Severe Hemolytic Exacerbations of Chinese PNH Patients infected SARS-CoV-2 Omicron

Hui Yang[1], Xingxing Chai[2], Yuemin Gong[1], Xinyu Zhang[1], Lingling Wang[3], Xin Zhou[3], Xiaoyu Chen[1], Jinge Xu[4], Dan Xu[5], Jianyong Li[1], and Guangsheng He[1]

[1]Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
[2]second people's hospital of Lianyungang
[3]Wuxi People's Hospital
[4]The Second Affiliated Hospital of Xuzhou Medical University
[5]Funing People's Hospital

January 30, 2024

Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by hemolytic anemia, bone marrow failure, thrombophilia. COVID-19, caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with many variants including Omicron. This study depicted demographic and clinical characteristics of 20 PNH patients with SARS-Cov2 Omicron infection. All the patients hadn't previously been administrated with complement inhibitors. They all were with high disease activity (HDA), and LDH level exceeded any documented since the diagnosis of PNH, and those reported in the literature for previously stable treatment with complement inhibitors. D-dimer level elevated in 10 patients. 2 patients developed mild pulmonary artery hypertension. Glomerular filtration rate (GFR) declined in 5 patients. 1 patient developed acute renal failure and underwent hemodialysis. Anemia and hemolysis were improved in 5 patients treated with eculizumab. Hemolytic exacerbation of PNH with COVID-19 is severe and eculizumab may be an effective treatment.

Severe Hemolytic Exacerbations of Chinese PNH Patientsinfected SARS-CoV-2 Omicron

Hui Yang[1]#, Xingxing Chai[2]#, Yuemin Gong[1], Xinyu Zhang[1], Lingling Wang[3], Xin Zhou[3], Xiaoyu Chen[1], Jinge Xu[4], Dan Xu[5], Guangsheng He[1*], Jianyong Li[1]

[1]Department of Hematology; The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital in Nanjing, Key Laboratory of Hematology of Nanjing Medical University, Collaborative Innovation Center for Cancer Personalize

300# Guangzhou Road, Nanjing, Jiangsu Province, China (210029)

[2]Department of Hematology; The second people's hospital of Lianyungang

41# Hailiandong Road, Lianyungang, Jiangsu Province, China (222000)

[3]Department of Hematology; Wuxi People's Hospital affiliated to Nanjing Medical University

299# Qingyang Road, Wuxi, Jiangsu Province, China (214002)

[4]Department of Hematology, The Second Affiliated Hospital of Xuzhou Medical University

32# Meijian Road, Xuzhou, Jiangsu Province, China (221004)

[5]Department of Hematology; Funing People's Hospital

109# Fucheng Street, Yancheng, Jiangsu Province, China (224400)

*Correspondence:

Guangsheng He, Department of Hematology; The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital in Nanjing, Key Laboratory of Hematology of Nanjing Medical University, Collaborative Innovation Center for Cancer Personalize

300# Guangzhou Road, Nanjing, Jiangsu Province, China (210029)

Email: heguangsheng1972@sina.com

#These authors contributed equally to this work and shared first authorship.

Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by hemolytic anemia, bone marrow failure, thrombophilia. COVID-19, caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with many variants including Omicron. This study depicted demographic and clinical characteristics of 20 PNH patients with SARS-Cov2 Omicron infection. All the patients hadn't previously been administrated with complement inhibitors. They all were with high disease activity (HDA), and LDH level exceeded any documented since the diagnosis of PNH, and those reported in the literature for previously stable treatment with complement inhibitors. D-dimer level elevated in 10 patients. 2 patients developed mild pulmonary artery hypertension. Glomerular filtration rate (GFR) declined in 5 patients. 1 patient developed acute renal failure and underwent hemodialysis. Anemia and hemolysis were improved in 5 patients treated with eculizumab. Hemolytic exacerbation of PNH with COVID-19 is severe and eculizumab may be an effective treatment.

