



Oxidative stress and PARP activation in the lungs is an early event in COVID-19 pneumonia

Péter Juhász^{a,1}, Péter Bohus^b, Adrienn Sipos^c, Nicola Curtin^d, Gábor Méhes^{a,*}, Péter Bai^{d,efgh,**}

^a Department of Pathology, Faculty of Medicine, University of Debrecen, 4032, Debrecen, Hungary

^b Sátorajaiújhely Erzsébet Hospital, Sátorajaiújhely, 3980, Hungary

^c Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, Debrecen, 4032, Hungary

^d Translational and Clinical Research Institute, Newcastle University Centre for Cancer, Faculty of Medical Sciences, Newcastle University, NE2 4HH, Newcastle Upon Tyne, UK

^e HUN-REN Cell Biology and Signaling Research Group, Debrecen, 4032, Hungary

^f The Hungarian Academy of Sciences, Center of Excellence, Debrecen, Hungary

^g MTA-DE Lendület Laboratory of Cellular Metabolism, Debrecen, 4032, Hungary

^h Research Center for Molecular Medicine, Faculty of Medicine, University of Debrecen, Debrecen, 4032, Hungary

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ABSTRACT

Oxidative stress and poly (ADP-ribosylation) (PARylation) leads to tissue damage and inflammation in multiple lung diseases, likely in COVID-19. In a previous study we evidenced PARylation in multiple pulmonary cell types in patients who died of COVID-19, but not in patients who died of non-COVID-19 causes. We extended these observations in this retrospective immunohistochemical study by enlarging and stratifying the study population to identify subpopulations with high expression of the markers assessed in the study. We showed that pulmonary PARylation and oxidative stress peaked in the exudative and then decreased in the proliferative phase. PARylation correlated with viral load and with the oxidative stress in the tissues, however, correlation between viral load and oxidative stress was marginal suggesting that oxidative stress and the presence of SARS-CoV-2 can independently induce PARylation. Pulmonary oxidative stress, PARylation and TNF α expression correlated with the serum markers of liver and kidney damage, oxygen transport, tissue hypoxia, lymphocytopenia, blood clotting and disseminated intravascular coagulation. In males the time of hospitalization (time to death) was inversely correlated with pulmonary PARylation. Furthermore, males, died of COVID-19, were ~15 years younger than females, however, there was no difference in pulmonary oxidative stress and PARylation between genders at death. Taken together, pulmonary PARylation and oxidative stress manifests early, in the exudative phase of COVID-19 and PARylation contributes to worse clinical outcome for males. These results suggest repurposing pharmacological PARP inhibitors for acute COVID-19 to counteract tissue damage.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 was the third leading cause of death in the United States in 2022 [1]. The etiology of COVID-19 disease is not fully established, nevertheless, oxidative tissue damage was evidenced in multiple organs [2–7] that likely has pathogenic significance. COVID-19 disease, especially its severe form, are characterized by excessive inflammation and cytokine storm [8]. The predisposing factors for severe or fatal COVID-19 in-

clude advanced age [9,10], male sex [11–13], chronic diseases as metabolic diseases [14–18] or cardiovascular diseases [19,20].

PARP enzymes constitute a family of 17 members in humans [21–23], of which PARP1 and PARP2 are responsible for the bulk of cellular PARP activity (reviewed in Ref. [24]). PARP1, PARP2 and PARP3 can be activated by oxidative stress-evoked DNA damage [21–23]. When activated, PARPs cleave NAD⁺ into ADP-ribose and nicotinamide, with the ADP-ribose units being transferred onto acceptor proteins, generating poly (ADP-ribose) (PAR) that is a marker of PARP activation. This process is called PARylation. Cellular PARP activity is re-

* Corresponding author. University of Debrecen, Faculty of Medicine, Department of Pathology, Nagyerdei krt. 98 Debrecen, 4032, Hungary.

** Corresponding author. University of Debrecen, Faculty of Medicine, Department of Medical Chemistry, Egyetem tér 1 Debrecen, 4032, Hungary.

E-mail addresses: gabor.mehes@med.unideb.hu (G. Méhes), baip@med.unideb.hu (P. Bai).

¹ joint first authorship.

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Table 1
Common features of low NAD⁺ levels, COVID-19 and PARP activation.

Predisposing factor for severe or fatal COVID-19	Relation to PARP activation
Inflammatory response and cytokine storm [8].	PARP1 and PARP2 are proinflammatory [31,32].
Advanced age [9,10].	PARP activity increases in aging [42–45].
Metabolic diseases (type II diabetes, metabolic syndrome, and obesity) [14,15].	PARP overactivation acts as a metabolic disruptor and contributes to obesity and diabetes [46,47].
Mitochondrial damage and metabolic rearrangement [16–18].	PARP activation disrupts mitochondrial oxidation [48].
Men are at higher risk [11–13].	PARP activity is higher in men [49–51].
Cardiovascular diseases [19,20].	PARP activation contributes to cardiovascular diseases [52–55].

sponsible for the conversion of a large fraction of cellular NAD⁺ to nicotinamide and ADP-ribose [25,26].

PARP activation is associated with multiple events related to COVID-19 pneumonia (listed in Table 1 and reviewed in Ref. [27]), as oxidative stress-induced apoptotic or necrotic tissue damage [23,28–30], inflammation [31,32], acute respiratory distress syndrome [33], fibrosis [34–38], or mechanical lung injury [39–41]. PARP activation was demonstrated in the lung biopsies of patients who died of COVID-19 [7], however the study by Papp and colleagues [7] did not aim at understanding changes to PARP activity and related processes on the course of the disease. Therefore, in this study we aimed to assess how PARP activity changes with the resolution of COVID-19 and whether PARP activation may contribute to differences in the outcome of the disease between sexes.

2. Materials and methods

2.1. Patients

An ethical permit was issued for the retrospective human study by the Regional Ethical Committee of the University of Debrecen under the registration number DE RKEB/IKEB 6240-2022, the date of issuing the ethical permit is December 8, 2022. Demographics of patient cohorts are in Table 2.

We assessed all patients who died of COVID-19 at Szent Erzsébet Hospital (Sátoraljaújhely, Hungary) between November 30, 2020 – 6th February 2021. A part of this patient cohort was assessed already [7], in this study we complemented that study by assessing all patients who died of COVID-19 during the indicated period. We *excluded* all patients with nosocomial infections and one young female COVID-19 patient due to long-standing alcoholism (alcoholism induces PARP activity, e.g. Ref. [56]). A total of 40 patients were enrolled to the study, of which 28 fulfilled the aforementioned criteria. COVID-19 patients had severe pneumonia involving both lungs (90–100 % area inflamed). Patients were stratified as a function of the stage of the disease (exudative vs. proliferative) based on the histology findings that was verified by two independent pathologists; no ambiguous cases were identified.

