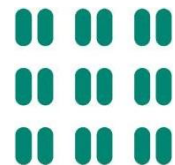


Convalescent plasma as a therapeutic modality in hematological patients with COVID19 pneumonia - a review of the results of patients treated in University Hospital Dubrava

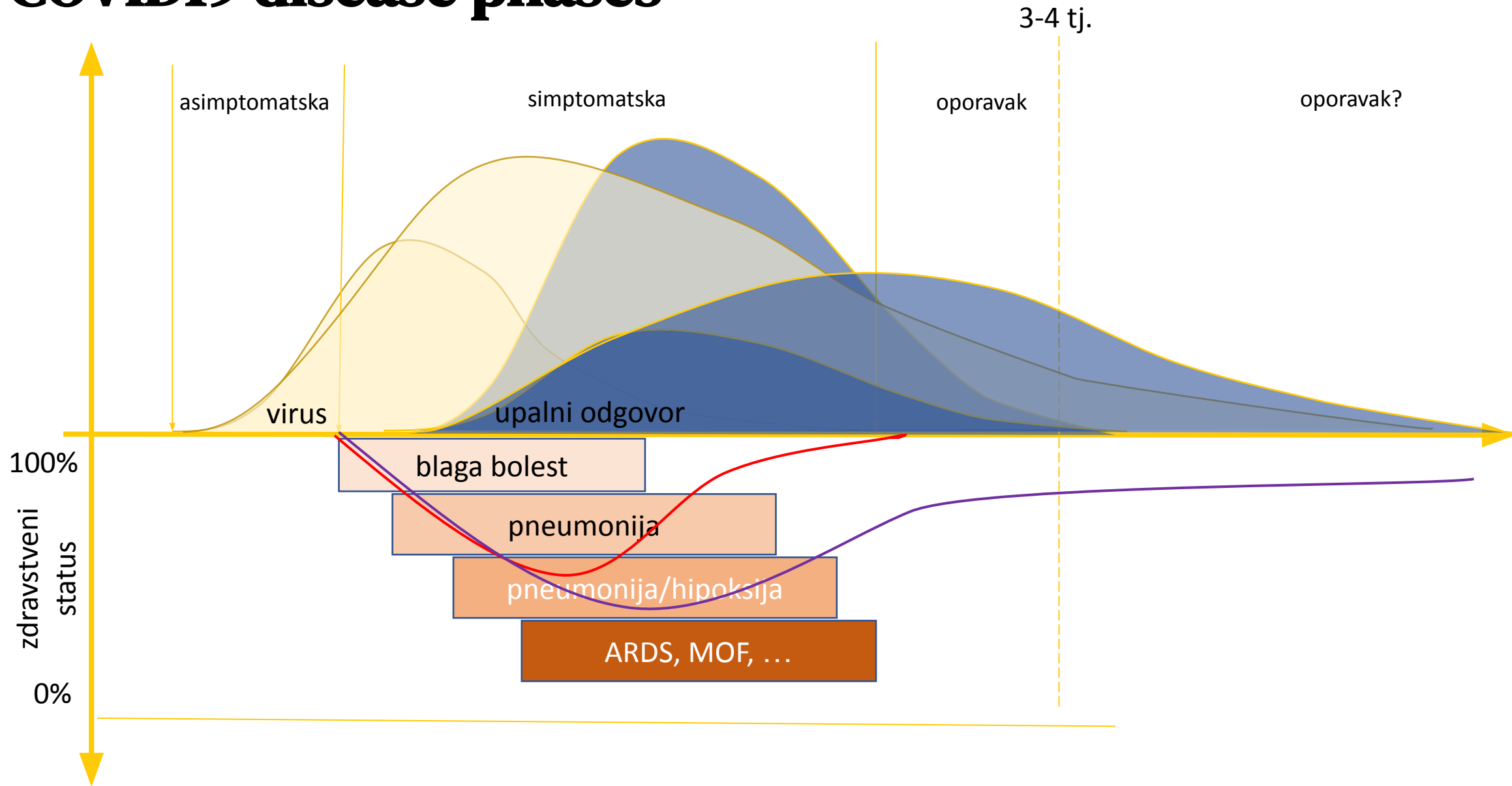
Ena Soric, MD, Gorana Dzepina, MD, Ana Hecimovic, MD, Martina Sedinic, MD, Marija Ivic, MD, Sara Tomasinec, MD, Antica Pasaric, MD, David Cicic, MD, Zeljko Jonjic, MD, Mario Pirsic, MD, Marko Lucijanic, MD, Beata Halassy, PhD, Ozren Jaksic, MD, PhD

