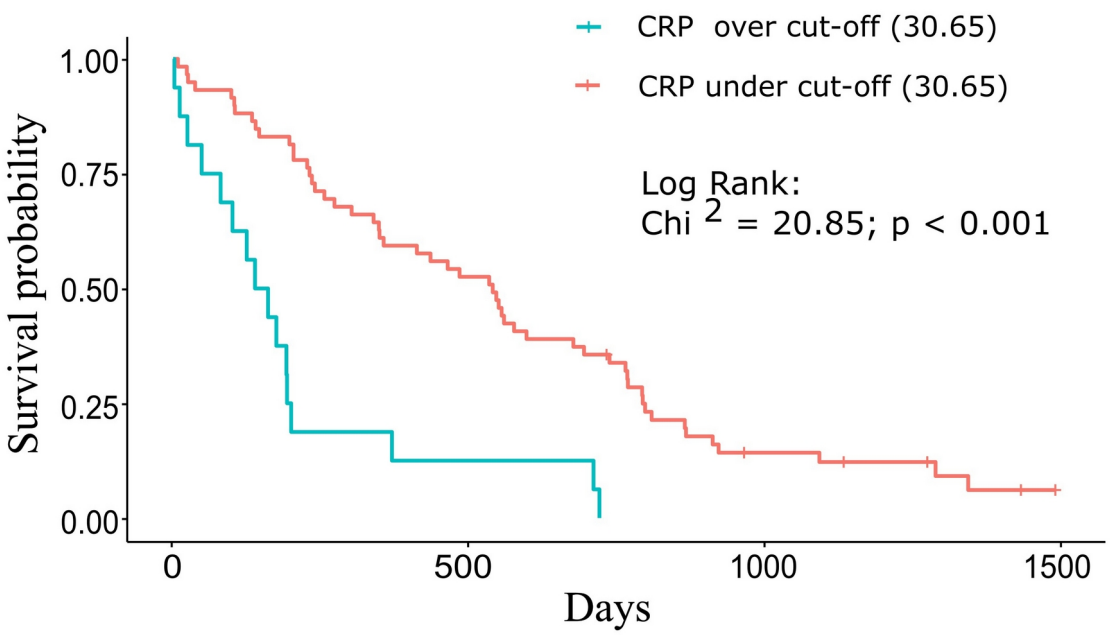

Fig. 2a. Kaplan-Meier plot for CRP biomarker [87]

Longer survival was found below the cut-off (30.65 mg/L) value:
539 vs. 149 days (17.71 vs. 4.89 months).

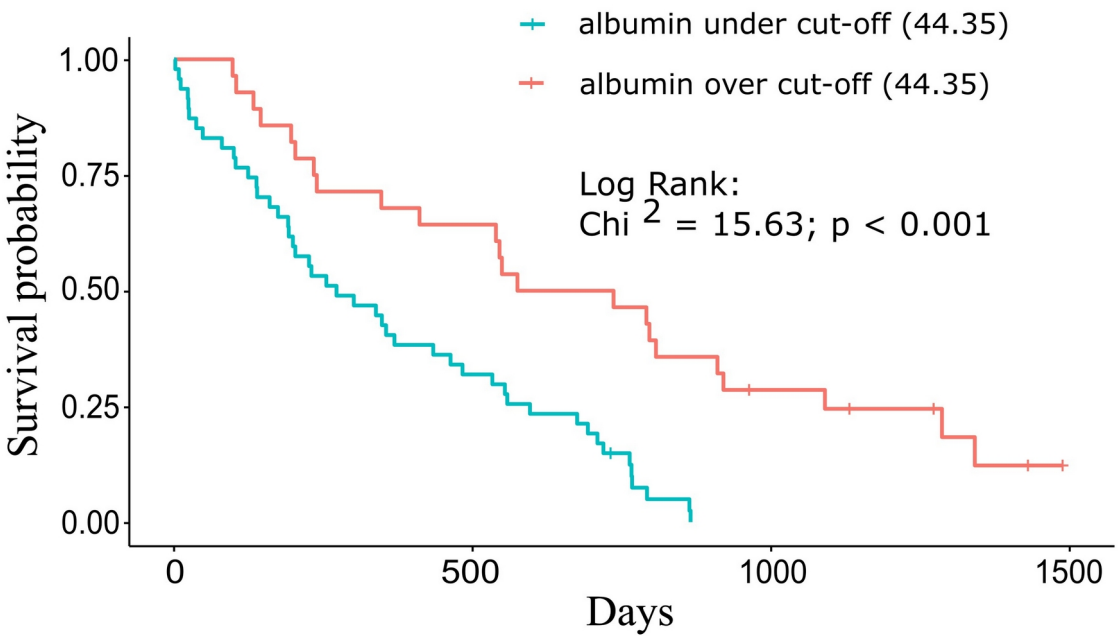

Fig. 2b. Kaplan-Meier plot for albumin biomarker [87]

Longer survival was found above the cut-off (44.35 g/L) value:

655.5 vs. 272 days (21.54 vs. 8.94 months).

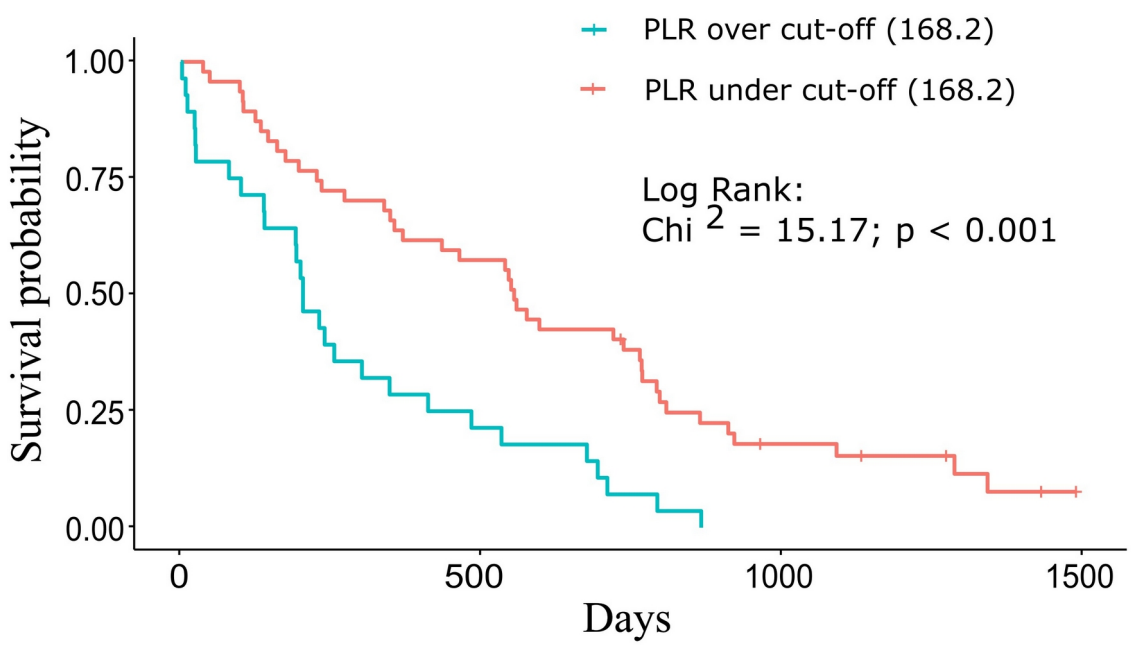

Fig. 2c. Kaplan-Meier plot for PLR biomarker [87]

Longer survival was found below the cut-off (168.20) value:

554 vs. 203 days (18.20 vs. 6.67 months).