2.2. Medical records

The time of hospitalization was counted in days and each 24 h that was begun was counted as a whole day (e.g. 36 h of hospitalization counts as 2 days).

Interim blood tests (if performed) were reviewed and the results for 1) admission, 2) closest to/before death and 3) with the maximum/minimum of change in a parameter were identified. If one single blood test result was available that result was used as admission, death and maximum/minimum data.

The following clinical data was extracted from the medical records; the abbreviations in the online file are in brackets): days of hospitaliza-

tion, serum sodium (SNA), serum potassium (SK), serum chloride (SCL), serum total calcium (SCA), serum phosphate (SP), serum magnesium, serum glucose (EGLU), serum urea (UREA), serum kreatinin (KREA), serum total bilirubin (TBIL), direct bilirubin (DBIL), glomerular filtration rate (GFR), serum creatinine kinase (CK), cardiac-type creatinine kinase (CKMB), cardiac troponin T (cTnT), lactate dehydrogenase (LDH), glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), C-reactive protein (CRPS), white blood cell count (WBC), lymphocyte count (LYM), monocyte count (MON), granulocyte count (GRN), eosinophil count (EOS), basophil count (BAS), lymphocyte % (LYM%), monocyte % (MON%), granulocyte % (GRN%), eosinophil % (EOS%), basophil % (BAS%), red blood cell count (RBC), hemoglobin (HGB), hematocrit% (HCT%), mean corpuscular volume (MCV), Mean Corpuscular Hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width% (RDW%), platelet count (PLT), platelet % (PLT%), plateletocrit (PCT%) mean platelet volume (MPV), platelet distribution width (PDW), partial thromboplastin time (PTT), international normalized ratio (INR), fibrin (FIBR), D-dimer (DDIM), ferritin (FERR), IL-6, thrombin time (TT), activated partial thrombin time (APTT), serum triglyceride (TG), hemoglobin A1c (HBA1C), serum lipase, serum cholesterol (CHOL). All extracted data can be found in the online Graphpad spreadsheets (at <https://figshare.com/s/725650d2036f586f065f>) and only the significant data are displayed in the manuscript.

2.3. Immunohistochemistry

The description of the immunohistochemistry protocol is provided in the Supplementary materials.

2.4. Statistical evaluation

GraphPad Prism v. 8.0.1 was used for statistics. Statistical tests are indicated in the figure or table captions.

3. Results

3.1. Oxidative stress and PARYlation is stronger in the exudative versus the proliferative phase of COVID-19

Previously we showed that markers of oxidative stress and PARYlation are present in the lung biopsies of patients who died of COVID-19 [7]. In this study we enlarged the patient cohort by recruiting all patients who died of COVID-19, but did not have nosocomial infections between November 30, 2020 – 6th February 2021 at the Erzsébet Hospital in Sátoraljaújhely. Immunohistochemical sections of all eligible patients were scored for spike, 4HNE, PAR and TNF α immunostaining intensity and the percent of 4HNE+, PAR+ or TNF α + cells was determined (latter denoted as 4HNE%, PAR% and TNF α %) and patients were stratified as a function of whether they died in the exudative or proliferative phase of COVID-19 [57]. All histological scores were higher in patients who died in the exudative versus those died in the proliferative phase with the exception of TNF α intensity and 4HNE% that was not statistically different between stages, nevertheless, in the case of TNF α intensity we observed a downward trend (Fig. 1A). Endothelial cells and pneumocytes were spike, PAR and TNF α + positive in all cases in both phases. While pneumocytes were 4HNE positive in all cases in both phases in contrast to endothelial cells. The proportion of negative cases where 4HNE staining in the endothelium was negative was 29 % in the exudative and 9 % in the proliferative phase (Fig. 1B).

PAR% correlated with spike intensity and 4HNE intensity in all patients (Fig. 2, Table S2). However, 4HNE indices and spike intensity had no correlation, suggesting that the two PARYlation inducers are likely unrelated (Fig. 2). The percent of TNF α positive cells correlated with

Table 2

Patient characteristics comparing the age between subgroups of patients, normality was checked using the Shapiro-Wilk test then one-way ANOVA test followed by the Kruskal-Wallis test was applied and all groups were compared in all combinations; none of the comparisons proved to be significant except of the comparison between males and females ($p < 0.001$, marked by ***). In all lines the average $\pm$ SD is marked, below which the number of patients with the clinical read-out is presented (i.e. n number).