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This work has been supported by Croatian Science Foundation under the project IP-CORONA-04-2053

COVID19 disease phases



Outcomes in hematological patients w/ COVID19 disease in Croatia

1. all patients (outcome after 6 weeks)

a. death	29,0%
b. long COVID19	4,3%
c. recovery	66,7%

2. mortality

a. outpatient	- 1,5%
b. inpatient	- 39,0%
i. department	- 25,4%
ii. ICU	- 73,3%

- **w/o requirement for oxygenotherapy -9,3%**
- **O₂ standard flow- 29,7%**
- **O₂ high-flow - 51,4%**
- **mechanical ventilation - 95,4%**
- **ECMO- 66,6%**

History of COVID19 diagnostics in UH Dubrava

- 12/2020 - semiquantitative antibody analysis
- 01/2021 - quantitative antibody analysis
- 02/2021 - viremia

Available therapies

- LMWH
- corticosteroids
- remdesivir
- oxygenotherapy
- convalescent plasma

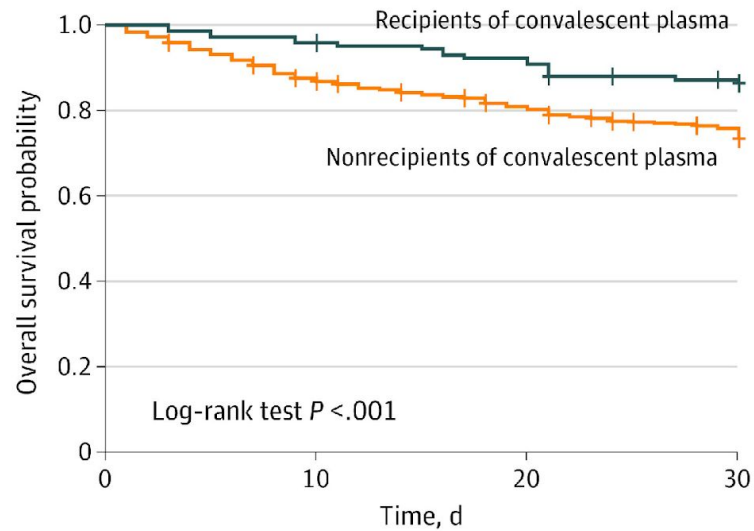
Convalescent plasma (rFFP)

- **passive immunotherapy is over 100 y/o**
- **neutralising antibodies directed against the infectious pathogen**
- **potential to shorten the duration or severity of illness sufficiently to prevent serious or life-threatening complications**



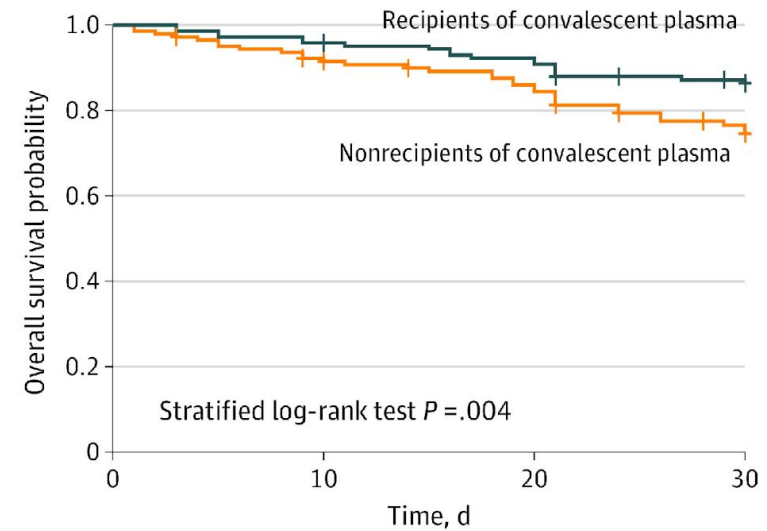
Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19

A Overall comparison



No. at risk				
Nonrecipients of convalescent plasma	823	702	613	507
Recipients of convalescent plasma	143	137	129	108

B Propensity score-matched comparison



No. at risk				
Nonrecipients of convalescent plasma	143	128	109	79
Recipients of convalescent plasma	143	137	129	108



How did we administer convalescent plasma?