Keyword

Paroxysmal nocturnal hemoglobinuria; COVID-19; Omicron; complement inhibitor therapy; hemolysis;

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired and clonal disease characterized by hemolytic anemia, bone marrow failure, thrombophilia and multi-organ damage, which results from the mutation of the *X* -linked *PIGA* gene. The blockade of glycosylphosphatidylinositol (GPI) synthesis caused by mutation results in the absence of GPI-anchored protein (such as CD55 and CD59), and CD55-deficient and CD59-deficient blood cells are more susceptible to complement attack and lysis[1,2]. Coronavirus disease 2019 (COVID-2019) first emerged in Wuhan, Hubei, China, by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3]. SARS-CoV-2 was reported multiple variants, including Alpha, Beta, Gamma, Delta, Omicron, and Omicron shows a 13-fold increase in viral infectivity than Delta variant[4]. SARS-CoV-2 activate the complement system through the classical pathway, lectin pathway and the alternative pathway. Specific antibody directed against the receptor-binding domain of the spike protein initiates the classical pathway, the binding of mannose-binding lectin (MBL) with SARS-CoV-2 spike protein triggers the lectin pathway and SARS-CoV-2 spike protein may dysregulate the alternative pathway by binding heparan sulfate and competing with factor H, which is a negative regulator of complement activity[5,6]. After SARS-CoV-2 infection, patients with PNH more likely suffered the hemolysis[7–16], patients usually presented visible hemoglobinuria and a small number patients showed pancytopenia[17]. Terminal complement inhibitors (such as eculizumab) are promising in COVID-19 treatment by blocking the formation of membrane attack complex (MAC) and reducing pro-inflammatory and prothrombotic influence[5,6,18]. Due to the rarity of PNH, the clinical features of patients infected with SARS-CoV-2 were mostly case reports. China has been heavily affected by the SARS-CoV-2 Omicron outbreak with the peak in mid-December 2022. We collected clinical data from 20 PNH patients infected with SARS-CoV-2 Omicron and treated 5 patients with eculizumab.

2. Patients and Methods

2.1 Patients

The study enrolled 20 patients with PNH infected SARS-CoV-2 Omicron prospectively registered in the Chinese Eastern Collaboration Group of Anemia (ChiCTR2100050945), which was conducted by four centers: the First Affiliated Hospital with Nanjing Medical University (Nanjing, China), the second people's hospital of Lianyungang (Lianyungang, China), Wuxi People's Hospital (Wuxi, China) and Funing People's Hospital (Funing, China) from December 2022 to February 2023. Patients signed informed consent. The study was conducted according the Declaration of Helsinki and approved by the hospital ethics committee.

2.2 Diagnostic criteria

All the patients developed fever, cough, nasal congestion, sore throat, or other uncomfortable symptoms. Reverse transcription polymerase chain reaction (RT-PCR) or antigen testing for SARS-Cov-2 was positive.

High disease activity (HDA) was defined as evidence of hemolysis (elevated lactate dehydrogenase [LDH][?]1.5 times upper limit of normal [ULN]) and a history of at least 1 of the following signs or symptoms— fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia (hemoglobin < 100 g/L), MAVEs (including TEs), dysphagia, or erectile dysfunction[19].

2.3 Methods

A collection on 20 patients with PNH registered in 4 centers is to evaluate the occurrence and clinical characteristics of SARS-CoV-2 infection, and the efficacy of eculizumab.

3. Statistics analysis

Categorical variables were described using frequencies and percentages, and continuous variables were described using median, minimum and maximum. Shapiro-Wilk test is used to test whether the data conform to a normal distribution. The degree of SARS-CoV-2-induced hemolysis compared with the literature was examined by Mann-Whitney U test. Paired samples conformed to a normal distribution use paired sample T test, otherwise Wilcoxon test is used for examination. All of the analyses were performed using the statistical package SPSS 26.0, p¡0.05 was considered statistically significant.

4. Results

4.1 Status of hemolytic episodes with SARS-CoV-2 Omicron infection

A total of 20 PNH patients diagnosed with SARS-CoV-2 Omicron infection were enrolled in this study. 6 (30%, 6/20) were male, 14 (70%, 14/20) were female and the median age was 37 years (range 15–75years). Eleven patients (55%, 11/20) presented classical PNH and nine patients (45%, 9/20) were diagnosed with PNH/AA. They accepted glucocorticoid maintenance and transfusion in the past. None of them were treated with complement inhibitors. The median time to episode occurred is three days after SARS-CoV-2 Omicron infection (1-5 days).

10 patients (50%, 10/20) complained of hemoglobinuria. Other 10 patients (50%, 10/ 20) presented with worsen fatigue and cytopenia. Although no thrombotic event happened, D-dimer (median 2.55mg/L, range 0.57– 4.47mg/L) was elevated in 10 patients, and all of them received prophylactic low molecular weight heparin.