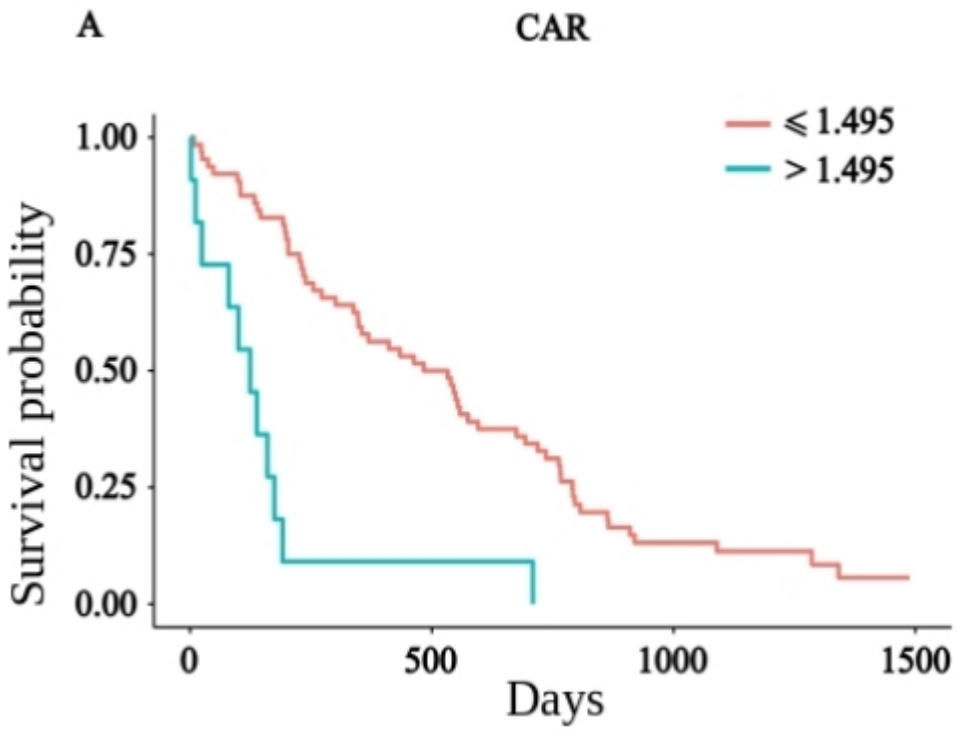

Fig. 3a. Kaplan-Meier curve for CAR biomarker-combination (unpublished data).

Longer survival is observed under the cut-off value (1.4950 mg/L / g/L):

508 vs. 124 days (16.7 vs. 4,1 months)

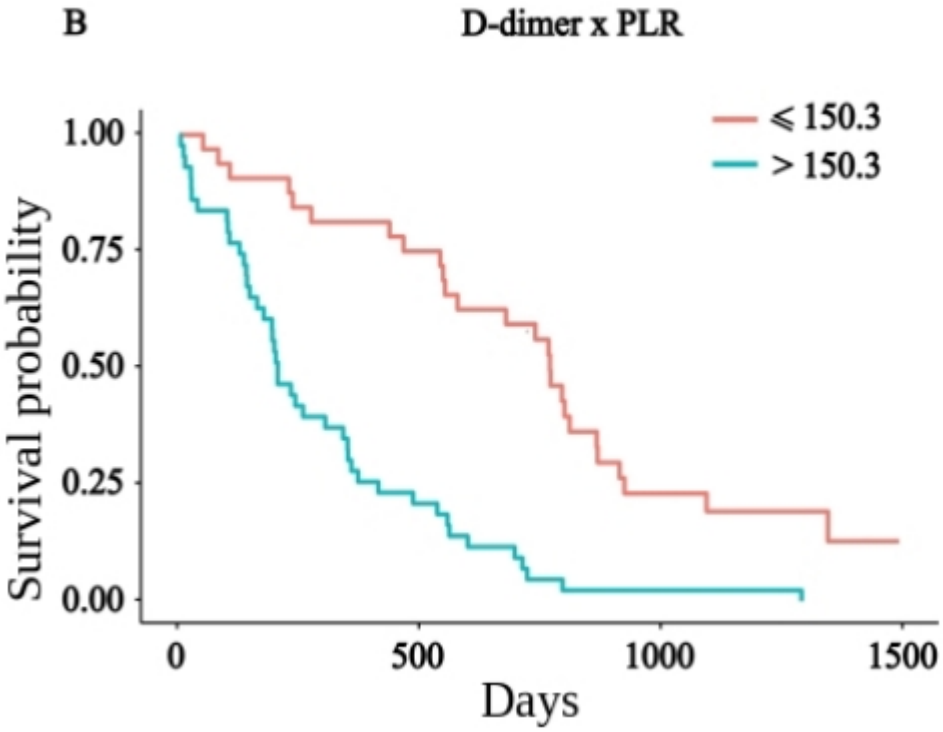

Fig. 3b. Kaplan-Meier curve for D-dimer and PLR scalar biomarker-combination (unpublished data).

Longer survival is observed under the cut-off value (150.3 µg/mL):
764.5 vs. 203 days (25.1 vs. 6.7 months).

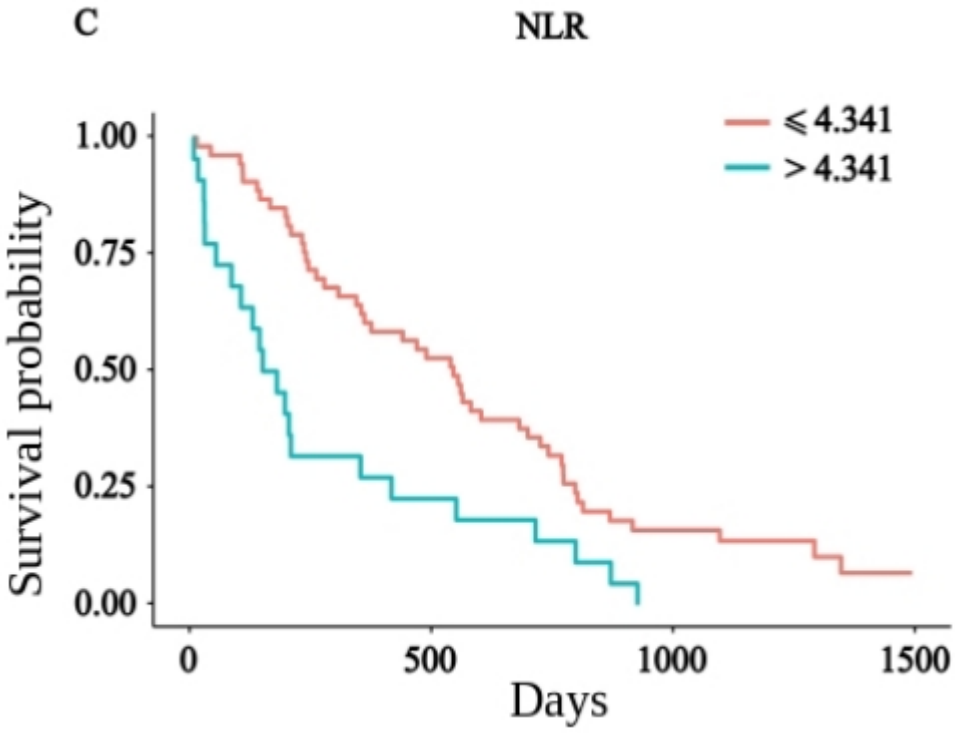

Fig. 3c. Kaplan-Meier curve for NLR [88]

Longer survival is observed under the cut-off values (4.34):

539 vs. 159.5 days (17.71 vs. 5.24 months).

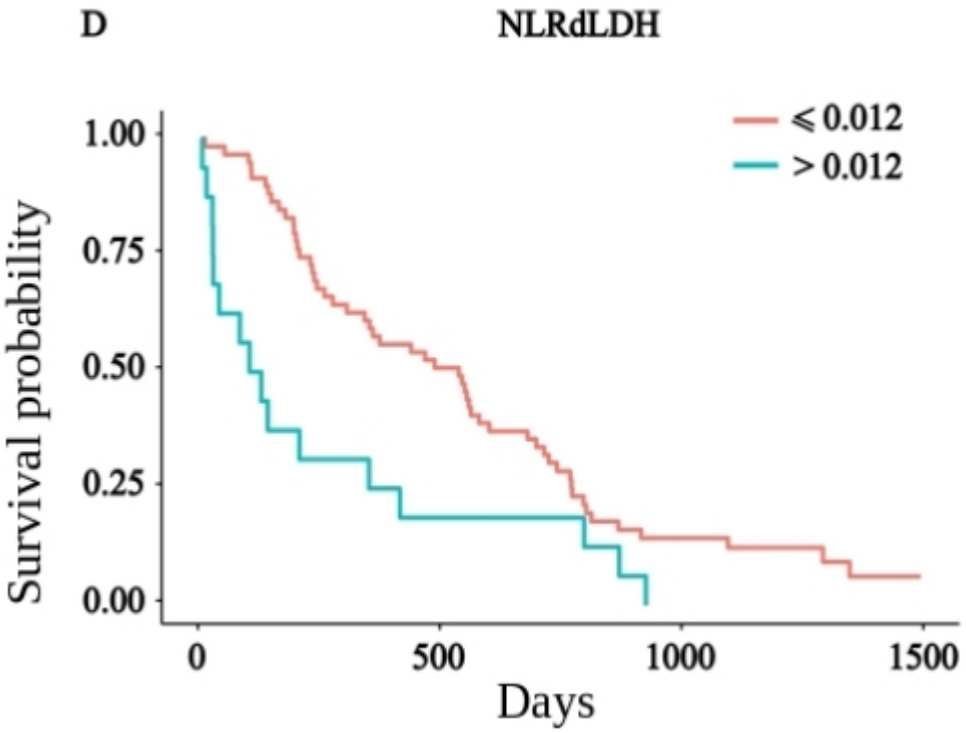

Fig. 3d. Kaplan-Meier curve for NLR to LDH ratio biomarker-combination (unpublished data).