Average ± SD Number of values (n)								
			Ref. range	All	Female	Male	Ex.	Prolif.
Percent of all patients				100 %	50 %	50 %	60.7 %	39.3 %
Age (years)				68.8 ± 12.4	76.7 ± 10.7	59.8 ± 7.9 ***	71.0 ± 14.3	65.3 ± 8.1
hospitalization (days)				28	14	14	17	11
				7.96 ± 6.22	9.57 ± 5.93	6.36 ± 6.30	7.41 ± 6.36	8.82 ± 6.19
SK (mmol/L)				28	14	14	17	11
adm.	3.5–5.3		4.15 ± 0.63	4.08 ± 0.73	4.23 ± 0.52	4.13 ± 0.74	4.18 ± 0.45	
			23	12	11	14	9	
		death	4.44 ± 0.92	4.52 ± 1.09	4.35 ± 0.74	4.78 ± 0.98	3.93 ± 0.54	
			22	11	11	13	9	
SCL (mmol/L)				99.18 ± 6.79	101.70 ± 3.94	96.20 ± 8.40	100.00 ± 8.23	97.60 ± 2.88
adm.	99–111		22	12	10	14	8	
		death	101.70 ± 5.36	104.30 ± 4.38	98.90 ± 5.07	103.00 ± 3.98	100.00 ± 7.03	
			21	11	10	13	8	
SCA (mmol/L)				2.18 ± 0.31	2.16 ± 0.09	2.20 ± 0.40	2.08 ± 0.34	2.34 ± 0.18
adm.	2.1–2.6		13	5	8	8	5	
		death	2.21 ± 0.17	2.08 ± 0.08	2.29 ± 0.16	2.15 ± 0.13	2.30 ± 0.19	
			13	5	8	8	5	
min.			2.14 ± 0.31	2.08 ± 0.08	2.18 ± 0.39	2.05 ± 0.35	2.28 ± 0.19	
			13	5	8	8	5	
		SMG (mmol/L)				0.91 ± 0.26	1.07 ± 0.38	0.83 ± 0.16
adm.	0.60–1.10		9	3	6	5	4	
		death	1.04 ± 0.30	1.27 ± 0.40	0.93 ± 0.18	1.22 ± 0.29	0.83 ± 0.05	
			9	3	6	5	4	
EGLU (mmol/L)				10.86 ± 5.31	9.24 ± 3.83	12.63 ± 6.26	11.5 ± 5.52	9.91 ± 5.13
adm.	3.6–6.0		23	12	11	14	9	
		death	11.51 ± 6.11	9.15 ± 4.68	13.88 ± 6.64	11.8 ± 6.39	11.2 ± 6.04	
			22	11	11	13	9	
max.			12.38 ± 6.13	10.68 ± 5.10	14.07 ± 6.82	13 ± 6.22	11.5 ± 6.25	
			22	11	11	13	9	
		UREA (mmol/L)				12.70 ± 10.80	15.45 ± 13.91	9.71 ± 4.89
adm.	2.8–8.0		23	12	11	14	9	
		death	17.81 ± 18.30	23.75 ± 23.87	11.34 ± 4.49	23.10 ± 21.60	9.63 ± 6.05	
			23	12	11	14	9	
TBIL (μmol/L)				12 ± 3.06	11.58 ± 3.40	12.45 ± 2.74	12.8 ± 3.17	10.72.54
adm.	<20		21	11	10	13	8	
		death	17.37 ± 26.30	22.48 ± 37.42	12.25 ± 2.24	22.00 ± 33.70	10.40 ± 3.30	
			20	10	10	12	8	
max.			17.99 ± 26.10	23.05 ± 37.16	12.92 ± 2.15	22.50 ± 33.50	11.20 ± 2.27	
			20	10	10	12	8	
		DBIL (μmol/L)				3.32 ± 1.66	3.46 ± 2.20	3.17 ± 0.87
adm.	<5		21	11	10	14	7	
		death	7.49 ± 18.40	11.80 ± 25.96	3.17 ± 0.92	9.87 ± 22.80	3.06 ± 1.24	
			20	10	10	13	7	
max.			7.58 ± 18.40	11.80 ± 25.96	3.35 ± 0.78	10.00 ± 22.70	3.06 ± 1.24	
			20	10	10	13	7	
		LDH (U/L)				712 ± 553	761 ± 683	662 ± 411
adm.	135–220		22	11	11	14	8	
		death	829 ± 736	1012 ± 971	663 ± 410	1017 ± 892	524 ± 103	
			21	10	11	13	8	
max.			836 ± 733	1022 ± 967	668 ± 406	1020 ± 889	540 ± 122	
			21	10	11	13	8	
		GOT (U/L)				139 ± 252	186 ± 326	88 ± 131
adm.	<40		23	12	11	14	9	
		death	128 ± 215	163 ± 278	93 ± 130	181 ± 270	52 ± 27	
			22	11	11	13	9	
max.			155 ± 254	216 ± 332	94 ± 130	223 ± 317	56 ± 30	
			22	11	11	13	9	
		min.	117 ± 217	147 ± 282	87 ± 131	169 ± 275	44 ± 18	
			22	11	11	13	9	
GPT (U/L)				78 ± 144	94 ± 183	62 ± 90	107 ± 181	35 ± 24
adm.	<40		23	12	11	14	9	
		death	89 ± 148	113 ± 191	65 ± 89	127 ± 185	36 ± 25	
			22	11	11	13	9	
max.			91 ± 147	117 ± 190	65 ± 89	127 ± 185	40 ± 26	
			22	11	11	13	9	

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Table 2 (continued)

Average ± SD Number of values (n)							
		Ref. range	All	Female	Male	Ex.	Prolif.
GGT (U/L)	min.		79 ± 148 22	96 ± 192 11	62 ± 90 11	113 ± 187 13	30 ± 21 9
	adm.	7–50	113 ± 160 23	125 ± 214 12	100 ± 72 11	117 ± 195 14	109 ± 93 9
	death		186 ± 467 22	271 ± 662 11	101 ± 62 11	240 ± 606 13	109 ± 99 9
	max.		190 ± 467 22	275 ± 660 11	104 ± 71 11	240 ± 606 13	119 ± 102 9
	adm.	40–115	112 ± 92 22	102 ± 57 12	124 ± 124 10	86 ± 39 14	158 ± 136 8
ALP (U/L)	death		167 ± 238 21	198 ± 313 11	134 ± 119 10	168 ± 290 13	168 ± 132 8
	max.		169 ± 237 21	200 ± 312.26 11	135 ± 120 10	169 ± 289 13	168 ± 132 8
	min.		114.1 ± 93.9 21	104.7 ± 59.55 11	124.5 ± 124.3 10	87.2 ± 41.3 13	158 ± 136.9 8
	adm.	<5	126 ± 93 24	146 ± 93 12	106 ± 91 12	117 ± 83 14	140 ± 108 10
	death		105 ± 83 24	83 ± 81 12	126 ± 82 12	102 ± 90 14	109 ± 76 10
CRPS (mg/L)	max.		146 ± 84 23	166 ± 85 11	127 ± 81 12	129 ± 78 13	168 ± 90 10
	death	4–10	14.19 ± 7.0 24	15.2 ± 8.4 12	13.0 ± 5.5 12	14.7 ± 8.1 14	13.2 ± 5.6 10
	LYM (giga/L)	adm.	0.89 ± 0.83 24	0.77 ± 0.39 12	1.00 ± 1.12 12	0.82 ± 0.64 14	0.99 ± 1.06 10
	death		0.93 ± 0.83 24	0.72 ± 0.37 12	1.14 ± 1.10 12	0.79 ± 0.6 14	1.13 ± 1.08 10
	MON (giga/L)	adm.	0.67 ± 0.44 24	0.80 ± 0.39 12	0.53 ± 0.46 12	0.7 ± 0.43 14	0.61 ± 0.47 10
BAS (giga/L)	death		0.72 ± 0.42 24	0.71 ± 0.36 12	0.72 ± 0.49 12	0.66 ± 0.34 14	0.79 ± 0.53 10
	adm.	0–0.1	0.03 ± 0.03 21	0.04 ± 0.042 11	0.04 ± 0.02 10	0.04 ± 0.04 12	0.02 ± 0.01 9
	death		0.04 ± 0.04 21	0.05 ± 0.04 11	0.03 ± 0.03 10	0.04 ± 0.04 12	0.04 ± 0.03 9
	LYM (%)	adm.	8.87 ± 6.98 23	7.39 ± 5.18 12	10.49 ± 8.48 11	7.99 ± 5.98 13	10 ± 8.29 10
	death		7.9 ± 6.98 23	6.46 ± 5.47 12	9.47 ± 8.30 11	6.64 ± 4.97 13	9.54 ± 8.99 10
MON (%)	adm.	2–6	6.17 ± 4.59 23	7.43 ± 5.15 12	4.78 ± 3.64 11	6.78 ± 5.52 13	5.37 ± 3.13 10
	death		5.85 ± 3.92 23	6.10 ± 4.37 12	5.58 ± 3.55 11	5.55 ± 4.33 13	6.24 ± 3.50 10
	EOS (%)	adm.	0.34 ± 0.39 9	0.13 ± 0.15 6	0.77 ± 0.42 3	0.33 ± 0.40 4	0.36 ± 0.43 5
	death		0.43 ± 0.42 8	0.22 ± 0.30 5	0.77 ± 0.42 3	0.33 ± 0.49 3	0.48 ± 0.43 5
	BAS (%)	adm.	0.22 ± 0.17 21	0.24 ± 0.22 11	0.20 ± 0.11 10	0.27 ± 0.21 12	0.16 ± 0.07 9
RBC (tetra/L)	death		0.24 ± 0.19 21	0.26 ± 0.25 11	0.22 ± 0.12 10	0.23 ± 0.14 12	0.27 ± 0.26 9
	adm.	male: 4.0–5.2; female: 4.5–5.9	4.44 ± 0.72 24	4.31 ± 0.73 12	4.58 ± 0.71 12	4.42 ± 0.71 14	4.47 ± 0.77 10
	death		4.43 ± 0.82 24	4.11 ± 0.79 12	4.76 ± 0.74 12	4.54 ± 0.80 14	4.28 ± 0.86 10
	HGB (g/dL)	adm.	12.79 ± 1.94 24	12.82 ± 2.14 12	12.76 ± 1.82 12	12.70 ± 2.21 14	12.90 ± 1.60 10
	death		12.75 ± 2.42 24	12.13 ± 2.36 12	13.37 ± 2.43 12	13.10 ± 2.64 14	12.30 ± 2.15 10
HCT (%)	adm.	male: 41–50; female: 36–44	38.12 ± 5.65 24	37.75 ± 6.30 12	38.48 ± 5.18 12	37.90 ± 5.81 14	38.40 ± 5.72 10
	death		38.71 ± 7.09 24	36.45 ± 6.20 12	40.99 ± 7.46 12	39.20 ± 7.65 14	38.00 ± 6.57 10
	MCV (fL)	adm.	86.92 ± 5.82 24	88.75 ± 4.16 12	85.08 ± 6.80 12	86.10 ± 5.51 14	88.10 ± 6.33 10
	death		87.75 ± 6.62 24	89.33 ± 5.61 12	86.17 ± 7.40 12	86.40 ± 6.61 14	89.60 ± 6.52 10
	MCH (pg/cell)	adm.	29.04 ± 2.20 24	29.75 ± 1.29 12	28.33 ± 2.71 12	28.90 ± 2.34 14	29.20 ± 2.09 10