Mild pulmonary hypertension was found in two patients (32mmHg and 35mmHg, respectively). The glomerular filtration rate in five patients (25%, 5/20) was lower than 60ml/min/1.73m^2. One patient underwent hemodialysis due to acute renal failure.

The level of LDH (2555U/L vs 1542U/L, 9.43×ULN vs 5.62×ULN, p=0.011), total bilirubin (TBIL) (49.56μmol/L vs 28.92 μmol/L, p=0.031) and indirect bilirubin (IBIL) (29.31 μmol/L vs 17.8μmol/L, p=0.017) were higher than the most severe hemolysis previously recorded. Anemia became worsened compared to the previous period — RBC (2.17×1012/L vs 2.42×1012/L, p=0.356), Hb (66 g/L vs 71 g/L,

p=0.459) (Table 1). The decrease in GFR was nearly statistically significant(113.65 ml/min/1.73m^2 vs 118.3 ml/min/1.73m^2, p=0.055).

4.2 Efficacy of eculizumab

5 patients were administrated with eculizumab. After eculizumab treatment, hemolysis was controlled (LDH 13.53xULN vs 3.38xULN, p=0.028), and RBC count (1.96x10^{12}/L vs 2.45x10^{12}/L, p=0.01), and level of hemoglobin (64 g/L vs 83 g/L, p=0.005) were also improved significantly (Table 2) (Figure 1). The improvement in IBIL was nearly statistically significant (31.7 1μmol/L vs 20.69 μmol/L, p=0.057). The elevated D-dimers in two patients also decreased significantly after treatment— 4.04 mg/L vs 1.47 mg/L, 2.15 mg/L vs 1.37 mg/L, respectively. During hemolysis, one patient had a high IL-6 serum concentration, 31.29 times higher than the upper limit of the normal —165.83 pg/mL while after eculizumab treatment IL-6 drops to 4.98 pg/mL. Because of emergency use, the patients treated by eculizumab could not be vaccinated against Neisseria meningitidis and Streptococcus pneumoniae in advance, but infection did not occur with the whole course of penicillin prophylaxis.

4.3 Outcomes of COVID-19 and PNH

In our study, 12 of 20 (60%) were hospitalized. 2 (2/20, 10%) patients developed severe COVID-19—one with severe viral pneumonia but recovered after two doses of eculizumab with oxygen support and the other with acute renal failure but recovered after hemodialysis.

Of the 5 patients using eculizumab, 2 were not in HDA status. But 13 of the other 15 patients remained in HDA status during the second week after infection with SARS-CoV-2 Omicron.

5. Discussion

PNH is a complement-mediated hemolytic anemia[1]and SARS-CoV-2 activates complement and inflammatory factor storm[6]. PNH patients infected with SARS-CoV-2 are more likely to have hemolytic episodes. 20 patients all had HDA in this study and had severe hemolysis and anemia: LDH, indirect bilirubin increased and red blood cell count, hemoglobin declined significantly.

Current study found that Omicron-induced hemolysis was more intense than ever happened since diagnosis. On the one hand, SARS-CoV-2 triggered complement activation through three pathways[5,6]and on the other hand, coronavirus infection activates monocyte, macrophage, and dendritic cell, then releases IL-6 and amplifies cytokine cascade[20]. Under dual attack, it causes severe hemolysis in patients suffering from PNH.

In this study, there was no thromboembolism, but D-dimer values of a half of patients were beyond the upper limit of normal. Zlatko et al.[16] reported one PNH patient who presented with deep vein thrombosis as the first sign of COVID-19. SARS-CoV-2 may increase thrombophilia in PNH in the context of multiple triggers, such as increased inflammatory factors, endothelial injury, platelet and thrombin activations. Acute kidney injury of PNH will be caused by a variety of reasons, such as the direct toxicity of free hemoglobin released by broken red blood cells, the constriction of renal blood vessels caused by NO consumption, and the direct damage caused by the coronavirus and cytokine storm[2,21,22]. In our cohort, there were 5 patients with severe renal function decline (glomerular filtration rate [?] 60ml/min/1.73m^2), even one accepted hemodialysis.