Longer survival is observed under the cut-off value (0.012 U/L):
533 vs. 112 days (17.51 vs. 3.68 months).

Table 6. The four prognostic groups based on the established cut-off values of the selected three biomarkers (CRP, albumin and PLR) [87]

	Group 1	Group 2			Group 3			Group 4
CRP (mg/L)	≤30.65	**>30.65**	≤30.65	≤30.65	**>30.65**	**>30.65**	≤30.65	**>30.65**
albumin (g/L)	>44.35	>44.35	**≤44.35**	>44.35	**≤44.35**	>44.35	**≤44.35**	**≤44.35**
PLR	≤168.20	≤168.20	≤168.20	**>168.20**	≤168.20	**>168.20**	**>168.20**	**>168.20**

Out of range values (ORV) of the biomarkers are in bold style.

Significant differences were detected between these groups (Fig. 4), (Table 7). The Likelihood ratio test of Cox-model regression parameters for the four groups was 29.5 ($p < 0.001$).

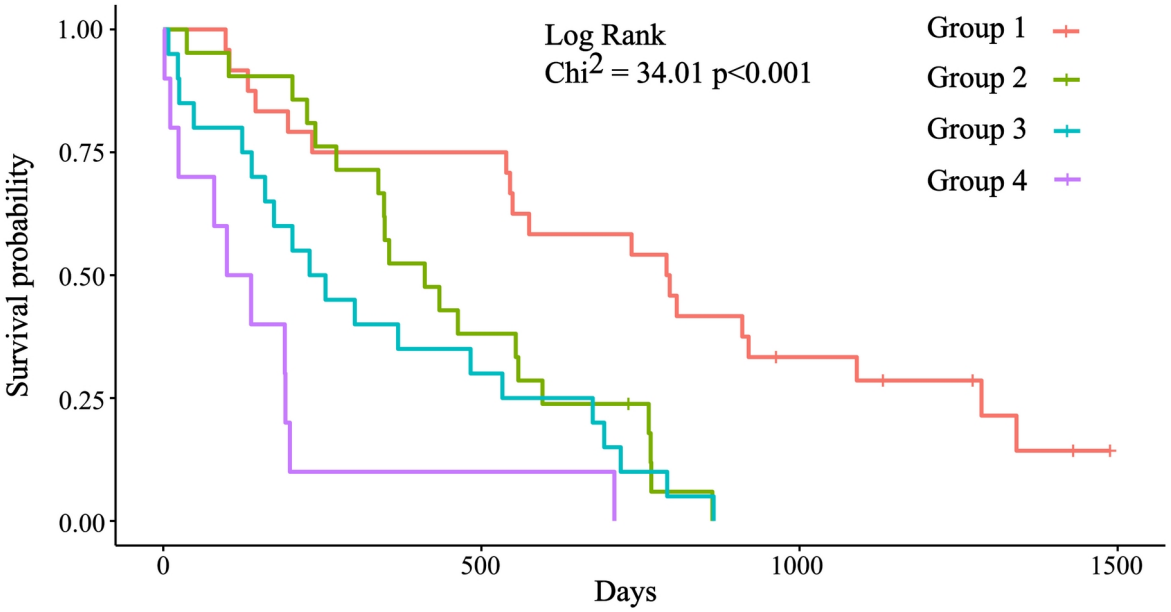

Fig. 4. Kaplan-Meier survival plots for the four prognostic groups (CRP, albumin, PLR) [87]

Group 1: median OS = 793.5 days (26.07 months); Group 2: median OS = 411.0 days (13.50 months); Group 3: median OS = 242.5 days (7.97 months); Group 4: median OS = 119 days (3.91 months). Significant differences were detected between the Group 1 (reference) and Group 2-3-4 ($p = 0.003$; $p < 0.001$; $p < 0.001$).

Table 7. Prognostic significance of the four prognostic groups [87]

Group	n=	Median OS (months)	HR (95% CI)	p-value	Power (95% CI)
1	24	26.07	1	-	-
2	21	13.50	3.0 (1.5 – 6.2)	0.003	0.896 (0.242-0.997)
3	20	7.97	4.1 (2.0 – 8.3)	<0.001	0.976 (0.570-0.999)
4	10	3.91	10.2 (4.2 – 24.6)	<0.001	0.999 (0.981-1)

4.5.2. Application of three biomarker-combinations (CAR, PLR-D-dimer scalar, NLR)

Regarding the biomarker-combinations, patients classification to risk groups were most balanced with the usage of CAR, PLR and D-dimer scalar (PLRxD-dimer) and NLR, than using NLR to LDH ratio (NLRdLDH), therefore these three combinations were analysed further. Four prognostic groups were generated based on the cut-off values of each biomarker-combination (Table 8.).

Table 8. Four prognostic groups based on the cut-off values of the three biomarker-combinations [CAR (mg/L / g/L), PLRxD-dimer (ug/mL) and NLR]

	Ref.	**1 ORV biomarker-comb.**			**2 ORV biomarker-comb.**			**3 ORV biomarker-comb.**
CAR	≤ 1.4950	**> 1.4950**	≤ 1.4950	≤ 1.4950	**> 1.4950**	**> 1.4950**	≤ 1.4950	**> 1.4950**
PLRx D-dimer	≤ 150.30	≤ 150.30	**> 150.30**	≤ 150.30	**> 150.30**	≤ 150.30	**> 150.30**	**> 150.30**
NLR	≤4.34	≤4.34	≤4.34	**> 4.34**	≤4.34	**> 4.34**	**> 4.34**	**> 4.34**

Values above the cut-off in bold style; PLRxD-dimer = PLR and D-dimer scalar;

Significant differences were detected between the groups (Table 9.), (Fig. 5). The Likelihood ratio test of Cox-model regression parameters for the four groups was 32.124 (p <0.001) (unpublished data).

Table 9. Prognostic importance of the four biomarker-combination groups (CAR, PLRxD-dimer and NLR)

Group	n=	Median OS (months)	HR (95% CI)	p-value	Power (95% CI)
Reference	27	25.16	1	-	-
1 ORV biomarker-comb.	29	11.10	3.0 (1.7 – 5.4)	<0.001	0.929 (0.434-0.996)
2 ORV biomarker-comb.	10	5.89	5.3 (2.4 – 11.7)	<0.001	0.998 (0.714-0.999)
3 ORV biomarker-comb.	9	4.07	9.0 (3.9 – 20.8)	<0.001	0.999 (0.979-1)

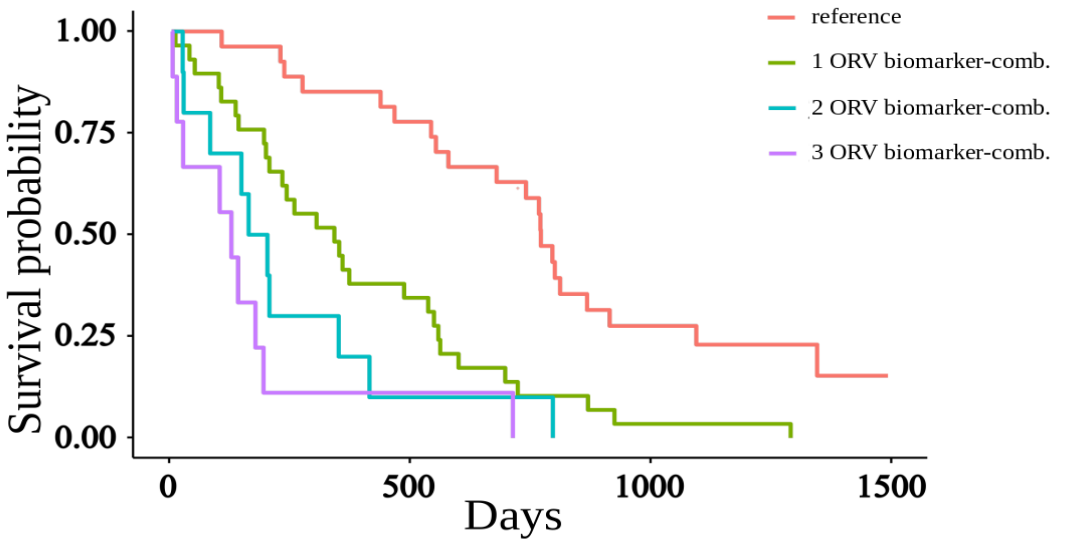

Fig. 5. Kaplan-Meier curves of the four biomarker-combination prognostic groups (CAR, PLRxD-dimer and NLR)

1. group: median OS = 766 days (25.16 months); 2. group: median OS = 338 days (11.10 months); 3. group: median OS = 179.5 days (5.89 months); 4. group: median OS = 124 days (4.07 months). Significant differences were observed between 1. (reference) group and groups 2-3-4 ($p < 0.001$).