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Table 2 (continued)

Average $\pm$ SD Number of values (n)						
		Ref. range	All	Female	Male	Ex. Prolif.
MCHC (g/dL)	death		28.92 $\pm$ 2.12 24	29.58 $\pm$ 1.24 12	28.25 $\pm$ 2.63 12	28.70 $\pm$ 2.23 14
	adm.	33–36	33.33 $\pm$ 1.58 24	33.58 $\pm$ 1.24 12	33.08 $\pm$ 1.88 12	33.50 $\pm$ 1.65 14
	death		32.92 $\pm$ 1.50 24	33.08 $\pm$ 1.38 12	32.75 $\pm$ 1.66 12	33.20 $\pm$ 1.67 14
RDW (%)	adm.	12–15	13.49 $\pm$ 1.25 14	13.18 $\pm$ 1.21 5	13.66 $\pm$ 1.31 9	13.3 $\pm$ 1.02 6
	death		14.06 $\pm$ 1.56 14	14.48 $\pm$ 2.20 5	13.82 $\pm$ 8.00 9	14.30 $\pm$ 2.05 6
	adm.	150–400	228 $\pm$ 123 24	263 $\pm$ 129 12	193 $\pm$ 111 12	222 $\pm$ 139 14
PCT (%)	death		246 $\pm$ 140 24	241 $\pm$ 118 12	251 $\pm$ 165 12	233 $\pm$ 140 14
	adm.	0.22–0.24	0.25 $\pm$ 0.13 23	0.28 $\pm$ 0.14 12	0.21 $\pm$ 0.12 11	0.24 $\pm$ 0.16 13
	death		0.27 $\pm$ 0.14 23	0.26 $\pm$ 0.13 12	0.27 $\pm$ 0.17 11	0.26 $\pm$ 0.15 13
MPV (fL)	adm.	7–12	10.87 $\pm$ 1.23 23	10.69 $\pm$ 0.61 12	11.06 $\pm$ 1.68 11	10.80 $\pm$ 0.97 13
	death		10.97 $\pm$ 1.38 23	10.84 $\pm$ 1.12 12	11.12 $\pm$ 1.66 11	11.00 $\pm$ 1.09 13
	adm.	8.1–25.0	12.74 $\pm$ 3.17 23	12.17 $\pm$ 1.70 12	13.36 $\pm$ 4.25 11	12.70 $\pm$ 2.43 13
PDW (fL)	death		13.35 $\pm$ 3.75 23	12.67 $\pm$ 3.06 12	14.09 $\pm$ 4.42 11	13.10 $\pm$ 2.63 13
	adm.	200–400	463 $\pm$ 138 6	530 $\pm$ 90 2	430 $\pm$ 157 4	458 $\pm$ 194 3
	death		463 $\pm$ 138 6	530 $\pm$ 90 2	430 $\pm$ 157 4	458 $\pm$ 194 3
DDIM (ngFEU/mL)	adm.	500	4105 $\pm$ 5000 15	3001 $\pm$ 3532 9	5762 $\pm$ 6675 6	4592 $\pm$ 6060 7
	death		4781 $\pm$ 4895 14	3865 $\pm$ 3428 8	6002 $\pm$ 6536 6	5544 $\pm$ 6201 6
	max.		6294 $\pm$ 6747 14	6514 $\pm$ 7342 8	6002 $\pm$ 6536 6	8226 $\pm$ 8373 6
FERR (μ g/L)	adm.	Male: 24–336; Female: 11–307	1076 $\pm$ 385 8	1253 $\pm$ 388 3	969 $\pm$ 382 5	1285 $\pm$ 435 3
	death		1858 $\pm$ 2197 8	3208 $\pm$ 3511 3	1048 $\pm$ 314 5	3173 $\pm$ 3540 3
	max.		1995 $\pm$ 2203 8	3544 $\pm$ 3317 3	1065 $\pm$ 324 5	3173 $\pm$ 3540 3
IL-6 (pg/mL)	adm.	<17.4	102.7 1		102.7 $\pm$ 1	102.7 1
	death		87.1 1		87.1 1	87.1 1
TG (mmol/L)		<1.7	4.32 $\pm$ 3.11 2	4.32 $\pm$ 3.11 2		6.52 1
HBA1C (%)		4.2–6.1	5.31 $\pm$ 1.71 2	5.31 $\pm$ 1.71 2		6.52 1
LIPAZ (U/L)		<70	65 1	65 1		65 1
CHOL (mmol/L)		<5	3.7 1	3.7 1		3.7 1