WHO?

- hematologic patients
- negative or low antibody titer
- positive viremia
- in need for oxygenotherapy (including HFOT and MV)

WHEN?

- 2nd - 102nd day of disease
- median D18

HOW MUCH?

- 1 - 15 doses
 - median 4 doses
 - mostly 1-2 a day
 - dependent on availability
- 

Patients

- 40 patients w/ hematologic disease (24 male, 16 female)
- average age 65 years (range 28 - 88)
- all w/ bilateral pneumonia
- median day of disease at the time of hospitalization: 11 (range 1 - 90)
- 3 were vaccinated w/ 1 dose
- comorbidities:
 - hypertension: 18 (45%)
 - diabetes: 8 (20%)
 - AI disease 7 (17,5%)
 - COPD 3 pts, chronic kidney disease 3 pts, coronary artery disease 1 pt
 - one patient had another active malignant disease (breast cancer)

Hematologic hx

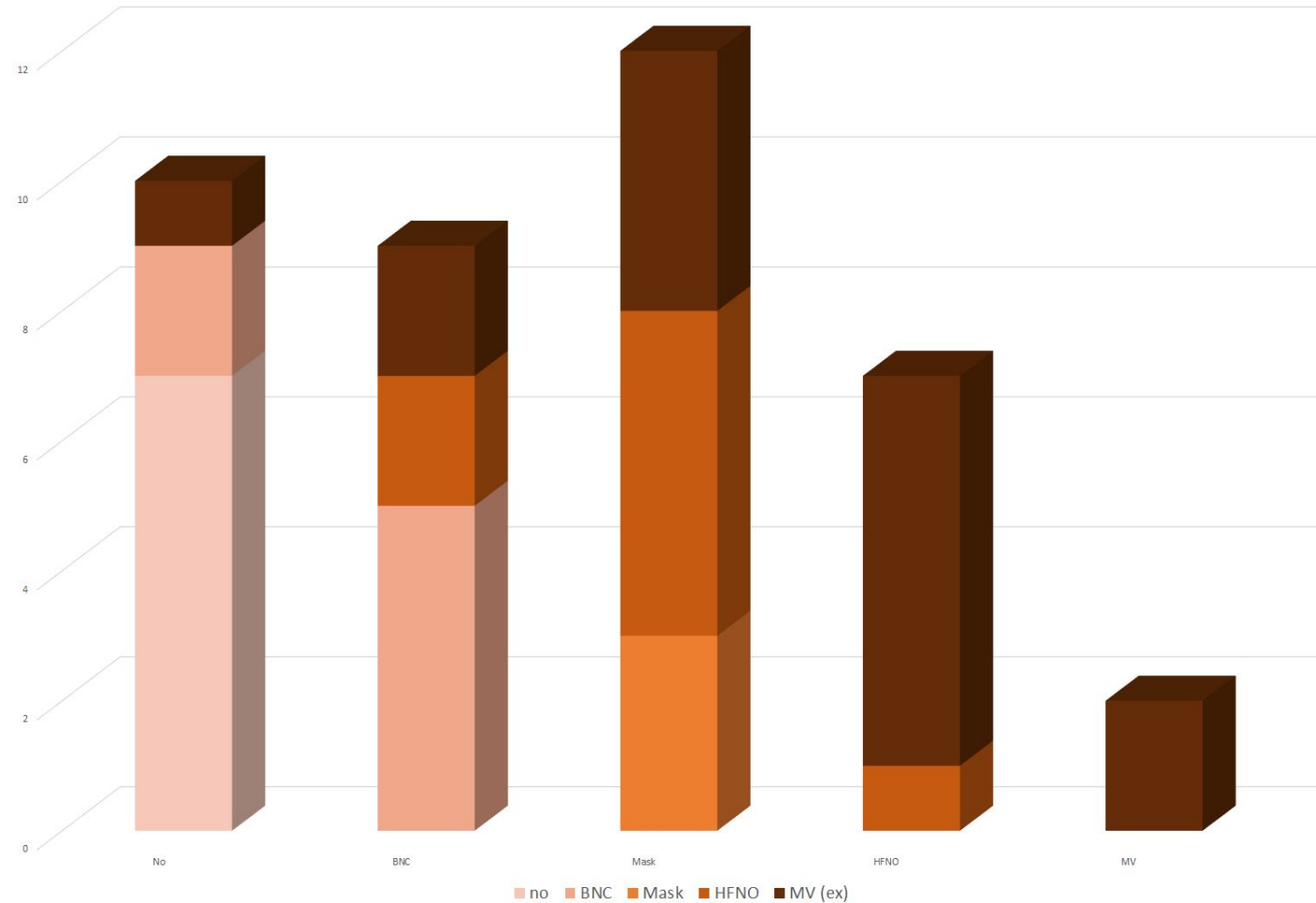
- **most common was chronic lymphocytic leukemia (13 pts, 32,5%)**
- **other:**
 - **follicular lymphoma - 5**
 - **mantle cell lymphoma - 3**
 - **multiple myeloma - 3**
 - **acute myeloid leukemia - 2**
- **history of treatment:**
 - **30 pts (75%) had hx of chemotherapy**
 - **23 pts (57,5%) received therapy in last 3 months:**
 - **rituximab - 14**
 - **obinutuzumab - 1**
 - **fludarabine - 0**
 - **bendamustine - 3**
 - **4 pts had hx of bone marrow transplantation**