4.6. Comparison the clinical utility of three biomarkers and biomarker-combinations

Addressing the question, whether the application of three biomarkers (CRP, albumin and PLR) or three biomarker-combinations (CAR, PLRxD-dimer and NLR) may predict overall survival more accurately, the sensitivity, specificity, positive and negative predictive values of the biomarkers and the biomarker- combinations at the time interval of death occured in one year or in two years were compared.

Survival rates of the prognostic groups of three biomarkers (CRP, albumin and PLR) at one year and at two years were calculated (Table 10.).

Table 10. Survival rates (%) of the prognostic groups of CRP, albumin and PLR

	At 1 year	**At 2 years**
Group 1	75.0	58.3
Group 2	52.4	23.8
Group 3	25.0	10.0
Group 4	10.0	0.0

Based on the time intervals of one and two years, sensitivity, specificity, positive and negative predictive values were determined [89] and the results are summarized in Table 11.

Table 11. Sensitivity, specificity, positive and negative predictive values of CRP, albumin and PLR at the time interval of one and two years

Death occured in	**Sensitivity** (%, 95% CI)	**Specificity** (%, 95% CI)	**Pos. Pred. value** (%, 95% CI)	**Neg. Pred. value** (%, 95% CI)
1 year	85.0 (70.2-94.3)	51.4 (33.9-68.2)	66.6 (58.1-74.2)	75.0 (57.3-87.0)
2 years	81.5 (68.6-90.7)	66.6 (43.0-85.4)	86.3 (77.2-92.1)	58.3 (42.6-72.5)

Survival rates of the prognostic groups of three biomarker-combinations (CAR, PLRxD-dimer and NLR) at one year and at two years were calculated (Table 12.).

Table 12. Survival rates (%) of the prognostic groups of CAR, PLRxD-dimer and NLR

	At 1 year	At 2 years
Reference	85.2	62.9
1 ORV biomarker-comb.	41.4	10.3
2 ORV biomarker-comb.	20.0	10.0
3 ORV biomarker-comb.	11.1	0.0

Based on the time intervals of one and two years, sensitivity, specificity, positive and negative predictive values were determined [89] and the results are summarized in Table 13.

Table 13. Sensitivity, specificity, positive and negative predictive values of CAR, PLRxD-dimer and NLR at the time interval of one and two years

Death occured in	**Sensitivity** (%, 95% CI)	**Specificity** (%, 95% CI)	**Pos. Pred. value** (%, 95% CI)	**Neg. Pred. value** (%, 95% CI)
1 year	89.2 (74.6-96.9)	60.5 (73.4-75.9)	68.7 (59.3-76.8)	85.2 (68.7-93.7)
2 years	81.5 (68.6-90.7)	80.9 (58.1-94.5)	91.6 (81.8-96.4)	62.9 (48.3-75.5)

Both one and two years survivals can be more accurately predicted with the application of the biomarker-combinations of CAR, PLRxD-dimer and NLR than the three biomarkers of CRP, albumin and PLR.

5. Discussion

Chronic low grade and intensity inflammation might precede malignant transformation and is considered to be a predisposing factor in the pathogenesis of cancer [90]. Some extensively studied peripheral blood biomarkers related to cancer development were proven to be independent prognostic factors of cancer survival: CRP [9], albumin [24], D-dimer [30], LDH [40], CAR [91], LMR [87], NLR [88] and PLR [87]. However the different prognostic values established at different trials means uncertainty of the application these.

Several analyses have addressed the question, whether combinations of biomarkers could provide prognostic scores for survival prediction in cancer. For instance, CAR is regarded to be superior to other inflammation-based prognostic scores, including NLR and PLR, and therefore is recognized as the most useful prognostic marker [92]. Furthermore the combined application of CAR, CRP and the GPS, which also include CRP and albumin levels, may provide more accurate clinical utility of prognosis prediction in colorectal cancer [93]. The mGPS, which consist of different cut-off levels of CRP and albumin, in combination with LMR can stratify patients according to prognosis in lung adenocarcinoma without driver mutations [94]. Combined fibrinogen and albumin levels might be a potential prognostic biomarker for low grade gliomas, and a reliable point-based nomogram may have clinical relevance [95]. LDH to albumin ratio is an independent predictor of the prognosis of colon cancer patients [96]. Albumin to D-dimer ratio was found to be an independent prognostic factor in advanced gastric cancer [97]. The combination of LDH, CRP, cancer antigen (CA) 15-3, and CA 125 were indentified to be related to the prognosis in metastatic breast cancer [98]. Prognostic risk scoring model based on the LDH level and the neutrophil count may help to estimate the prognosis in esophegal cancer [99]. Elevated NLR and PLR were associated with worse prognosis in breast cancer [100].

In this retrospective and confirmatory analysis, eight routinely measured clinical laboratory parameters (CRP, albumin, D-dimer, LDH, CAR and based on CBC, calculated LMR, NLR and PLR) were applied to a consecutive real-life patient population of locally advanced, recurrent and metastatic malignant diseases at a single

institution (Szent Lázár County Hospital), and searched for the most significant biomarkers and their combinations regarding OS.

It was demonstrated, that all biomarkers and biomarker-combinations studied were in significant correlation with the overall survival.

The two most significant serum biomarkers were CRP and albumin. The first significant blood cell count derived ratio was PLR. Overall survival was longer below the cut-off values of CRP and PLR, and above the cut-off value of albumin for the study population (Fig.2.), which are in accordance with the data of the literature.

Stratification of the patients in to one of the four groups was performed according to the number of ORV biomarkers (Table 6.). It was found, that these prognostic groups enable to identify the good, moderate, intermediate and the poor OS patients with reasonable accuracy (Fig. 4.), (Table 7.). [87]

Using biomarker-combinations (unpublished data), the three most significant combinations were: CAR, PLR and D-dimer scalar (PLRxD-dimer) and NLR [88]. Overall survival below the cut-off values of CAR, PLRxD-dimer and NLR was longer, than below the cut-off values (Fig.3.).

Patients were also stratified to one of the four groups generated by ORV biomarkers (Table 8.). These prognostic groups also enable to identify the good, moderate, intermediate and the poor OS patients (Fig. 5.), (Table 9.), furthermore predict overall survival more accurately than three biomarkers of CRP, albumin and PLR (Tables 11 and 13).

This analysis have some limitations. First, the patient population for this small scale retrospective analysis is histologically heterogenous. Second, regarding the stage, these unbalanced cohorts of advanced cancer patients are also heterogenous. Third, the identified cut-off values by this study for CRP, albumin and PLR are slightly different from used by other studies, therefore they need to be validated in a large scale prospective study. Fourth the CAR cut-off identified in this study is significantly different from that published in the literature. Fifth, there are multiple factors having a possible influence on the OS of patients, that were not monitored in this analysis. The clear distinction among the OS of the four biomarker and biomarker-combination groups however make this approach promising.

6. Conclusions

Based on this analysis it can be confirmed, that the combination of peripheral blood biomarkers measured at baseline could be applied for the estimation for the OS in real-life population of advanced cancer patients. It was possible to establish consistent prognostic groups using the most significant three biomarkers (CRP, albumin and PLR), and three biomarker- combinatons [CAR, PLR-D-dimer scalar (PLRxD-dimer) and NLR]. The OS was significantly different in each of the prognostic groups developed. One advantage of this study is, that these parameters can be routinely measured without additional costs. The author of this dissertation persuaded, that the prognostic significance of these and other biomarker patterns warrants further investigations and validations in large prospective cohorts in order to decide, whether the knowledge of these information may contribute better prediction of prognosis of advanced cancer patients.

New theses:

1.: Based on the baseline values of eight prognostic biomarkers [C-reactive protein (CRP), cross-linked fibrin degradation product (D-dimer), lactate dehydrogenase (LDH), albumin, CRP to albumin ratio (CAR), lymphocyte to monocyte ratio (LMR), neutrophil to lymphocyte ratio (NLR) and platelet to-lymphocyte ratio (PLR)] and the median overall survival cut-off values were determined, which provided the selection those biomarkers and biomarker-combinations exhibited the most significant association with overall survival.

2.: Application of the cut-off values of three biomarkers (CRP, albumin, PLR) or biomarker-combinations (CAR, PLRxD-dimer, NLR) four prognostic groups were generated in advanced cancer patients.

3.: In real-life situations these baseline values of peripheral blood biomarkers (CRP, albumin, PLR) and biomarker-combinations (CAR, PLRxD-dimer, NLR) may contribute to overall survival (OS) prediction in patients with advanced cancer.

