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RESEARCH LETTER

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Potential of high-titre IgA convalescent plasma to improve survival and symptoms in COVID-19 patients

Agnieszka Kuś[1] | **Szymon Wieczorek**[1] | **Jarosław Dybko**[2] | **Małgorzata Szymczyk-Nużka**[3] | **Aleksandra Butrym**[4] | **Sebastian Makuch**[5] | **Grzegorz Mazur**[1] | **Siddarth Agrawal**[1]

[1]Department and Clinic of Internal Medicine, Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, Wroclaw, Poland

[2]Department of Hematology and Cellular Transplantation, Lower Silesian Oncology Center, Wroclaw, Poland

[3]Regional Centre of Transfusion Medicine and Blood Bank (RCTMBB-W), Wroclaw, Poland

[4]Department of Cancer Prevention and Therapy, Wroclaw Medical University, Wroclaw, Poland

[5]Department of Clinical and Experimental Pathology, Wroclaw Medical University, Wroclaw, Poland

Correspondence
Siddarth Agrawal, Department and Clinic of Internal Medicine, Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, 50-556 Wroclaw, Poland.
Email: siddarth@agrawal.pl

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Over the past few years, we have witnessed the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, also known as COVID-19, which can cause severe illness and lead to death.[1] Various vaccines have been proved to reduce the likelihood of infection with SARS-CoV-2, but few treatments have shown efficacy.

Passive immunization using convalescent plasma (CP) obtained from patients who have humoral immunity against SARS-CoV-2 after recovering from a COVID-19 infection is a potential strategy to reduce the severity of illness.[2] However, the effects of CP therapy in patients hospitalized with COVID-19 remain uncertain. Although CP has the potential to benefit patients with COVID-19, fundamental questions remain unanswered regarding its efficacy, including which of the components of CP are responsible for its therapeutic effect.

Taking into account the variety of characteristics of CP (such as volume, the number of doses, and levels of antibody titres), clinical trials should focus more on identifying a correlation between these characteristics and the efficacy of the therapy to better understand the potential of this therapeutic tool against severe COVID-19.[3]

It is evident that antibodies play a key role in CP therapy. Unfortunately, there is a lack of scientific evidence showing an association between the level of antibodies within CP and COVID-19 outcomes. Our trial was aimed at investigating how the serum IgA, IgG, and IgM levels in a COVID-19 patient group correlate with their survival rate, length of hospital stay, and presence of symptoms. Considering that studies evaluating CP therapies concentrate predominantly on examining total immunoglobulin or IgG-specific anti-SARS-Cov-2 antibody levels,[4] in this prospective study, we focused on assessing IgA as a potential promising component of this therapeutic method.

In this open-label, multi-centre, phase IV, single-arm trial (ClinicalTrials.gov number NCT04642014), we analysed the results of 108 patients with COVID-19 who received plasma from donors between 15 December 2020 and 28 February 2022 (Table S1). The median age of patients treated with CP was 54.9 years (range 23–88), with

TABLE 1 Clinical characteristics of convalescent plasma recipients; survival mortality and presence of symptoms in COVID-19 patients who received CP with low (<1.15 AU/ml) or high IgA, IgM, or IgG antibody levels.