Results

- mortality - 16/40 patients - 40%
- median duration of hospitalization - 26 days
- median duration of hospitalization after rFFP administration - 12,5 days

MORTALITY IN RELATION TO OXYGEN FLOW REQUIREMENT AT THE TIME OF FIRST rFFP ADMINISTRATION:

- all patients who required mechanical ventilation died
- 6 out of 7 patients treated w/ high flow oxygenotherapy died



Progression after rFFP

progression after rFFP	23
HFOT as maximum OT after rFFP	8
MV after rFFP	16

Control after rFFP

- **19/25 (76%) ultimately had positive IgG SARS-CoV-2 antibodies**
- **only one patient w/ positive antibodies ultimately died**
- **at the time of control most patients (19) were independent of oxygenotherapy**
- **only 10 patients continued outpatient controls, of which 7 (70%) patients still had antibodies → all of them are respiratory sufficient**

Rehospitalization

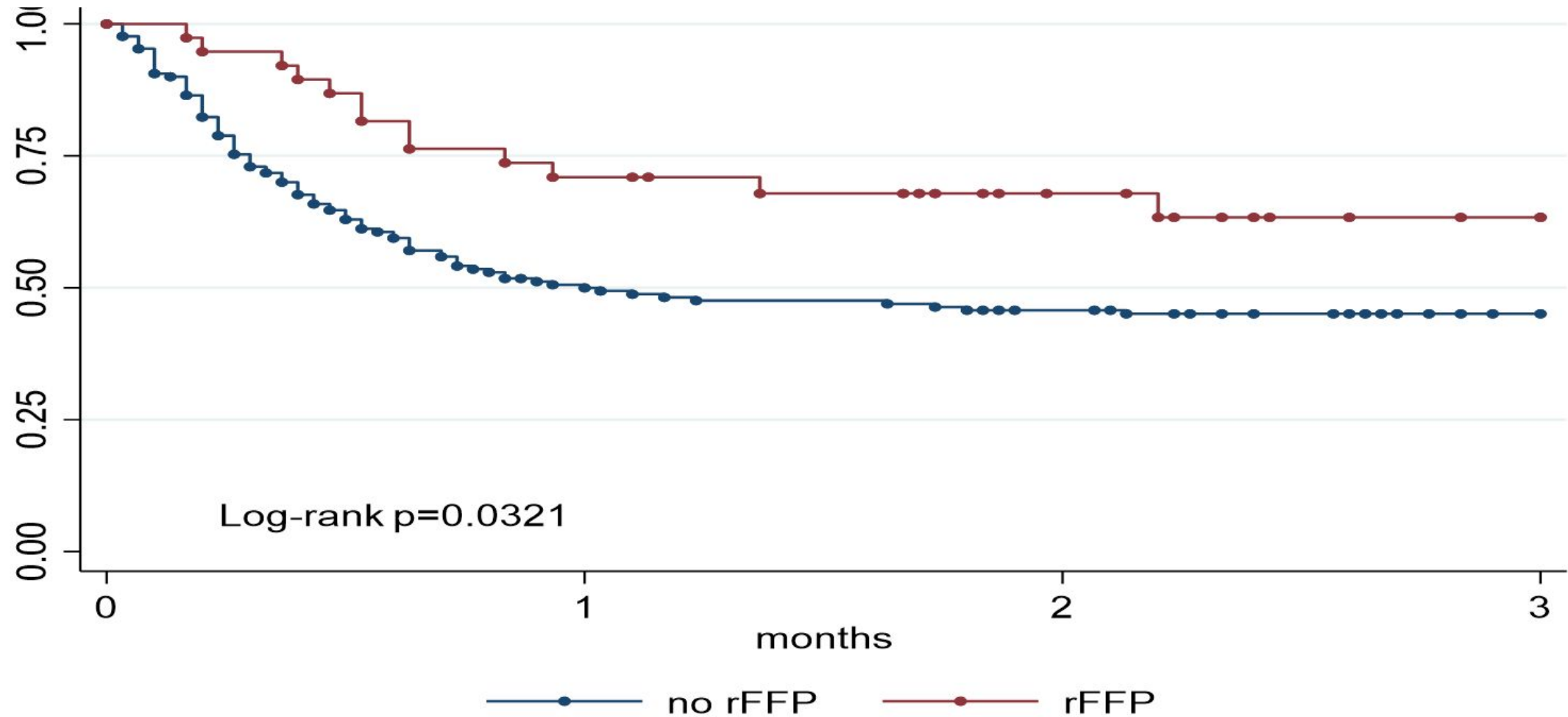
- **5 patients had more than one hospitalization**
- **all of them had at least one progression of COVID19 symptoms**
- **3 patients were electively hospitalized because of inpatient rFFP administration**
- **all of them survived**

Hematological patients who didn't receive rFFP

	rFFP	no rFFP	p
Number	40	171	
Age (median, range)	68 (28-88)	72(28-88)	<0.05
Sex M/F	22/18	90/81	NS
Charlson Comorbidity Score	5	6	<0.05
MEWS	3	3	NS

During the hospitalization 29.8% required HFOT, 25% mechanical ventilation, which survived only 3 patients. A total of 52% of patients survived.