4.: Prognostic biomarkers [C-reactive protein (CRP), cross-linked fibrin degradation product (D-dimer), lactate dehydrogenase (LDH), albumin, CRP to albumin ratio (CAR), lymphocyte to monocyte ratio (LMR), neutrophil to lymphocyte ratio (NLR) and platelet to-lymphocyte ratio (PLR)] can be routinely measured without additional costs.

5.: Exploration the prognostic importance of biomarker patterns and evaluation their role compared to the well-established prognostic systems need further investigations and validations in order to decide, what extent these knowledges contrubite to the therapy of the patients.

7. Summary

Consistent association between elevated baseline serum values each of the C-reactive protein (CRP), cross linked fibrin degradation product (D-dimer), lactate dehydrogenase (LDH), decreased baseline serum albumin, absolute lymphocyte count to absolute monocyte count ratio (LMR), elevated CRP to albumin ratio (CAR), absolute neutrophil count to absolute lymphocyte count ratio (NLR), elevated platelet count to absolute lymphocyte count ratio (PLR), combinations of some of these biomarkers and the short overall survival of patients with malignant diseases has already been reported.

The most significant biomarker combination of these values was searched and studied in real-life population of advanced cancer patients of a single center (n = 75). CRP, albumin and PLR showed marked association with OS. Based on assessed biomarker cut-offs, four patient groups were created whether biomarker values are out of range (ORV) compared to cut-off: (1) No ORV biomarkers (n = 24; OS = 26.1 months); (2) One ORV biomarker (n = 21; OS = 13.5 months); (3) Two ORV biomarkers (n = 20; OS = 7.9 months) and (4) Three ORV biomarkers (n = 10; OS = 3.9 months). Significant differences in OS were detected between the groups: for 1. vs. 2. hazard ratio (HR) = 3.0 (95% CI: 1.5 – 6.2), p = 0.003; for 1. vs. 3. HR = 4.1 (95% CI: 2.0 – 8.3), p < 0.001; for 1 vs. 4. HR = 10.2 (95% CI: 4.2 – 24.6), p < 0.001. CAR, PLR and D-dimer scalar (PLRxD-dimer) and NLR exhibited significant association with OS. Based on these biomarker-combination cut-offs four prognostic groups were created: (1) No ORV biomarkers (n = 27; OS = 25.2 months); (2) One ORV biomarker (n = 29; OS = 11.1 months); (3) Two ORV biomarkers (n = 10; OS = 5.9 months) and (4) Three ORV biomarkers (n = 9; OS = 4.1 months). OS differences were significant between the groups: 1. vs. 2. hazard ratio (HR) = 3.0 [95% CI: 1.7 – 5.4), p < 0.001; 1. vs. 3. HR = 5.3 (95% CI: 2.4 – 11.7), p < 0.001; 1 vs. 4. HR = 9.0 (95% CI: 3.9 – 20.8), p < 0.001.

Based on this analysis it can be confirmed, that the complex monitoring of CRP, albumin and PLR would contribute to the estimation of OS, however the combination of CAR, PLRxD-dimer and NLR allow better OS prediction. Large scale prospective studies are warranted to explore this and other useful combination of prognostic biomarkers and their relationship to the well-established prognostic systems in real-life.

8. References

[1] Biomarkers Definition Working Group Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. (2001) Clin Pharmacol Therapeutics, 69: 89–95.

[2] Hayes DF. Biomarkers. In: DeVita VT, Lawrence TS, Rosenberg SA (eds.), Cancer Principles & Practice of Oncology. 9th Ed. Lippincott Williams & Wilkins, a Wolters Kluwer business, Philadelphia, 2011: 694.

[3] Oldenhuis CN, Oosting SF, Gietema JA, de Vries EG. (2008) Prognostic versus predictive value of biomarkers in oncology. Eur J Cancer, 44: 946-953.

[4] Black S, Kushner I, Samols D. (2004) C-reactive Protein. J Biol Chem, 279: 48487-48490.

[5] Pepys MB, Hirschfield GM. (2003) C-reactive protein: a critical update. J Clin Invest. 111: 1805-1812.

[6] Deme D, Telekes A. (2017) [Prognostic importance of plasma C-reactive protein (CRP) in oncology]. Orv Hetil, 158: 243–256. Hungarian

[7] Coussens LM, Werb Z. (2002) Inflammation and cancer. Nature, 420: 860–867.

[8] Liao DW, Hu X, Wang Y, Yang ZQ, Li X. (2020) C-reactive Protein Is a Predictor of Prognosis of Prostate Cancer: A Systematic Review and Meta-Analysis. Ann Clin Lab Sci, 50:161–71.

[9] Chen Y, Cong R, Ji C, Ruan W. (2020) The Prognostic Role of C-reactive Protein in Patients with Head and Neck Squamous Cell Carcinoma: A Meta-analysis. Cancer Med, 9: 9541–9553.

[10] Bujacz A. (2012) Structures of bovine, equine and leporine serum albumin. Acta Crystallogr D Biol Crystallogr, 68: 1278-1289.

[11] Babson AL, Winnick T. (1954) Protein transfer in tumor-bearing rats. Cancer Res, 14: 606-611.

[12] Schmid M, Schindler R, Weigand K. (1986) Is albumin synthesis regulated by the colloid osmotic pressure? Effect of albumin and dextran on albumin and total protein synthesis in isolated rat hepatocytes. Klin Wochenschr, 64: 23-28.

[13] Nazha B, Moussaly E, Zaarour M, Weerasinghe C, Azab B. (2015) Hypoalbuminemia in colorectal cancer prognosis: Nutritional marker or inflammatory surrogate? World J Gastrointest Surg, 7: 370-377.

[14] Seaton, K.: Albumin concentration controls cancer. (2001) J Natl Med Assoc, 93: 490-493.

[15] Barber MD, Ross JA, Fearon KC. (1999) Changes in nutritional, functional, and inflammatory markers in advanced pancreatic cancer. Nutr Cancer, 35: 106-110.

[16] McMillan DC, Watson WS, O'Gorman P, Preston T, Scott HR, McArdle CS. (2001) Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. Nutr Cancer, 39: 210-213.

[17] Gabay C, Kushner I. (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med, 340: 448-454.

[18] Castell JV, Gómez-Lechón MJ, David M, Fabra R, Trullenque R, Heinrich PC. (1990) Acute-phase response of human hepatocytes: Regulation of acute-phase protein synthesis by interleukin-6. Hepatology, 12: 1179-1186.

[19] Chojkier M. (2005) Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. J Clin Gastroenterol, 2005, 39: S143-146.

[20] Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. (2012) Human serum albumin: from bench to bedside. Mol Aspects Med, 33: 209-290.

[21] Vaz J, Ansari D, Sasor A, Andersson R. (2015) SPARC: A Potential Prognostic and Therapeutic Target in Pancreatic Cancer. Pancreas, 44: 1024-1035.

[22] Don BR, Kaysen G. (2004) Serum albumin: relationship to inflammation and nutrition. Semin Dial, 17: 432–437.

[23] Deme D, Telekes A. [Prognostic importance of albumin in oncology]. (2018) Orv Hetil, 159: 96–106. Hungarian

[24] Liu J, Wang F, Li S, Huang W, Jia Y and Wei C. (2018) The Prognostic Significance of Preoperative Serum Albumin in Urothelial Carcinoma: a Systematic Review and Meta-Analysis. Biosci Rep, 38:BSR20180214. doi:10.1042/BSR20180214

[25] Gaffney PJ, Brasher M. (1973) Subunit structure of the plasmin-induced degradation products of crosslinked fibrin. Biochim Biophys Acta, 295: 308-313.

[26] Pizzo SV, Taylor LM Jr, Schwartz ML, Hill RL, McKee PA. (1973) Subunit structure of fragment D from fibrinogen and cross-linked fibrin. J Biol Chem, 248: 4584-4590.

[27] Gale AJ, Gordon SG. (2001) Update on Tumor Cell Procoagulant Factors. Acta Haematol, 106: 25–32.

[28] Cohen AT, Harrington R, Goldhaber SZ et al.: (2014) The design and rationale for the Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban (APEX) study. Am Heart J, 167: 335–341.

[29] Ma M, Cao R, Wang W, Wang B, Yang Y, Huang Y, Zhao G, Ye L. (2021) The D-Dimer Level Predicts the Prognosis in Patients with Lung Cancer: a Systematic Review and Meta-Analysis. J Cardiothorac Surg, 16:243. doi:10.1186/s13019-021-01618-4

[30] Deme D, Telekes A. (2017) [Prognostic importance of cross-linked fibrin degradation products (D-dimer) in oncology]. Magy Onkol, 61: 319-326. Hungarian

[31] Meyerhof O. (1919) Pfluegers Arch. Gesamte Physiol. Menschen Tiere, 175: 20-87.