C5 inhibitors have been recommended as the first line treatment for PNH[23], greatly improving the poor prognosis of PNH. C5 inhibitors protect PNH clone from attack by blocking the complement activation pathway and significantly improve hemolytic anemia, reduce events of thrombosis, and alleviate damage of renal function[24–27]. Meanwhile, eculizumab has been used to treat severe COVID-19 [28]. Excess C5a induces the release of pro-inflammatory cytokines from innate immune cells which is thought to play a key role in acute lung injury[29]. After eculizumab stops the cleavage of C5, the production of C5a is reduced. In an Annane's study[30]of 80 patients with severe COVID-19, 35 patients treated with additional eculizumab showed higher survival rate (82.9% vs 62.2%, p=0.04) and improved tissue oxygenation compared with 45 patients who received supportive care alone. Another case reported that after Diurno[31] administrated eculizumab to 4 patients with severe COVID-19, their inflammatory markers declined and recovery time was

cut short. The literature[10,12–14,16] documented less frequent hemolysis following SARS-CoV-2 infection in PNH patients who regularly used complement inhibitors. Compared with cases with LDH values reported in the literature, hemolysis in current study was more severe (LDH 7.47×ULN vs 2.04×ULN, p¡0.001). In our study, 5 patients receiving eculizumab achieved improvement in hemolysis and anemia, and COVID-19 was also relieved. Eculizumab maybe a good choice for patients with PNH after SARS-CoV-2 infection.

In conclusion, our study preliminarily demonstrate SARS-CoV-2 infection could induce a hemolytic exacerbation in patients with PNH but eculizumab can effectively control acute hemolysis. A large amount of long-term follow-up data are still needed to assess the impact of SARS-CoV-2 on patients with PNH, evaluate the dose and duration of eculizumab, and develop better prevention and control plans.

6. Acknowledgements

We thank everyone involved in medical care and epidemic prevention for their efforts during the COVID-19 pandemic. We thank everyone at Jiangsu Provincial People's Hospital, the second people's hospital of Lianyungang, Wuxi People's Hospital affiliated to Nanjing Medical University

and Funing People's Hospital. We thank patients' understanding and support for study.

7. Data availability statement

This article contains all the data generated or analyzed during this study. Any further queries should be directed to the corresponding author.

8. Funding

This work was supported by the National Natural Science Foundation of China (81900109), Jiangsu Innovative Talents Subsidized Project [(2019)30357], Jiangsu Province Capability Improvement Project through Science, Technology and Education (ZDXK202209) and 2022 Research Development Fund of Kangda College of Nanjing Medical University (KD2022KYJJZD045).

9. Conflict of interest

The authors declare no conflict of interest.

10. Author contributions

Research idea and study design: Hui Yang and Xingxing Chai. Data collection: Hui Yang, Yuemin Gong, Xinyu Zhang, Lingling Wang, Jinge Xu, Dan Xu. Data analysis: Hui Yang, Xingxing Chai and Xiaoyu Chen. Wrote the manuscript: Hui Yang and Xingxing Chai. Supervision or mentorship: Xin Zhou, Jianyong Li and Guangsheng He.

11. Ethics statement

This study was approved by the First Affiliated Hospital of Nanjing Medical University ethics committee (Ethics approval document 2020-SR-421) conducted following the principle of the Helsinki Declaration.

12. Consent to participate

Informed consent was obtained from all individual participants included in the study.

13. Consent to publication

The authors confirms that the work has not been published before and the publication has been approved by all co-authors.

Reference

[1] Brodsky R A. How I Treat Paroxysmal Nocturnal Hemoglobinuria[J]. Blood, 2021, 137(10): 1304–1309. DOI: 10.1182/blood.2019003812

[2] Devalet B, Mullier F, Chatelain B, et al. Pathophysiology, diagnosis, and treatment of paroxysmal nocturnal hemoglobinuria: a review[J]. European Journal of Haematology, 2015, 95(3): 190–198. DOI: 10.1111/ejh.12543

[3] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China[J]. Lancet (London, England), 2020, 395(10223): 497–506. DOI: 10.1016/S0140-6736(20)30183-5

[4] Aleem A, Akbar Samad A B, Slenker A K. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19) [A]. In: StatPearls[M]. Treasure Island (FL): StatPearls Publishing, 2022.