Abbreviations: ALP - alkaline phosphatase, BAS - basophil count, BAS% - basophil %, CK - serum creatinine kinase, CKMB - cardiac-type creatinine kinase, CHOL - serum lipase, serum cholesterol, CRPS - C-reactive protein, cTnT - cardiac troponin T, DBIL - direct bilirubin, DDIM - D-dimer, EGLU - serum glucose, EOS - eosinophil count, EOS% - eosinophil %, FERR - ferritin, FIBR - fibrin, GFR - glomerular filtration rate, GGT - gamma-glutamyl transferase, GOT - glutamic-oxaloacetic transaminase, GPT - glutamic-pyruvic transaminase, HBA1C - hemoglobin A1c, HCT% - hematocrit%, HGB - hemoglobin, KREA - serum kreatinin, LDH - lactate dehydrogenase, LYM - lymphocyte count, LYM% - lymphocyte %, MCH - Mean Corpuscular Hemoglobin, MCHC - mean corpuscular hemoglobin concentration, MCV - mean corpuscular volume, MON - monocyte count, MON% - monocyte %, MPV - mean platelet volume, PCT% - plateletocrit, PDW - platelet distribution width, PLT - platelet count, PLT% - platelet %, RBC - red blood cell count, RDW% - red cell distribution width %, SCA - serum total calcium, SCL - serum chloride, SK - serum potassium, SMG - serum magnesium, TBIL - serum total bilirubin, TG - serum triglyceride, UREA - serum urea, WBC - white blood cell count, adm. - admission, min. - minimum, max. - maximum.

the intensity of the PAR staining in the tissue, but not with any other indices (Fig. 2).

The histology scores were correlated with serum parameters. Parameters characterizing kidney function (serum ions and serum urea) showed widespread correlation with PAR indices (PAR intensity and PAR%) and only serum potassium (at death) correlated with 4HNE intensity and serum urea (at admission) with TNF α (Fig. 3). Parameters

reflecting liver function (total and direct bilirubin at various stages of hospital stay) showed widespread correlation with TNF α indices (TNF α intensity and TNF α %) and limited number of correlation with PAR indices, but not with 4HNE indices (4HNE intensity and 4HNE%) (Fig. 3). Parameters related to anemia, red blood cell production or oxygen transport (hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width%) correlated with 4HNE and TNF α indices,

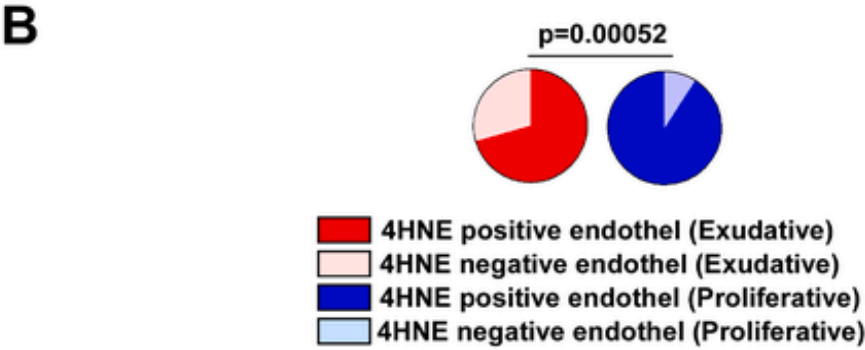
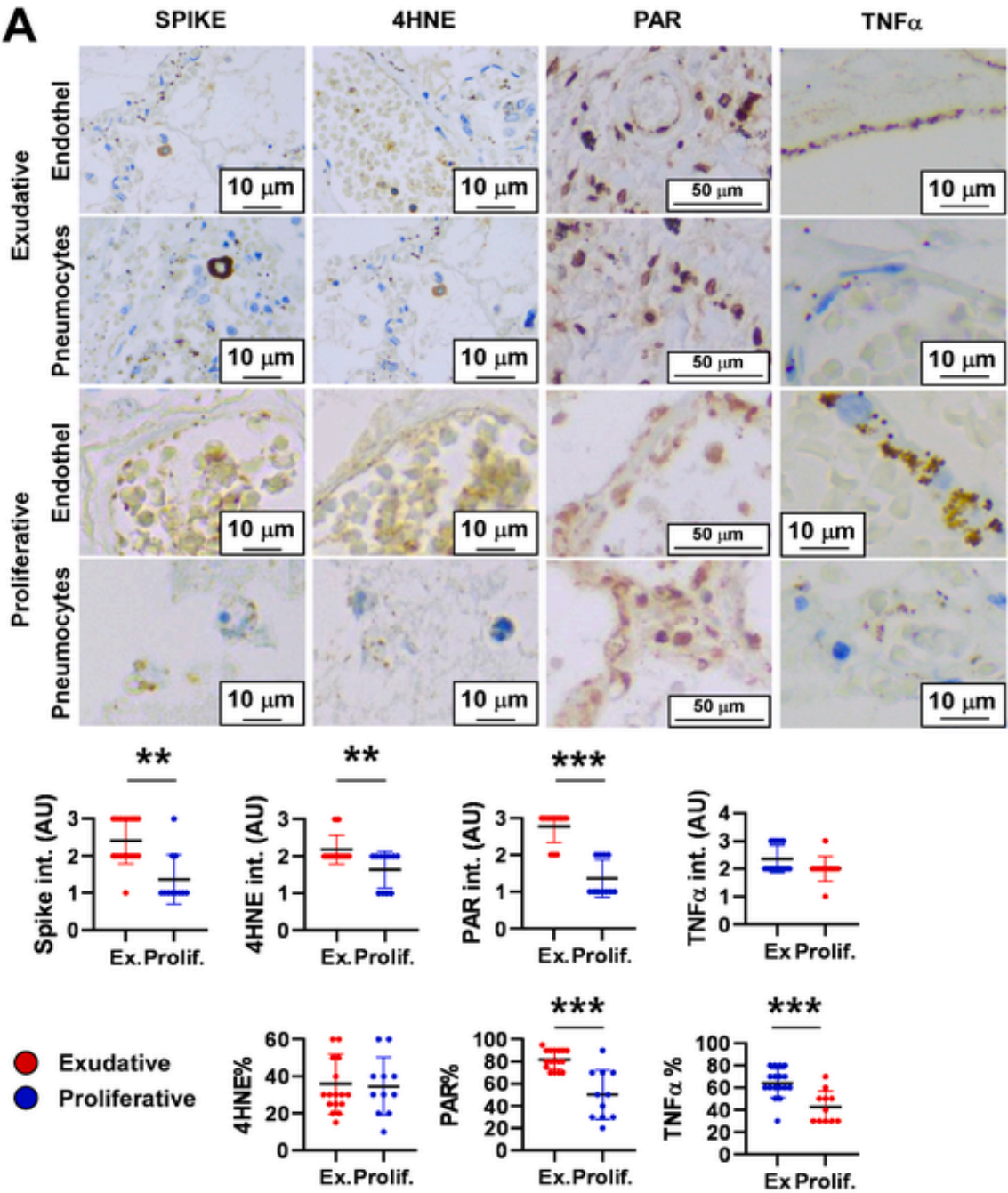


Fig. 1. Oxidative stress and PARP activity is higher in the exudative than in the proliferative phase of COVID-19

(A) The indicated immunohistochemistry reactions were scored for the cases in the patient cohorts. Scale bar is 10 μ m. Normality was checked using the Shapiro-Wilk test. In all cases Mann-Whitney test was applied to assess statistical significance with the exception of TNF α %, where unpaired two-tailed *t*-test was used. Average $\pm$ SD are depicted. ** or *** symbolize statistically significant difference between the indicated groups at *p* < 0.01 or 0.001, respectively. (B) The proportions of the endothelial PAR positive and negative cases were plotted for patients died in the exudative and the proliferative phase of the disease. Statistical significance was assessed using the khi-square test. Abbreviations: Ex. – exudative, prolif. – proliferative.