Overall survival by rSSP administration



Case 1: female, 52 y/o

- B-CLL □ treated w/ FCRx6 □ last cycle applied in October
- first day of symptoms: 04/11/2020
- test positive 05/11/2020
- initially treated in UH Merkur
- 27/11/2020 – clinical and laboratory deterioration □ transferred to UH Dubrava
- no CoVlg

Hematologija	REZULTAT	JEDINICA	REF. INTERVAL	OPASKA
(K) Leukociti	2.4 L	x10 ⁹ /L	3.4 - 9.7	
(K) Eritrociti	3.26 L	x10 ¹² /L	3.86 - 5.08	
(K) Hemoglobin	100 L	g/L	119 - 157	
(K) Hematokrit	0.302 L	L/L	0.356 - 0.470	
(K) MCV (prosječan volumen eritrocita)	92.5	fL	83.0 - 97.2	
(K) MCH (prosječan sadržaj hemoglobina u eritrocitu)	30.7	pg	27.4 - 33.9	
(K) MCHC (prosječna koncentracija hemoglobina u eritrocitima)	332	g/L	320 - 345	
(K) RDW (raspodjela eritrocita po volumenu)	16.1 H	%	9.0 - 15.0	
(K) Trombociti	90 L	x10 ⁹ /L	158 - 424	
(K) MPV (prosječan volumen trombocita)	9.6	fL	6.8 - 10.4	
(K) Neutrofilni granulociti	90.40 H	%	44 - 72	
(K) Limfociti	3.60 L	%	20 - 46	
(K) Monociti	4.30	%	2 - 12	
(K) Eozinofilni granulociti	0.10	%	0 - 7	
(K) Bazofilni granulociti	0.20	%	0 - 1	
(K) LUC	1.50	%	< 4	
(K) Neutrofilni granulociti	2.13	x10 ⁹ /L	2.06 - 6.49	
(K) Limfociti	0.08 L	x10 ⁹ /L	1.19 - 3.35	
(K) Monociti	0.10 L	x10 ⁹ /L	0.12 - 0.84	
(K) Eozinofilni granulociti	0.00	x10 ⁹ /L	0.00 - 0.43	
(K) Bazofilni granulociti	0.00	x10 ⁹ /L	0.00 - 0.06	
(K) LUC	0.04	x10 ⁹ /L	< 0.4	
Napomena	ANIZOCITOZA			

LUC odgovara atipičnim limfocitima, blastima i drugim abnormalnim mononuklearnim stanicama.