Variable	All patients, $N = 108$	Alive patients, $N = 100$	Deceased patients, $N = 8$	p	OR (95% CI)
Sex				.257	
Female	34 (31.5%)	30 (30.0%)	4 (50.0%)		
Male	74 (68.5%)	70 (70.0%)	4 (50.0%)		
Age (years)				.401	
M ± SD	54.9 ± 13.1	53.8 ± 12.5	68.6 ± 12.5		
Me [Q1; Q3]	55 [45; 66]	54 [44; 65]	68 [61; 76]		
Min–Max	23–88	23–86	49–88		
BMI (kg/m^2)				.944	
M ± SD	28.0 ± 3.9	27.9 ± 3.9	28.6 ± 4.1		
Me [Q1; Q3]	27 [25; 31]	27 [25; 30]	26 [26; 32]		
Min–Max	20.2–38.4	20.2–38.4	25.2–35.6		
Antibody level					
IgA ≥ 1.15 AU/ml	102 (94.4%)	96 (96.0%)	6 (75.0%)	**.013**	**7.92 (1.20–52.3)**
IgA < 1.15 AU/ml	6 (5.5%)	4 (4.0%)	2 (25.0%)		**1.00 (ref.)**
IgM ≥ 0.68 AU/ml	27 (25%)	26 (26%)	1 (12.5%)	.676	2.49 (0.29–21.2)
IgM < 0.68 AU/ml	81 (75%)	74 (74%)	7 (87.5%)		1.00 (ref.)
IgG ≥ 7.6 AU/ml	55 (50.9%)	54 (54%)	1 (12.5%)	.031	8.07 (0.96–68.0)
IgG < 7.6 AU/ml	53 (49.1%)	46 (46.5%)	7 (87.5%)		1.00 (ref.)
Symptoms					
Loss of appetite	17 (15.7%)	17 (17.0%)	0 (0.0%)	.352	
Diarrhoea	19 (17.6%)	18 (18.0%)	1 (12.5%)	1.000	
Muscle pain	27 (25.0%)	25 (25.0%)	2 (25.0%)	1.000	
Dyspnea	97 (89.8%)	90 (90.0%)	7 (87.5%)	0.589	
Headache	20 (18.5%)	20 (20.0%)	0 (0.0%)	0.347	
Fever	83 (76.8%)	78 (78.0%)	5 (62.5%)	0.383	
Cough	78 (72.2%)	72 (72.0%)	6 (75.0%)	1.000	
Skin lesions	2 (1.8%)	2 (2.0%)	0 (0.0%)	1.000	
Taste perversion	11 (10.2%)	11 (11.0%)	0 (0.0%)	1.000	
Dysosmia	12 (11.1%)	12 (12.0%)	0 (0.0%)	0.594	
Mild fever	58 (53.7%)	56 (56.0%)	2 (25.0%)	0.141	
Fatigue	69 (63.9%)	65 (65.0%)	4 (50.0%)	0.456	
Quarantine before hospitalization	45 (41.7%)	41 (41.0%)	4 (50.0%)	0.717	
Diastolic blood pressure (mm Hg)				0.138	
M ± SD	76.2 ± 8.8	75.9 ± 8.8	79.4 ± 8.6		
Me [Q1; Q3]	78 [70; 80]	76 [70; 80]	80 [80; 82]		
Min–Max	60–100	60–100	60–90		
Systolic blood pressure (mm Hg)				0.837	
M ± SD	130.5 ± 14.6	130.6 ± 15.1	129.8 ± 7.3		
Me [Q1; Q3]	130 [120; 140]	130 [120; 140]	130 [124; 136]		
Min–Max	90–170	90–170	120–140		
Pulse (1/min)				0.837	
M ± SD	84.5 ± 13.8	84.9 ± 13.6	79.0 ± 16.2		
Me [Q1; Q3]	85 [75; 92]	85 [75; 93]	83 [65; 89]		
Min–Max	55–120	57–120	55–103		

TABLE 1 (Continued)

Variable	All patients, $N = 108$	Alive patients, $N = 100$	Deceased patients, $N = 8$	p	OR (95% CI)
IgA anti-SARS-CoV-2				**0.041**	
Positive	70 (65.4%)	68 (68.9%)	2 (25.0%)		
Ambiguous result	3 (2.8%)	3 (3.0%)	0 (0.0%)		
Negative	34 (31.8%)	28 (28.3%)	1 (12.5%)		
Leucocytes				**0.036**	
Norm or above range	91 (86.7%)	86 (88.7%)	5 (62.5%)		
Below normal range	14 (13.3%)	11 (11.3%)	3 (37.5%)		
Haematocrit				**0.001**	
Norma	78 (74.3%)	74 (76.3%)	4 (50.0%)		
Above normal range	1 (1.0%)	0 (0.0%)	1 (12.5%)		
Below normal range	26 (24.8%)	23 (23.7%)	3 (37.5%)		
RDW				**0.001**	
Norm	94 (89.5%)	89 (91.8%)	5 (62.5%)		
Above normal range	3 (2.9%)	1 (1.0%)	2 (25.0%)		
Below normal range	8 (7.6%)	7 (7.2%)	1 (12.5%)		
Monocytes				**0.029**	
Norm	87 (82.9%)	82 (84.5%)	5 (62.5%)		
Above normal range	7 (10.5%)	7 (7.2%)	0 (0.0%)		
Below normal range	11 (7.6%)	8 (8.3%)	3 (37.5%)		
pCO_2				**0.041**	
Norma	63 (62.4%)	57 (61.3%)	6 (75.0%)		
Above normal range	2 (2.0%)	1 (1.1%)	1 (12.5%)		
Below normal range	36 (35.6%)	35 (37.6%)	1 (12.5%)		
$PaO_2 \geq 80$ mm Hg				**0.049**	
Yes	71 (65.7%)	63 (63.0%)	8 (100.0%)		
No	37 (34.3%)	37 (37.0%)	0 (0.0%)		