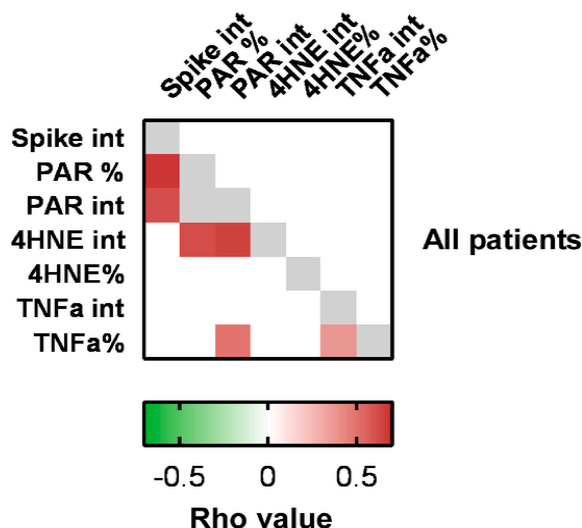


Fig. 2. PAR indices correlate with spike and 4HNE indices

Correlation between the indicated histology indices were calculated using Spearman correlation. Those R values are depicted on the panel that belong to correlations with *p* < 0.05. Grey boxes symbolize self-correlations (i.e. spike intensity vs. spike intensity with *R* = 1). The top part which is symmetrical to the bottom half is not depicted. Abbreviations: 4HNE – 4-hydroxynonenal, int. – intensity, PAR – poly (ADP-ribose).

but not with PAR indices (Fig. 3), nevertheless, these clinical measures were mostly within the reference range. Indices of 4HNE, PAR and TNF α correlated with white blood cell indices (white blood cell count, lymphocyte count and %, monocyte count; Fig. 3). Lymphocyte count and %, monocyte count showed negative correlation with histology indices. Indices of 4HNE, PAR and TNF α correlated with parameters of blood clotting or disseminated intravascular coagulation (DIC) (ferritin,

D-dimer levels, thrombin time and platelet count; Fig. 3). TNF α positively correlated with serum glucose levels at admission (Fig. 3).

3.2. Oxidative stress and PARylation in the lungs supports negative outcomes in males

Mindful that PARylation levels are higher in males in non-COVID19 models [49–51] similar to the fatality rate of COVID-19 [11–13,58] we assessed sex-associated differences. Surprisingly, there was no difference between genders in histological indices, moreover, surprisingly, PAR% was higher in females (Fig. 4A). Nevertheless, we found that female patients were older than males (Fig. 4B) and PAR% showed a marginal positive correlation with age that correlates well with previous studies showing positive correlation between PARylation and age in humans [42–45] (Fig. 4C). We observed different pattern of the correlation coefficients in males and females. There were numerous positive correlations between the histological indices in males (Fig. 5) similar to the case when all patients were assessed (Fig. 2), but not in females (Fig. 5) both when all correlation coefficients were considered, as well as, when only those R values were regarded for which *p* values were less than 0.05. TNF α indices correlated with PAR levels in males, but not in females (Fig. 5). Importantly, PARylation indices positively correlated with time of hospitalization (time to death) in males but not in females (Fig. 6).

4. Discussion

In this retrospective study pulmonary oxidative stress and PARylation was evidenced in COVID-19 patients similar to Refs. [2–7,59]. In COVID-19 patients oxidative stress and PARylation was present throughout the tissue. Oxidative stress, virus load and PARylation peaked in the exudative phase and decreased in the proliferative phase. Markers of oxidative stress and spike protein correlated with PARylation, however, there was only a borderline correlation between 4HNE indices (oxidative stress markers) and spike protein suggesting that ox-

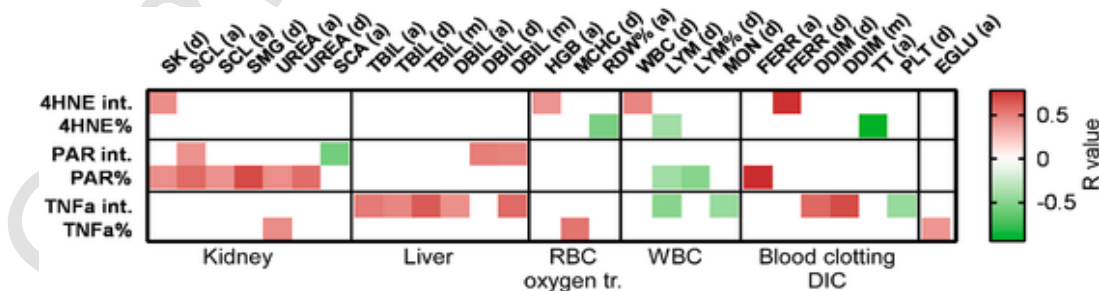


Fig. 3. Pulmonary 4HNE, PAR and TNF α scores correlate with serum chemistry and hemogram readouts The serum chemistry and hemogram parameters of the COVID-19 patients were correlated with 4HNE intensity, 4HNE%, PAR intensity, PAR%, TNF α intensity and TNF α % using Spearman correlation. Those R values are depicted on the panel that belong to correlations with *p* < 0.05.

Abbreviations: 4HNE – 4-hydroxynonenal, (a) – at admission, (d) – at death, DBIL – serum direct bilirubin concentration, DIC – disseminated intravascular coagulation, D DIM – D-dimer concentration, EGLU – serum glucose concentration, FERR – serum ferritin, HGB – hemoglobin concentration, int. – intensity, LYM – lymphocyte count, LYM% – lymphocyte percent, (m) – maximum/peak value, MCHC – mean corpuscular hemoglobin concentration, MON – monocyte count, PAR – poly (ADP-ribose), PLT – platelet count, RBC – red blood cell, RDW – red blood cell distribution, SCA – serum total calcium ion concentration, SCL – serum chloride ion concentration, SK – serum potassium ion concentration, SMG – serum magnesium ion concentration, TBIL – serum total bilirubin concentration, TT – thrombin time, WBC – white blood cell count.