[32] Curry JM, Tuluc M, Whitaker-Menezes D, Ames JA, Anantharaman A, Butera A, Leiby B, Cognetti DM, Sotgia F, Lisanti MP, Martinez-Outschoorn UE. (2013) Cancer metabolism, stemness and tumor recurrence: MCT1 and MCT4 are functional biomarkers of metabolic symbiosis in head and neck cancer. Cell Cycle, 12: 1371–1384.

[33] Lamb R, Harrison H, Hulit J, Smith DL, Lisanti MP, Sotgia F. (2014) Mitochondria as new therapeutic targets for eradicating cancer stem cells: quantitative proteomics and functional validation via MCT1/2 inhibition. Oncotarget, 5: 11029–11037.

[34] Miao P, Sheng S, Sun X, Liu J, Huang G. (2013) Lactate dehydrogenase A in cancer: a promising target for diagnosis and therapy. IUBMB Life, 65: 904-910.

[35] Pavlides S, Whitaker-Menezes D, Castello-Cros R, Flomenberg N, Witkiewicz AK, Frank PG, Casimiro MC, Wang C, Fortina P, Addya S, Pestell RG, Martinez-Outschoorn UE, Sotgia F, Lisanti MP. (2009) The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. Cell Cycle, 8: 3984–4001.

[36] Hunt TK, Aslam RS, Beckert S, Wagner S, Ghani QP, Hussain MZ, Roy S, Sen CK. (2007) Aerobically derived lactate stimulates revascularization and tissue repair via redox mechanisms. Antioxid Redox Signal, 9: 1115–1124.

[37] Porporato PE, Payen VL, De Saedeleer CJ, Préat V, Thissen JP, Feron O, Sonveaux P. (2012) Lactate stimulates angiogenesis and accelerates the healing of superficial and ischemic wounds in mice. Angiogenesis, 15: 581–592.

[38] Vegran, F., Boidot, R., Michiels, C., et al.: (2011) Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-kappaB/IL-8 pathway that drives tumor angiogenesis. Cancer Res, 71: 2550–2560.

[39] Li F, Xiang H, Pang Z, Chen Z, Dai J, Chen S, Xu B, Zhang T. (2020) Association between Lactate Dehydrogenase Levels and Oncologic Outcomes in Metastatic Prostate Cancer: A Meta-analysis. Cancer Med, 9: 7341–51.

[40] Deme D, Telekes A. (2017) [Prognostic importance of lactate dehydrogenase (LDH) in oncology]. Orv Hetil, 158: 1977-1988. Hungarian

[41] Liu Y, Chen S, Zheng C, Ding M, Zhang L, Wang L, Xie M, Zhou J. (2017) The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. BMC Cancer, 17: 285. doi:10.1186/s12885-017-3220-x.

[42] Koh YW, Lee HW. (2017) Prognostic impact of C-reactive protein/albumin ratio on the overall survival of patients with advanced nonsmall cell lung cancers receiving palliative chemotherapy. Medicine (Baltimore), 96: e6848. doi: 10.1097/MD.0000000000006848.

[43] He X, Li JP, Liu XH, Zhang JP, Zeng QY, Chen H, Chen SL (2018) Prognostic value of C-reactive protein/albumin ratio in predicting overall survival of Chinese cervical cancer patients overall survival: comparison among various inflammation based factors. J Cancer, 9: 1877-1884.

[44] Tsujino T, Komura K, Hashimoto T, Muraoka R, Satake N, Matsunaga T, Tsutsumi T, Yoshikawa Y, Takai T, Minami K, Uehara H, Hirano H, Nomi H, Ibuki N, Takahara K, Inamoto T, Ohno Y, Azuma H. (2019) C-reactive protein-albumin ratio as a prognostic factor in renal cell carcinoma - A data from multi-institutional study in Japan. Urol Oncol, 37: 812.e1-812.e8.

[45] Yang S, Zhao K, Ding X, Jiang H, Lu H. (2019) Prognostic Significance of Hematological Markers for Patients with Nasopharyngeal Carcinoma: A Meta-analysis. J Cancer, 10: 2568-2577.

[46] Kudou K, Saeki H, Nakashima Y, Kamori T, Kawazoe T, Haruta Y, Fujimoto Y, Matsuoka H, Sasaki S, Jogo T, Hirose K, Hu Q, Tsuda Y, Kimura K, Ando K, Oki E, Ikeda T, Maehara Y. (2019) C-reactive protein/albumin ratio is a poor prognostic factor of esophagogastric junction and upper gastric cancer. J Gastroenterol Hepatol, 34: 355-363.

[47] Fan Z, Fan K, Gong Y, Huang Q, Yang C, Cheng H, Jin K, Ni Q, Yu X, Luo G, Liu C. (2019) The CRP/Albumin Ratio Predicts Survival And Monitors Chemotherapeutic Effectiveness In Patients With Advanced Pancreatic Cancer. Cancer Manag Res, 11: 8781-8788.

[48] Ishibashi Y, Tsujimoto H, Hiraki S, Kumano I, Yaguchi Y, Horiguchi H, Nomura S, Ito N, Shinto E, Aosasa S, Yamamoto J, Ueno H. (2018) Prognostic Value of Preoperative Systemic Immunoinflammatory Measures in Patients with Esophageal Cancer. Ann Surg Oncol, 25: 3288-3299.

[49] Wang Q, Song X, Zhao Y, He Q, Shi M, Xu P, Ni S, Chen Y, Lin J, Zhang L. (2019) Preoperative high c-reactive protein/albumin ratio is a poor prognostic factor of oral squamous cell carcinoma. Future Oncol, 15: 2277-2286.

[50] Burgassi F, Paillaud E, Poisson J, Bousquet G, Pamoukdjian F. (2021) Prognostic Value of Prospective Longitudinal CRP to Albumin Ratio among Older Outpatients with Cancer. Cancers, 13: 5782. https://doi.org/10.3390/cancers13225782

[51] Yu J, Liu H, Zeng X, Zhao Y, Jiang D, Lu H, Qian J. (2021) Prognostic and clinicopathological significance of C-reactive protein/albumin ratio (CAR) in patients with gastric cancer: A meta-analysis, PLoS One. 16: e0250295.

[52] Fang Y, Zheng T, Zhang C. (2021) Prognostic Role of the C-Reactive Protein/Albumin Ratio in Patients With Gynecological Cancers: A Meta-Analysis. Front Oncol, 11: 737155. doi: 10.3389/fonc.2021.737155.

[53] Hajdu SI. (2003) The Discovery of Blood Cells. Ann Clin Lab Sci, 33: 237-238.

[54] Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E. (2014) Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst, 106: dju124. doi: 10.1093/jnci/dju124.
[55] Yang Y, Liu R, Ren F, Guo R, Zhang P. (2018) Prognostic and clinicopathological significance of neutrophil-to-lymphocyte ratio in patients with oral cancer. Biosci Rep, 38. pii: BSR20181550.
[56] Chen G, Zhu L, Yang Y, Long Y, Li X, Wang Y. (2018) Prognostic Role of Neutrophil to Lymphocyte Ratio in Ovarian Cancer: A Meta-Analysis. Technol Cancer Res Treat, 17:1533033818791500. doi:10.1177/1533033818791500.
[57] Liu G, Ke LC, Sun SR. (2018) Prognostic value of pretreatment neutrophil-to-lymphocyte ratio in patients with soft tissue sarcoma: A meta-analysis. Medicine (Baltimore), 97:e12176. doi:10.1097/MD.0000000000012176.
[58] Pirozzolo G, Gisbertz SS, Castoro C, van Berge Henegouwen MI, Scarpa M. (2019) Neutrophil-to-lymphocyte ratio as prognostic marker in esophageal cancer: a systematic review and meta-analysis. J Thorac Dis, 11: 3136-3145.
[59] Wang Z, Zhan P, Lv Y, Shen K, Wei Y, Liu H, Song Y. (2019) Prognostic role of pretreatment neutrophil-to-lymphocyte ratio in non-small cell lung cancer patients treated with systemic therapy: a meta-analysis. Transl Lung Cancer Res, 8: 214-226.
[60] Ding Y, Zhang S, Qiao J. (2018) Prognostic value of neutrophil-to-lymphocyte ratio in melanoma: Evidence from a PRISMA-compliant meta-analysis. Medicine (Baltimore), 97:e11446. doi: 10.1097/MD.0000000000011446
[61] Maretty-Nielsen K. (2014) Prognostic factors in soft tissue sarcoma. Population-based studies on comorbidity, biomarkers, and methodological aspects. Dan Med J, 61: B4957
[62] Cho JK, Kim MW, Choi IS, Moon UY, Kim MJ, Sohn I, Kim S, Jeong HS. (2018) Optimal cutoff of pretreatment neutrophil-to-lymphocyte ratio in head and neck cancer patients: a meta-analysis and validation study. BMC Cancer, 18: 969.
[63] Mantovani A, Allavena P, Sica A, Balkwill F. (2008) Cancer-related inflammation. Nature, 454: 436-444.