[5] Afzali B, Noris M, Lambrecht B N, et al. The state of complement in COVID-19[J]. Nature Reviews. Immunology, 2022, 22(2): 77–84. DOI: 10.1038/s41577-021-00665-1

[6] Noris M, Benigni A, Remuzzi G. The case of complement activation in COVID-19 multiorgan impact[J]. Kidney International, 2020, 98(2): 314–322. DOI: 10.1016/j.kint.2020.05.013

[7] A H, N H, J B. COVID-19 infection presenting as paroxysmal nocturnal hemoglobinuria[J]. Clinical case reports, Clin Case Rep, 2021, 9(8). DOI: 10.1002/ccr3.4636

[8] A G, T C, P B, et al. Severe COVID-19 infection in a patient with paroxysmal nocturnal hemoglobinuria on eculizumab therapy[J]. Leukemia & lymphoma, Leuk Lymphoma, 2021, 62(6). DOI: 10.1080/10428194.2020.1869963

[9] Sokol J, Nehaj F, Mokan M, et al. COVID19 infection in a patient with paroxysmal nocturnal hemoglobinuria[J]. Medicine, 2021, 100(20): e25456. DOI: 10.1097/MD.0000000000025456

[10] Shikdar S, Borogovac A, Mohamad E, et al. COVID19 infection in a patient undergoing treatment for Paroxysmal Nocturnal Hemoglobinuria (PNH) with Ravulizumab[J]. Thrombosis Journal, 2021, 19: 75. DOI: 10.1186/s12959-021-00330-6

[11] Araten D J, Belmont H M, Schaefer-Cutillo J, et al. Mild Clinical Course of COVID-19 in 3 Patients Receiving Therapeutic Monoclonal Antibodies Targeting C5 Complement for Hematologic Disorders[J]. The American Journal of Case Reports, 2020, 21: e927418-1-e927418-4. DOI: 10.12659/AJCR.927418

[12] Pike A, Muus P, Munir T, et al. COVID-19 infection in patients on anti-complement therapy: The Leeds National Paroxysmal Nocturnal Haemoglobinuria service experience[J]. British Journal of Haematology, 2020, 191(1): e1–e4. DOI: 10.1111/bjh.17097

[13] Barcellini W, Fattizzo B, Giannotta J A, et al. COVID-19 in patients with paroxysmal nocturnal haemoglobinuria: an Italian multicentre survey[J]. British Journal of Haematology, 2021, 194(5): 854–856. DOI: 10.1111/bjh.17558

[14] Kulasekararaj A G, Lazana I, Large J, et al. Terminal complement inhibition dampens the inflammation during COVID-19[J]. British Journal of Haematology, 2020, 190(3): e141–e143. DOI: 10.1111/bjh.16916

[15] Schuller H, Klein F, Lubbert M, et al. Hemolytic crisis in a patient treated with eculizumab for paroxysmal nocturnal hemoglobinuria possibly triggered by SARS-CoV-2 (COVID-19): a case report[J]. Annals of Hematology, 2021, 100(3): 841–842. DOI: 10.1007/s00277-020-04318-6

[16] Pravdic Z, Mitrovic M, Bogdanovic A, et al. COVID-19 Presented with Deep Vein Thrombosis in a Patient with Paroxysmal Nocturnal Haemoglobinuria[J]. Hamostaseologie, Georg Thieme Verlag KG, 2021, 41(5): 397–399. DOI: 10.1055/a-1554-6432

[17] Iannuzzi A, Parrella A, De Ritis F, et al. Pancytopenia in a Case of Aplastic Anaemia/Paroxysmal Nocturnal Haemoglobinuria Unmasked by SARS-CoV-2 Infection: A Case Report[J]. Medicina, 2022, 58(9): 1282. DOI: 10.3390/medicina58091282

[18] Barcellini W, Fattizzo B, Quattrocchi L, et al; COVID-19 Infection in Patients with Paroxysmal Nocturnal Hemoglobinuria in Italy. Blood 2020; 136 (Supplement 1): 36–37. DOI: https://doi.org/10.1182/blood-2020-138721

[19] Schrezenmeier H, Roth A, Araten D J, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry[J]. Annals of Hematology, 2020, 99(7): 1505–1514. DOI: 10.1007/s00277-020-04052-z

[20] Moore J B, June C H. Cytokine release syndrome in severe COVID-19[J]. Science, American Association for the Advancement of Science, 2020, 368(6490): 473–474. DOI: 10.1126/science.abb8925