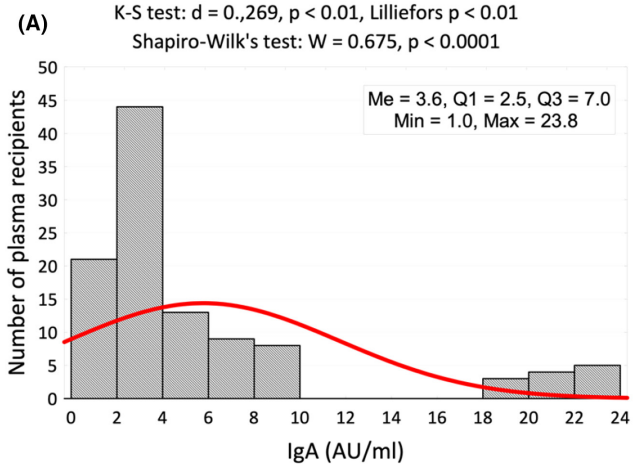
Note: Low and high values are represented by cut-offs of each antibodies level.

Bold values denote statistical significance at the $p < .05$ and 95% CI > 1.00.

25% of patients older than 66 years. The plasma recipients were adult patients diagnosed with COVID-19 according to the WHO Interim Guidance with confirmation by real-time RT-PCR assay. The inclusion criteria to receive CP involved at least one of following: respiratory distress with tachypnoea ≥30 breaths per minute, oxygen level <94% in resting-state, partial pressure of oxygen (PO2) ≤ 80 mm Hg. Patients who met the criteria received one dose (200 ml) of ABO compatible inactivated CP with a confirmed neutralization activity. The donor's blood was collected after 4 weeks post-onset of illness. A comprehensive analysis of the impact of the level of antibodies in the donor's plasma on the clinical response in patients with COVID-19 was performed. IgA anti-SARS-Cov-2, leucocytes, haematocrit, RDW, monocytes, pCO2, and PaO2 ≥ 80 mm Hg have been identified as variables associated with the survival of CP recipients (Table 1). All data is included in the manuscript or supporting information. Reporting of the study conforms to broad EQUATOR guidelines.[5]

According to our results, among COVID-19 patients who received CP with a level of IgA antibodies ≥1.15 AU (arbitrary units)/ml, the percentage of surviving patients compared to deceased patients was significantly higher (96.0% vs. 75.0%; $p = .013$, Table 1). Interestingly, patients who received plasma with IgA ≥1.15 AU/ml displayed an eight-fold increase in survival compared to patients who received CP with IgA < 1.15 AU/ml (OR = 7.92 95% CI 1.20–52.3; Table 1). Additionally, every patient that received plasma with IgA > 19 AU/ml had survived. The level of IgA in the plasma of donors is presented in Figure 1A. It is worth mentioning, similarly to IgA levels, there was an increased survival of patients receiving >7.6 AU/ml of IgG compared to deceased patients (50.9% vs. 12.5%, $p = .031$; Table 1).

A weak but statistically significant negative correlation was also observed between the levels of IgA and IgG in donor plasma; increases in IgA levels were accompanied by a decrease in the levels of IgG (rho = −0.240) (Figure 1B). Despite these associations, IgG level remain high, significantly



(B)

All patients	IgA	IgM	IgG
IgA	*rho* = 1.000	*rho* = 0.183	*rho* = -0.240
IgM		*rho* = 1.000	*rho* = 0.222
IgG			*rho* = 1.000