Lipidi i lipoproteini

Specifični proteini

	REZULTAT	JEDINICA	REF. INTERVAL	OPASKA
(S) Imunoglobulin A (IgA)	0.56 L	g/L	0.7 - 4.0	Imunoturbidimetrija, Beckman Coulter AU
(S) Imunoglobulin G (IgG)	3.86 L	g/L	7.0 - 16.0	Imunoturbidimetrija, Beckman Coulter AU
(S) Imunoglobulin M (IgM)	< 0.20 L	g/L	0.40 - 2.30	Imunoturbidimetrija, Beckman Coulter AU

Therapy

- oxygenotherapy □ initially 4L/min □ range 2-5 L/min
- LWMH
- antibiotics (meropenem, azythromicin)
- corticosteroids
- IVIg
- convalescent plasma x6 (consequently) □ first dose was given on D62 of the disease



Results - 6 days after the last dose od rFFP

(S) IgG protutijela na SARS-CoV-2	45.7	AU/mL	negativna: < 50 > 50	pozitivna: > 50	Kemiluminiscencija, Abbott Architect i1000SR
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**... but indepedent of oxygenotherapy.
Discharged w/ corticosteroids and NOAC.**

17/02/2021 – Outpatient control

(S) Imunoglobulin A (IgA)	0.18 L	g/L	0.7 - 4.0	Imunoturbidimetrija, Beckman Coulter AU
(S) Imunoglobulin G (IgG)	3.39 L	g/L	7.0 - 16.0	Imunoturbidimetrija, Beckman Coulter AU
(S) Imunoglobulin M (IgM)	< 0.20 L	g/L	0.40 - 2.30	Imunoturbidimetrija, Beckman Coulter AU
(S) C reaktivni protein (CRP)	154.9 H	mg/L	< 5.0 trudnice < 15.0	Imunoturbidimetrija, Beckman Coulter AU
(S) IgG protutijela na SARS-CoV-2	< 21.0	AU/mL	negativna: < 50 pozitivna: > 50	Kemiluminiscencija, Abbott Architect i1000SR

SARS-CoV-2
SARS-CoV-2

REZULTAT
Negativan

JEDINICA

REF. INTERVAL

OPASKA

negativan

Pozitivan - dokazan je
genom virusa. Negativan -
nije dokazan genom virusa.

Kliničko tumačenje:

-

Komentar:

-

Materijal:

Serum

clinically: long term fatigue, afebrile, respiratory sufficient

Rehospitalization - 30/05/2021

(K) Limfociti	0.60	L	x10 ⁹ /L	1.19 - 3.35
(S) Imunoglobulin A (IgA)	0.28	L	g/L	0.7 - 4.0
(S) Imunoglobulin G (IgG)	2.08	L	g/L	7.0 - 16.0
(S) Imunoglobulin M (IgM)	< 0.20	L	g/L	0.40 - 2.30
(S) C reaktivni protein (CRP)	201.0	H	mg/L	< 5.0 trudnice < 15.0
(S) IgG protutijela na SARS-CoV-2	< 21.0		AU/mL	negativna: < 50 pozitivna: > 50
SARS-CoV-2	Pozitivan			negativan
Kliničko tumačenje:	-			
Komentar:	-			
Materijal:	Serum			

Rehospitalization - 30/05/2021

- progression of pneumonia on CT scan
- respiratory sufficient but w/ prolonged fatigue
- treated w/ remdesvir /10 days and rFFP x6 (+ chronic therapy – corticosteroids and NOAC)