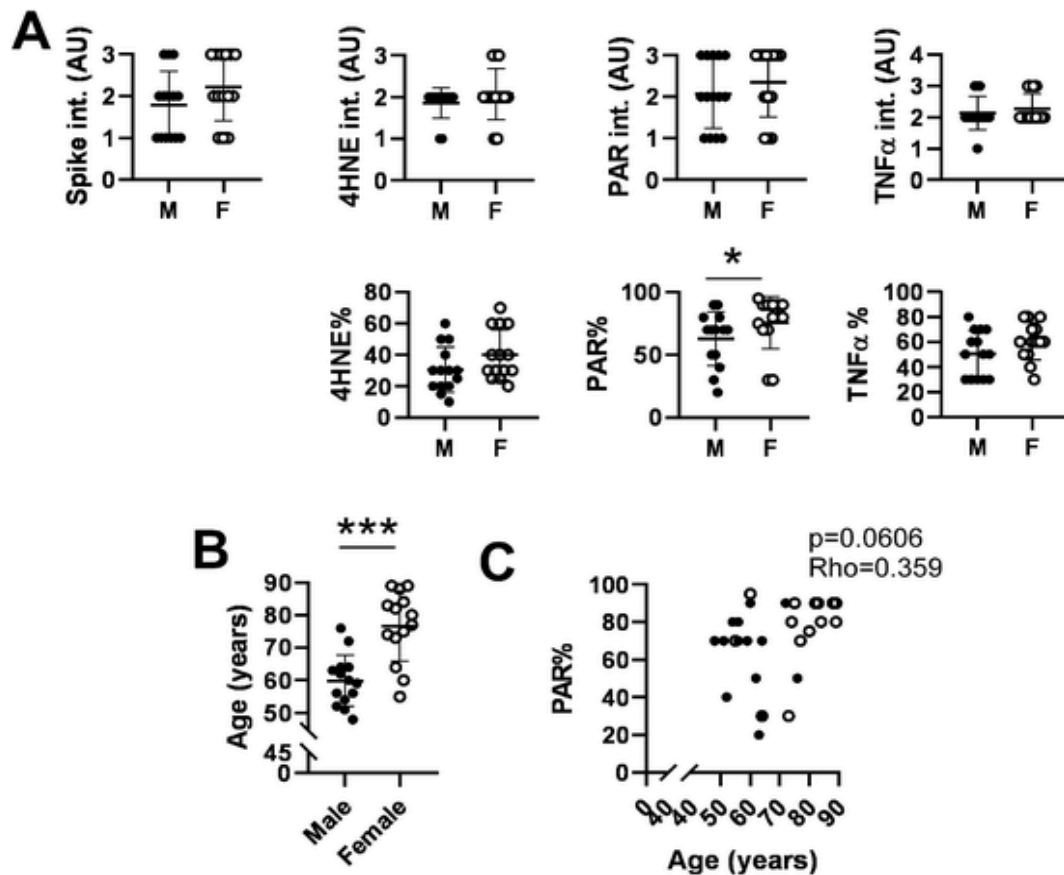


Fig. 4. PARYlation in the lungs negatively correlates with the time of hospitalization

(A) The indicated immunohistochemistry reactions were scored for the cases in the patient cohorts. Scale bar is 10 μ m. Normality was checked using the Shapiro-Wilk test. In all cases Mann-Whitney test was applied to assess statistical significance. Average $\pm$ SD are depicted.

(B) The age of the individuals was compared between males and females. Normality was checked using the Shapiro-Wilk test. Two-sided unpaired *t*-test was used to assess statistical significance. Average $\pm$ SD are depicted.

(C) Correlation between age and PAR% was assessed using Spearman correlation. Normality was checked using the Shapiro-Wilk test. *, ** or *** symbolize statistically significant difference between the indicated groups at $p < 0.05$, 0.01 or 0.001 , respectively. Abbreviations: 4HNE – 4-hydroxynonenal, F – female, int. – intensity, M – male, PAR – poly (ADP-ribose). Key: closed circles = male and open circles = female.

idative stress and virus load are independent pathways, both converging on inducing PARYlation.

When comparing males and females, we observed higher percent of PAR positive cells in females as compared to males. This observation contradicts to higher PARYlation levels in males over females in non-COVID19 models [49–51]. However, male patients were younger than females and PAR levels increased with age among males, similar to Refs. [42–45,49]. In fact, higher PARP activity was reported in males compared with females under 60 years of age [49]. Apparently, males become vulnerable to PARYlation-mediated tissue damage at an earlier age as compared to women. This hypothesis is supported by widespread correlation of PAR indices with other histology indices (including TNF α indices) in males, but not in females. In line with these, there was a negative correlation between pulmonary PARYlation and the time to death in males that accords with the higher fatality rate of COVID-19 among males [11–13,58] and with the higher sensitivity of males to PARYlation-induced tissue damage [49–51]. Taken together, PARYlation can contribute to the higher male mortality rate in COVID-19 [11–13,58] and the data also suggest that high PARYlation levels may be an indication of worse disease outcome.

These data suggest that pulmonary oxidative stress and PARYlation is involved in the pathogenesis of COVID-19. Oxidative stress and PARYlation correlates with cell death and tissue damage (including kidneys and liver dysfunction), inflammation and blood clotting abnormal-

ities (the patients in this study were screened for DIC), therefore, ultimately likely contribute to fatal outcomes [60,61].

Importantly, the retrospective nature of the study represents a limitation, due unknown co-morbidities, differences in the lifestyle choices and behavior between sexes and inconsistent timing of blood collection. Nevertheless, the results of the study build a case for repurposing of pharmacological PARP inhibitors for acute COVID-19. Through preventing early stage permanent tissue damage, early application of PARP inhibitors may preserve tissue structure and function that is likely to be beneficial in the subsequent post-COVID timeframe as well.

CRediT authorship contribution statement

Péter Juhász: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Data curation. **Péter Bohus:** Writing – original draft, Validation, Project administration, Methodology. **Adrienn Sipos:** Writing – original draft, Validation, Data curation. **Nicola Curtin:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Gábor Méhes:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Data curation. **Péter Bai:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision,