[64] Dunn GP, Old LJ, Schreiber RD. (2004) The immunobiology of cancer immunosurveillance and immunoediting. Immunity, 21: 137-148.
[65] Shibutani M, Maeda K, Nagahara H, Ohtani H, Sakurai K, Yamazoe S, Kimura K, Toyokawa T, Amano R, Tanaka H, Muguruma K, Hirakawa K. (2015) Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer. World J Gastroenterol, 21: 9966-9973.
[66] Condeelis J, Pollard JW. (2006) Macrophages: Obligate partners for tumor cell migration, invasion, and metastasis. Cell, 124: 263-266.
[67] Qian BZ, Pollard JW. (2010) Macrophage diversity enhances tumor progression and metastasis. Cell, 141: 39-51.
[68] Shibutani M, Maeda K, Nagahara H, Iseki Y, Ikeya T, Hirakawa K. (2017) Prognostic significance of the preoperative lymphocyte-to-monocyte ratio in patients with colorectal cancer. Oncol Lett, 13: 1000-1006.
[69] Chang Y, An H, Xu L, Zhu Y, Yang Y, Lin Z, Xu J. (2015) Systemic inflammation score predicts postoperative prognosis of patients with clear-cell renal cell carcinoma. Br J Cancer, 113: 626-633.
[70] Zhou W, Kuang T, Han X, Chen W, Xu X, Lou W, Wang D. (2020) Prognostic role of lymphocyte-to-monocyte ratio in pancreatic neuroendocrine neoplasms. Endocr Connect, pii: EC-19-0541.R1. doi: 10.1530/EC-19-0541.
[71] Song L, Zhu J, Li Z, Wei T, Gong R, Lei J. (2019) The prognostic value of the lymphocyte-to-monocyte ratio for high-risk papillary thyroid carcinoma. Cancer Manag Res, 11: 8451-8462. doi: 10.2147/CMAR.S219163. eCollection 2019.
[72] Chen XQ, Xue CR, Hou P, Lin BQ, Zhang JR. (2019) Lymphocyte-to-monocyte ratio effectively predicts survival outcome of patients with obstructive colorectal cancer. World J Gastroenterol, 25: 4970-4984.
[73] Song Q, Wu JZ, Wang S. (2019) Low Preoperative Lymphocyte to Monocyte Ratio Serves as a Worse Prognostic Marker in Patients with Esophageal Squamous Cell Carcinoma Undergoing Curative Tumor Resection. J Cancer, 10: 2057-2062.
[74] Lu C, Zhou L, Ouyang J, Yang H. (2019) Prognostic value of lymphocyte-to-monocyte ratio in ovarian cancer: A meta-analysis. Medicine (Baltimore), 98: e15876. doi: 10.1097/MD.0000000000015876.

[75] Wang J, Zhou X, He Y, Chen X, Liu N, Ding Z, Li J. (2018) Prognostic role of platelet to lymphocyte ratio in prostate cancer: A meta-analysis. Medicine (Baltimore), 97: e12504. doi: 10.1097/MD.0000000000012504.
[76] Tian C, Song W, Tian X, Sun Y. (2018) Prognostic significance of platelet-to-lymphocyte ratio in patients with ovarian cancer: A meta-analysis. Eur J Clin Invest, 48: e12917. doi: 10.1111/eci.12917.
[77] Cao W, Yao X, Cen D, Zhi Y, Zhu N, Xu L. (2020) The prognostic role of platelet-to-lymphocyte ratio on overall survival in gastric cancer: a systematic review and meta-analysis. BMC Gastroenterol, 20: 16. doi.org/10.1186/s12876-020-1167-x
[78] Bardash Y, Olson C, Herman W, Khaymovich J, Costantino P, Tham T. (2019) Platelet-Lymphocyte Ratio as a Predictor of Prognosis in Head and Neck Cancer: A Systematic Review and Meta-Analysis. Oncol Res Treat, 42: 665-677.
[79] Wang X, Ni X, Tang G. (2019) Prognostic Role of Platelet-to-Lymphocyte Ratio in Patients With Bladder Cancer: A Meta-Analysis. Frontiers in Oncology, 9: 757. doi: 10.3389/fonc.2019.00757
[80] Zhang M, Huang X, Song Y, Gao P, Sun J, Wang Z. (2017) High Platelet-to-Lymphocyte Ratio Predicts Poor Prognosis and Clinicopathological Characteristics in Patients with Breast Cancer: A Meta-Analysis. BioMed Research International, 2017: 9503025. doi.org/10.1155/2017/9503025
[81] Tian C, Song W, Tian X, Sun Y. (2018) Prognostic significance of the platelet-to-lymphocyte ratio in ovarian cancer: a meta-analysis. Translational Cancer Research, 7: 552-560.
[82] Song W, Tian C, Wang K, Zhang Rj, Zou Sb. (2017) Preoperative platelet lymphocyte ratio as independent predictors of prognosis in pancreatic cancer: A systematic review and meta-analysis. PLOS ONE, 12: e0178762. doi: 10.1371/journal.pone.0178762
[83] You J, Zhu GQ, Xie L, Liu WY, Shi L, Wang OC, Huang ZH, Braddock M, Guo GL, Zheng MH. (2016) Preoperative platelet to lymphocyte ratio is a valuable prognostic biomarker in patients with colorectal cancer. Oncotarget, 7: 25516-25527. doi: 10.18632/oncotarget.8334

[84] Zhang X, Wang Y, Zhao L, Sang S, Zhang L. (2018) Prognostic value of platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: A systematic review and meta-analysis. The International Journal of Biological Markers, 33: 335-344.
[85] Lim JU, Yeo CD, Kang HS, Park CK, Kim JS, Kim JW, Kim SJ, Lee SH. (2019) Elevated pretreatment platelet-to-lymphocyte ratio is associated with poor survival in stage IV non-small cell lung cancer with malignant pleural effusion. Sci Rep, 9: 4721 doi.org/10.1038/s41598-019-41289-9
[86] Lee Y, Kim YW, Park DK, Hwang IC. (2017) Inverse Association between Platelet–Lymphocyte Ratio and Prognosis in Terminally Ill Cancer Patients: A Preliminary Study. Journal of Palliative Medicine, 20: 533-537.
[87] Deme D, Kovacs S, Telekes A. (2022) Overall survival prediction of advanced cancer patients by selection of the most significant baseline serum biomarker combination . Pathol Oncol Res, DOI: 10.3389/pore.2022.1610004
[88] Deme D. (2022) [Prognostic role of neutrophil to lymphocyte ratio determined by complete blood count in malignant diseases]. Orv Hetil, 2022; 163: 1066-1073. [Article in Hungarian].
[89] MedCalc Software Ltd. Diagnostic test evaluation calculator. https://www.medcalc.org/calc/diagnostic_test.php (Version 20.100; accessed on March 27, 2022)
[90] Greten, FR, and Grivennikov, SI. (2019) Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity, 51: 27–41.
[91] Zhang J, Zhang C, Li Q, Zhang J, Gu X, Zhao W, Chen M, Liu M, Zhang Z, Liao X, Cheng W. (2019) C-Reactive Protein/Albumin Ratio Is an Independent Prognostic Predictor of Survival in Advanced Cancer Patients Receiving Palliative Care. J Palliat Med, 22: 1536-1545.
[92] Yamagata K, Fukuzawa S, Ishibashi-Kanno N, Uchida F, Bukawa H. (2021) Association between the C-reactive protein/albumin ratio and prognosis in patients with oral squamous cell carcinoma. Sci Rep, 11: 5446. doi: 10.1038/s41598-021-83362-2.
[93] Zhou J, Wei W, Hou H, Ning S, Li J, Huang B, Liu K, Zhang L. (2021) Prognostic Value of C-Reactive Protein, Glasgow Prognostic Score, and C-Reactive Protein-to-