(S) C reaktivni protein (CRP)	5.5 H	mg/L	< 5.0 trudnice < 15.0
(S) IgG protutijela na SARS-CoV-2	1053.5	AU/mL	negativna: < 50 pozitivna: > 50
SARS-CoV-2	Negativan		negativan
Kliničko tumačenje:	-		
Komentar:	-		
Materijal:	Serum		

elective hospitalization in July/2021 □ 2x rFFP

SARS-CoV-2	Negativan	negativan
Kliničko tumačenje:	-	
Komentar:	-	
Materijal:	Bris nazofarinksa	

last control: September/2021

(K) Limfociti	-	1.39	x10 ⁹ /L	1.19 - 3.35
(S) Imunoglobulin A (IgA)	< 0.10 L	g/L	0.7 - 4.0	
(S) Imunoglobulin G (IgG)	2.86 L	g/L	7.0 - 16.0	
(S) Imunoglobulin M (IgM)	< 0.20 L	g/L	0.40 - 2.30	
(S) C reaktivni protein (CRP)	0.8	mg/L	< 5.0 trudnice < 15.0	

(S) IgG protutijela na SARS-CoV-2

639

AU/mL

negativna: < 50 pozitivna
> 50

SARS-CoV-2

Negativan

negativan

Kliničko tumačenje:

-

Komentar:

-

Materijal:

Serum

SARS-CoV-2

Negativan

negativan

Kliničko tumačenje:

-

Komentar:

-

Materijal:

Bris nazofarinksa

Case 2: female, 53 y/o

- **history: B-CLL** □ FCx6 + Rx8 (last in 09/2020.)
- **test +-ve 22/12/2020**

- **1st hospitalization: 01/2021: bilateral pneumonia and hypoxemia**
- **viremia and CoVlg weren't tested**
- **th: oxygenotherapy, corticosteroids, LMWH**
- **discharged after 4 days**

- **becomes febrile the next day**
- **hospitalized in UH Merkur** □ **CT scan: diffuse COVID19 pneumonia**
- **transferred to UH Dubrava**

(K) Limfociti	0.45	L	x10 ⁹ /L	1.19 - 3.35
(S) Imunoglobulin A (IgA)	0.46	L	g/L	0.7 - 4.0
(S) Imunoglobulin G (IgG)	3.96	L	g/L	7.0 - 16.0
(S) Imunoglobulin M (IgM)	< 0.20	L	g/L	0.40 - 2.30
(S) C reaktivni protein (CRP)	54.3	H	mg/L	< 5.0 trudnice < 15.0
(S) IgG protutijela na SARS-CoV-2	< 21.0		AU/mL	negativna: < 50 pozitivna: > 50

* viremia was not tested

* NF swab was +-ve

th: LMWH, corticosteroids □ **discharged after 13 days**

02/2021 – Outpatient control

(S) IgG protutijela na SARS-CoV-2

< 21.0

AU/mL

negativna: < 50 pozitivna:
> 50

SARS-CoV-2

Negativan

negativan

Kliničko tumačenje:

-

Komentar:

-

Materijal:

Serum

* symptoms in regression

3rd hospitalization – 03/2021

- febrile w/ SOB
- w/o need for oxygenotherapy
- CT scan – regression of pneumonia, 20-30% of parenchym
- lab: slight CRP elevation, lymphopaenia, hypogammaglobulinaemia
- negative CoVlg
- negative viremia
- negative NP swab

- th: corticosteroids, cefuroxime, IVlg, rFFP x2, NOAC

(S) IgG protutijela na SARS-CoV-2

30.1

AU/mL

negativna: < 50 pozitivna:
> 50

Aftermaths

- **4th hospitalization – elective – in 04/2021. □ negative viremia, NP swab and CoVig, clinically stable w/o need for oxygenotherapy**
- **received 1x rFFP**
- **outpatient control every 2 months: still w/o CoVig (last in 09/2021), but w/o symptoms; hematological remission**

(S) IgG protutijela na SARS-CoV-2

< 21

AU/mL

negativna: < 50 pozitivna
> 50



Conclusions

- **rFFP can be therapeutical option in hematologic patients with COVID19 disease**
- **passive immunization with rFFP may help control COVID-19 infection until patient's own immunological system recovers from consequences of previous immunosuppressive treatments**
- **rFFP has potential significance in patients not yet dependent on higher oxygen flows, whereas in patients on HFOT and mechanical ventilation this role is unlikely to be significant**