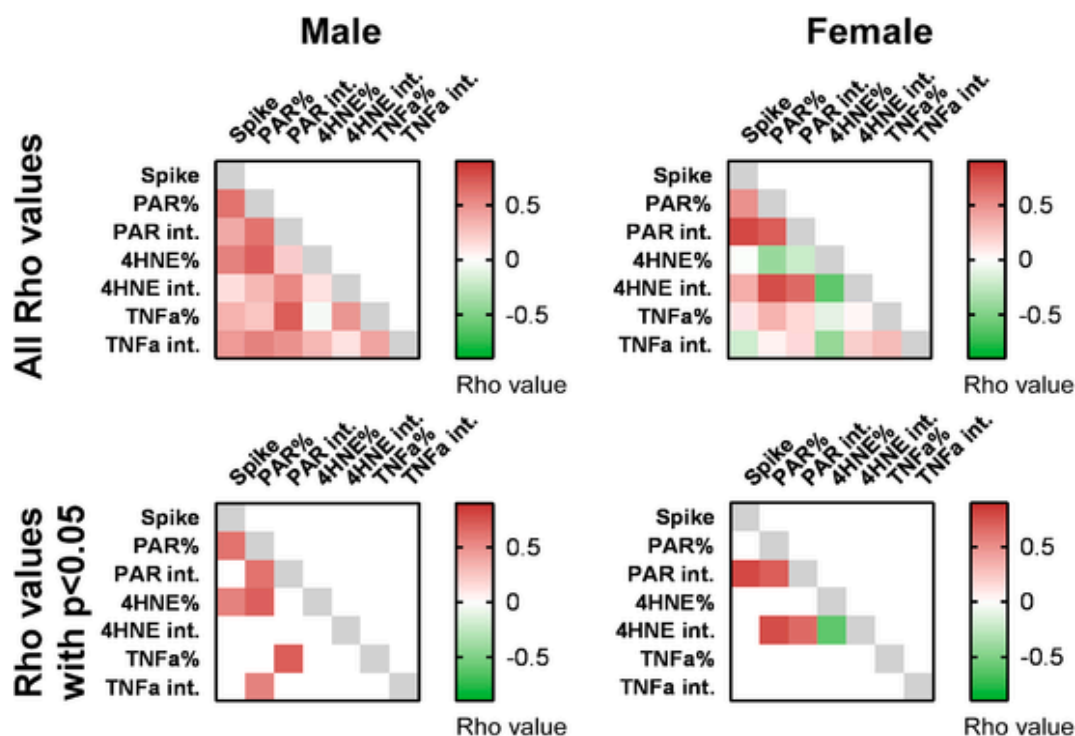


Fig. 5. Different correlation patterns are observed between the histological indices in males and females. Correlation between the indicated histology indices were calculated using Spearman correlation in male and female patients. On the top two panels all R values are depicted. On the bottom two panels those R values are depicted that belong to correlations with $p < 0.05$. Grey boxes symbolize self-correlations (i.e. spike intensity vs. spike intensity with $R = 1$). The top part which is symmetrical to the bottom half is not depicted. Abbreviations: 4HNE – 4-hydroxynonenal, int. – intensity, PAR – poly (ADP-ribose).

Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Patient consent statement

In the frame of the study post-mortem samples were assessed, hence patient consent is not needed.

Data availability statement

Primary data associated to this manuscript can be found at <https://figshare.com/s/725650d2036f586f065f> (<https://doi.org/10.6084/m9.figshare.22303120>).

Ethics approval statement

The study was authorized by the local ethical board (6043/2022).

Permission to reproduce material from other sources

There is no such item in the manuscript.

Clinical trial registration

Not applicable.

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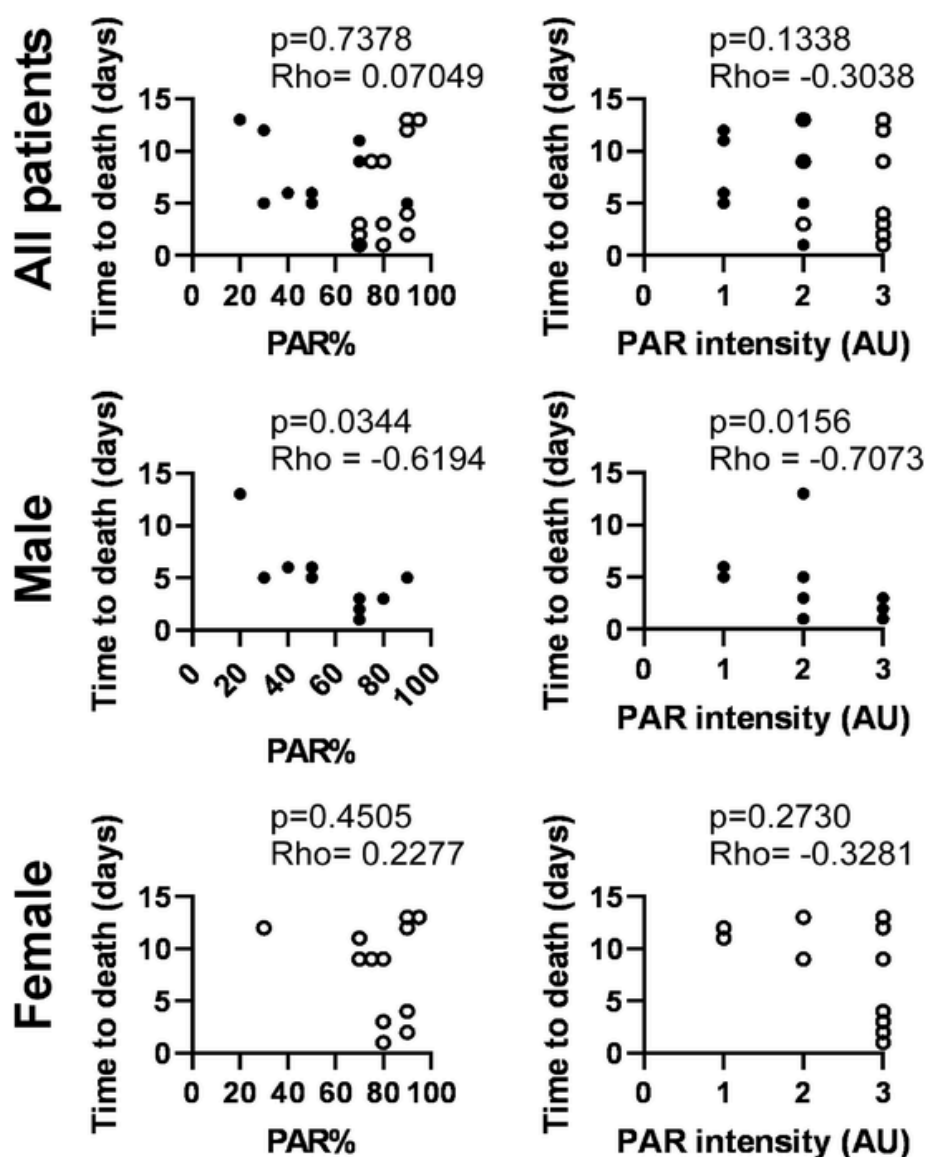


Fig. 6. PARylation in the lungs negatively correlates with the time of hospitalization

Correlation between time to death and PARylation indices was assessed using Spearman correlation considering all patients, males and females. In two males hospitalization time was omitted due to their extended length. Normality was checked using the Shapiro-Wilk test.

Abbreviations: PAR – poly (ADP-ribose). Key: closed circles = male and open circles = female.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.freeradbiomed.2025.06.010>.

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