Albumin Ratio in Colorectal Cancer. Front Cell Dev Biol, 9: 637650. doi: 10.3389/fcell.2021.637650.
[94] Minami S, Ihara S, Kim SH, Yamamoto S, Komuta K. (2018) Lymphocyte to Monocyte Ratio and Modified Glasgow Prognostic Score Predict Prognosis of Lung Adenocarcinoma Without Driver Mutation. World J Oncol, 9: 13-20.
[95] Jia T, Zhang R, Kong F, Zhang Q, Xi Z. (2021) The Prognostic Role and Nomogram Establishment of a Novel Prognostic Score Combining with Fibrinogen and Albumin Levels in Patients with WHO Grade II/III Gliomas. Int J Gen Med, 14: 2137-2145.
[96] Xie Z, Zhou H, Wang L, Wu Y. (2022) The Significance of the preoperative lactate dehydrogenase/albumin Ratio in the Prognosis of Colon Cancer: a retrospective study. PeerJ, 10: e13091. doi: 10.7717/peerj.13091.
[97] Zhang L, Wang Z, Xiao J, Zhang Z, Li H, Li F, Zhang L, Wang Y. (2021) Prognostic Value of Albumin to D-Dimer Ratio in Advanced Gastric Cancer. J Oncol, 2021: 9973743. doi: 10.1155/2021/9973743.
[98] Ma YY, Wang H, Zhao WD, Li YF, Wang JJ, Chen XY, Huang YQ, Wang WJ, Wang Y, Sun SC. (2022) Prognostic Value of Combined Lactate Dehydrogenase, C-Reactive Protein, Cancer Antigen 153 and Cancer Antigen 125 in Metastatic Breast Cancer. Cancer Control, 29: 10732748211053150. doi: 10.1177/10732748211053150.
[99] uo HS, Xu HY, Du ZS, Li XY, Wu SX, Huang HC, Lin LX. (2020) Prognostic Significance of Baseline Neutrophil Count and Lactate Dehydrogenase Level in Patients With Esophageal Squamous Cell Cancer Treated With Radiotherapy. Front Oncol, 10: 430. doi: 10.3389/fonc.2020.00430.
[100] Huszno J, Kolosza Z. (2019) Prognostic value of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratio in breast cancer patients. Oncol Lett, 18: 6275-6283.

9. Bibliography of the candidate's publications

9.1. Publications related to dissertation

1. Deme D, Kovacs S, Telekes A. (2022) Overall survival prediction of advanced cancer patients by selection of the most significant baseline serum biomarker combination. Pathol Oncol Res, DOI: 10.3389/pore.2022.1610004 (**Expected IF 2.874**)

2. Deme D. (2022) [Prognostic role of neutrophil to lymphocyte ratio determined by complete blood count in malignant diseases]. Perifériás vér neutrophil-lymphocyta arány prognosztikai értéke daganatos betegségekben. Orv Hetil, 2022; 163: 1066-1073. [Article in Hungarian]. (**Expected IF 0.707**)

9.2. Publications independent to dissertation

1. Deme D, Al-Hadad A, Varga T, Szántó E, Sándor K, Rakonczai E. (2009) [Maximal initial dose of simvastatin causing acute renal failure through rhabdomyolysis: risk factors, pathomechanism and therapy related to a case]. Maximális kezdődózissal indított és heveny veseelégtelenséggel szövődött simvastatin indukálta rhabdomyolysis: rizikófaktorok, patomechanizmus és kezelés egy eset kapcsán. Orv Hetil, 150: 265-269. [Article in Hungarian].

2. Deme D, Ragán M, Kalmár K, Kovács L, Varga E, Varga T, Rakonczai E. (2010) [Metastatic prostate cancer complicated with chronic disseminated intravascular coagulopathy causing acute renal failure, mimicking thrombotic thrombocytopenic purpura and hemolytic uremic syndrome: pathomechanism, differential diagnosis and therapy related to a case]. TTP-HUS klinikai képét utánzó és heveny veseelégtelenséggel szövődő krónikus DIC hátterében álló metasztatikus prosztatarák: patomechanizmus, differenciáldiagnózis és kezelés egy eset kapcsán. Magy Onkol, 54: 351-357. [Article in Hungarian].

3. Deme D, Telekes A. (2015) [Therapeutic options for synovial sarcoma]. Sarcoma synoviale kezelési lehetőségei. Orv Hetil, 156: 875-880. [Article in Hungarian]. (**IF 0.291**)

4. Deme D, Bishr AM, Nizar J, Telekes A. (2015) [Individualized therapy of synchronous ovarian and colon cancers with lymph]. Személyre szabott kezelés szinkron, nyirokcsomó pozitív petefészek- és vastagbéldaganatban. Orv Hetil, 156: 939-943. [Article in Hungarian]. (**IF 0.291**)

5. Deme D, Bishr AM, Telekes A. (2016) [Synovial sarcoma. Case report]. Sarcoma synoviale - esetismertetés. Orv Hetil, 157: 224-229. [Article in Hungarian]. (**IF 0.349**)

6. Deme D, Telekes A. (2016) [Close follow-up of oncologic patients with imaging - advantage or disadvantage?] Az onkológiai páciensek szoros képalkotó követése – előny vagy hátrány? Orv Hetil, 157: 1538-1545. [Article in Hungarian]. (**IF 0.349**)

7. Telekes A, Deme D. (2016) [Ramucirumab - a new anticancer agent]. Ramucirumab – új daganatellenes szer. Orv Hetil, 157: 1587-1594. [Article in Hungarian]. (**IF 0.349**)

8. Deme D, Telekes A. (2017) [Prognostic importance of plasma C-reactive protein (CRP) in oncology]. A plazma C-reaktív protein (CRP) prognosztikai jelentősége az onkológiában. Orv Hetil, 158: 243–256. [Article in Hungarian]. (**IF 0.322**)

9. Deme D, Telekes A. (2017) [Prognostic importance of lactate dehydrogenase (LDH) in oncology]. A laktát dehidrogenáz (LDH) prognosztikai jelentősége az onkológiában. Orv Hetil, 158:1977-1988. [Article in Hungarian]. (**IF 0.322**)

10. Deme D, Telekes A. (2017) [Prognostic importance of cross-linked fibrin degradation products (D-dimer) in oncology]. A keresztkötött fibrin degradációs termékek (D-dimer) prognosztikai jelentősége az onkológiában. Magy Onkol, 61: 319-26. [Article in Hungarian].

11. Deme D, Telekes A. (2018) [Prognostic importance of albumin in oncology]. Az albumin prognosztikai jelentősége az onkológiában. Orv Hetil, 159: 96–106. [Article in Hungarian]. (**IF 0.564**)

12. Deme D, Telekes A. (2018) [Effectivity of bevacizumab rechallenge treatment in liver metastasis of colon cancer. Case report]. Bevacizumab rechallenge kezelés hatékonysága vastagbél daganat májáttétje esetén – esetismertetés. Orv Hetil, 2018, 159: 1284-1290. [Article in Hungarian]. (**IF 0.564**)

13. Telekes A, Deme D. [Principles of pharmacotherapy in the elderly. Review.]. Az időskori gyógyszerterápia alapjai – áttekintő közlemény
Orv Hetil. 2019, 160: 896-907. [Article in Hungarian]. (**IF 0.417)**

10. Acknowledgements

Gloria in excelsis Deo!

I am grateful to my Parents, who supported me in my studies from the very beginning.

I am grateful to my teachers and school mates for the useful knowledge I earned.

I am grateful to Ferenc Szalay Professor of Semmelweis University, Budapest and late Péter Gyepes Chief Doctor of Internal Medicine of Szent Lázár Megyei Kórház, who taught me the patient-oriented attitude and encouraged me during the medical years. I am grateful to Lajos Bercsényi retired Director of Szent Lázár Megyei Kórház, as he left me in the care of excellent mentors during the medical years and after graduation. He also conducted me toward oncology and secured me with his support. I am grateful to Zsuzsanna Szőllősi retired Chief Doctor of Oncology of Szent Lázár Megyei Kórház for sharing with me her attitude of the complexity of medicine and oncology. I am grateful to Ervin Rakonczai retired Chief Doctor of Internal Medicine of Szent Lázár Megyei Kórház, who taught me for specialization. I am grateful to all advices and helps of the colleges of all doctors, nurses and co-workers of the Szent Lázár Megyei Kórház. I am grateful to Márta Baki, Candidate of Uzsoki Kórház, who supported me with her advices. I am grateful to Gábor Pajkos retired Candidate, who led me into the modern practise of oncological therapy. I am grateful to Professor András Telekes of Semmelweis University, who taught me the practical and scientific mindset for oncology, and he supported me both his professional and cordial advices. I am grateful to Abdulfatah M. Bishr Chief Doctor of Oncology of Szent Lázár Megyei Kórház, who supported my professional advance. I am grateful to Judit Molnár retired leader of the Clinical Laboratory Department of Szent Lázár Megyei Kórház, and all her colleges, whom I was cooperating to perform all the laboratory tests. I am grateful to Tamás Laczkó Strategic Director of Szent Lázár Megyei Kórház, who supported my scientific work. I am grateful to Sándor Kovács, Doctor of Phylosophy, Docent of the Department of Economical and Financial Mathematics at the University of Debrecen, who performed the statistical tests. I am grateful to Prof. Dr. Barna Vásárhelyi, the Director of the Department of Laboratory Medicine of the Semmelweis University, Budapest for the detailed evaluations and the valuable suggestions.

I am grateful to my wife, who is supporting me in everything.