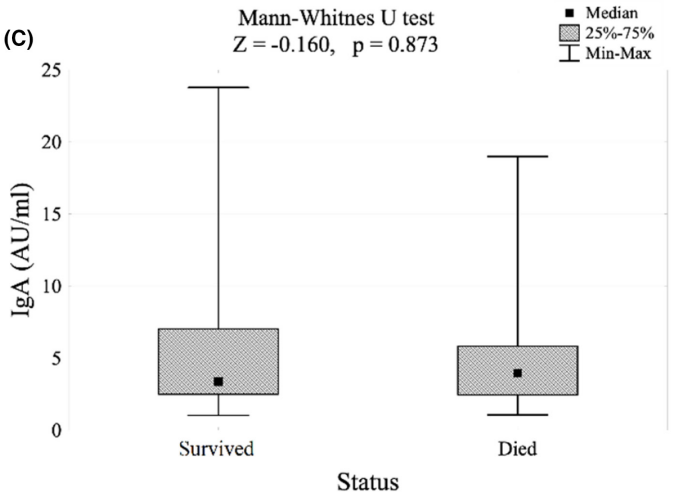


FIGURE 1 (A) Histogram of donor plasma IgA levels using a normality test; (B) Comparison of donor plasma IgA antibody levels and survival; (C) Spearman's rank correlation coefficients between antibody levels in the plasma of 44 donors.

higher than IgA (cut-off values for IgA = 1.15 AU/ml, and for IgG = 7.6 AU/ml). Therefore, IgG antibodies outnumber the amount of IgA levels, which is already known in the literature.[6] As shown in our study, IgA has an effect on the level of IgG antibodies in donor plasma. However, the question if received during CP transplantation IgA itself leads to the increase of overall survival among COVID-19 infected patients or is it due to the direct correlation with the level of other antibodies (e.g. IgG/IgM) require further investigation. Additionally, our study reveals the association between the IgM and IgG levels (rho = 0.222).

The length of hospitalization of CP recipients, who survived 28 days after CP transplantation, was also measured. This ranged from 2 to 67 days (Me = 10 days). However, there was no significant correlation between mortality, the duration of hospitalization and the level of IgA antibodies in the donors' plasma ($p > .05$; Figure 1C).

To better understand the impact of IgA levels on the presence of symptoms in the recipient group, we analysed the occurrence of the symptoms in correlation to the amount of IgA in CP. The results showed that patients who received CP with IgA ≥ 8.3 AU/ml had a 13.5 greater chance of an asymptomatic infection compared to patients who received plasma with IgA < 8.3 AU/ml (OR = 13.5 95% CI 2.25–81.5; Table 1).

Many comparative studies, both randomized and nonrandomized, have reported a promising role of CP in alleviating the symptoms of the virus.[2,7,8] However, various studies and clinical trials show contradicting results regarding the efficacy of CP in COVID-19 treatment.[9,10] Thus, due to the lack of decisive data on the effectiveness of CP therapy and no detailed analysis explaining the conflicting results, this therapeutic approach has been largely withdrawn from medical practice. Nevertheless, despite recommendations against its use, CP treatment continues to be extensively tested,[11] especially in countries that have been affected by COVID-19 the most.[12]

To minimize the uncertainties regarding the use of CP therapy in COVID-19 treatment, we took on the challenge

of determining the reason for these discrepancies. Our findings are in line with several recently published studies, which showed that IgA received by donors during CP therapy contributes to the neutralizing antibody response.[4,13,14] Our results may explain the apparent contradictions between the inauspicious results of randomized trials and the promising observational studies that demonstrate better outcomes for higher-titre CP. To the best of our knowledge, this is the first study that explains the direct impact of transfusing donor plasma with high levels of IgA antibodies on the mortality and symptom progression caused by COVID-19.

Nevertheless, despite conflicting results in the literature, we believe that CP therapy is a promising treatment strategy for COVID-19. Despite the limitations arising from the design of our study, which include a small sample size (108 patients with COVID-19 infection), a single-arm design, and the lack of randomization, our study proves that CP has the potential to increase the survival rate and suppress COVID-19 symptoms if the level of IgA is ≥1.15 and ≥8.3 AU/ml, respectively. However, to better understand the impact of high IgA CP on the outcomes of COVID-19, further properly designed clinical studies are needed.

AUTHOR CONTRIBUTIONS

S.A., and G.M. reviewed the literature, A.K., S.W. enrolled patients in the study, M.S.N. collected data, S.A., J.D., A.B., and G.M. analysed and interpreted data, S.A and S.M. wrote the manuscript; A.K., S.W. recruited donors.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

ORCID

Siddarth Agrawal https://orcid.org/0000-0003-1118-5090

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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