[21] Passoni R, Lordani T V A, Peres L A B, et al. Occurrence of acute kidney injury in adult patients hospitalized with COVID-19: A systematic review and meta-analysis[J]. Nefrologia, 2022, 42(4): 404–414. DOI: 10.1016/j.nefroe.2022.11.005

[22] Clark D A, Butler S A, Braren V, et al. The kidneys in paroxysmal nocturnal hemoglobinuria[J]. Blood, 1981, 57(1): 83–89. DOI: 10.1182/blood.V57.1.83.83

[23] Risitano A M, Peffault de Latour R. How we('ll) treat paroxysmal nocturnal haemoglobinuria: diving into the future[J]. British Journal of Haematology, 2022, 196(2): 288–303. DOI: 10.1111/bjh.17753

[24] Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria[J]. American Journal of Hematology, 2010, 85(8): 553–559. DOI: 10.1002/ajh.21757

[25] Brodsky R A, Young N S, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria[J]. Blood, 2008, 111(4): 1840–1847. DOI: 10.1182/blood-2007-06-094136

[26] Hillmen P, Muus P, Roth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria - Hillmen - 2013 - British Journal of Haematology - Wiley Online Library[J]. British Journal of Haematology, 2013, 162(1): 62–73. DOI: 10.1111/bjh.12347

[27] Hillmen P, Hall C, Marsh J C W, et al. Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria[J]. New England Journal of Medicine, Massachusetts Medical Society, 2004, 350(6): 552–559. DOI: 10.1056/NEJMoa031688

[28] Di Franco S, Alfieri A, Petrou S, et al. Current status of COVID-19 treatment: An opinion review[J]. World Journal of Virology, 2020, 9(3): 27–37. DOI: 10.5501/wjv.v9.i3.27

[29] Wang R, Xiao H, Guo R, et al. The role of C5a in acute lung injury induced by highly pathogenic viral infections[J]. Emerging Microbes & Infections, 2015, 4(5): e28. DOI: 10.1038/emi.2015.28

[30] Annane D, Heming N, Grimaldi-Bensouda L, et al. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: A proof-of-concept study[J]. EClinicalMedicine, 2020, 28: 100590. DOI: 10.1016/j.eclinm.2020.100590

[31] F D, Fg N, G P, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience[J]. European review for medical and pharmacological sciences, Eur Rev Med Pharmacol Sci, 2020, 24(7). DOI: 10.26355/eurrev_202004_20875

Table 1 Comparison of current hemolysis with the most severe hemolysis previously

	Current Omicron-induced hemolysis	Previous most drastic hemolysis	P value
Gender, n (%)	Gender, n (%)	Gender, n (%)	/
Male	5 (29.41%)	5 (29.41%)	
Female	12 (70.59%)	12 (70.59%)	
Median age (range) (years)	38 (17, 73)	38 (17, 73)	/

	Current Omicron-induced hemolysis	Previous most drastic hemolysis	P value
Classification, n (%)	Classification, n (%)	Classification, n (%)	/
Classical	10 (58.82%)	10 (58.82%)	
Combined with BMD	7 (41.18%)	7 (41.18%)	
Subclinical	0 (0%)	0 (0%)	
WBC (×109/L) (range)	3.11 (1.54, 10.54)	3.64 (2.23, 9.58)	0.796
ANC (×109/L) (range)	2.24 (0.68, 9.35)	1.8 (0.5, 7.81)	0.636
RBC (×1012/L) (range)	2.17 (1.14, 3.28)	2.42 (1.37, 3.27)	0.356
Hb (g/L) (range)	66 (38, 88)	71 (47, 94)	0.459
BPC (×109/L) (range)	140 (22, 306)	141 (12, 310)	0.446
LDH (U/L) (range)	2555 (672,8482)	1542 (733, 4157)	0.011
LDH (×ULN) (range)	9.43 (2.48, 31.3)	5.62 (2.7, 15.34)	0.011
Creatinine (μmol/L) (range)	68 (35.8, 186)	62 (38.3, 215)	0.113
GFR (ml/min/1.73m2) (range)	113.65 (32.44, 136.3)	118.3 (27.23, 143.59)	0.055
BUN (mmol/L) (range)	4.59(2.4, 10.38)	4.76(2.2, 11)	0.623
TBIL (μmol/L) (range)	49.56(11, 104.3)	28.92(12.4, 94.1)	0.031
IBIL (μmol/L) (range)	29.31(7.5, 84.9)	17.8(10.1, 72.2)	0.017
D-dimer (mg/L) (range)	0.6(0.31, 4.15)	0.59(0.12, 6.76)	0.695

Abbreviations: BMD, bone marrow disease; WBC, white blood cell count; ANC, absolute neutrophil count; RBC, red blood cell count; Hb, hemoglobin; BPC, blood platelet count; LDH, lactate dehydrogenase; ULN, upper limits of normal, GFR, glomerular filtration rate; BUN, blood urea nitrogen; TBIL, total bilirubin; IBIL, indirect bilirubin

Table 2 Improvement the of hemolysis by eculizumab

	Before eculizumab therapy	After eculizumab therapy	P value
Gender, n (%)			/
Male	1 (20%)	1 (20%)	
Female	4 (80%)	4 (80%)	
Median age (range) (year)	59 (26, 67)	59 (26, 67)	/
Classification, n (%)			/
Classical	3 (60%)	3 (60%)	
Combined with BMD	2 (40%)	2 (40%)	
Subclinical	0 (0%)	0 (0%)	
WBC ($\times 10^9$/L) (range)	2.85 (2.27, 10.54)	3.09 (2.1, 5.64)	0.504
ANC ($\times 10^9$/L) (range)	2.24 (0.74, 9.35)	1.79 (0.17, 4.62)	0.686
RBC ($\times 10^{12}$/L) (range)	1.96 (1.32, 2.47)	2.45 (2.24, 2.66)	0.01
Hb (g/L) (range)	64 (43, 80)	83 (67, 87)	0.005
BPC ($\times 10^9$/L) (range)	74 (50, 306)	81 (38, 319)	0.448
LDH (U/L) (range)	3667 (1075.1, 4887)	915 (460, 1822)	0.028
GFR (ml/min/1.73m^2) (range)	84.47 (36.31, 130.54)	85.53 (42.25, 129)	0.742
IBIL (μmol/L) (range)	31.71 (14.7, 83.5)	20.69 (4.3, 24.1)	0.057

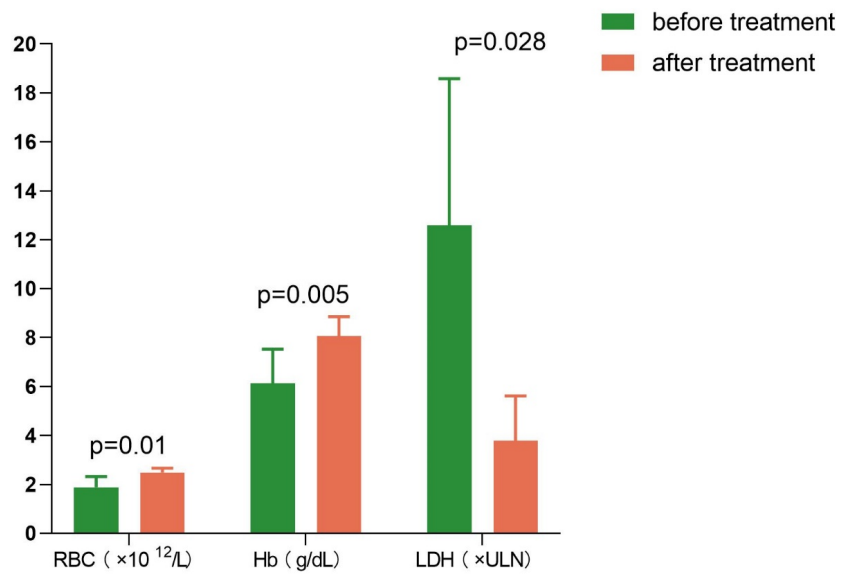

Figure 1 Eculizumab improved the RBC count (1.96×10^{12}/L vs 2.45×10^{12}/L, p=0.01), levels of Hb (64 g/L vs 83 g/L, p=0.005) and LDH (13.53×ULN vs 3.38×ULN, p=0.028) significantly.

Hosted file

`figure.docx` available at https://authorea.com/users/724224/articles/708310-severe-hemolytic-exacerbations-of-chinese-pnh-patients-infected-sars-cov-2-omicron