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Pathology

CROSS SECTIONAL STUDY OF COVID 19 CONVALESCENT PLASMA (COPLA) DONOR CHARACTERISTICS

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ABSTRACT **Background:** Although many trials are currently investigating the safety and efficacy of convalescent plasma (CP) in critically ill COVID-19 patients, there is a paucity of ongoing and published studies evaluating the CP donors' side. In this regard, this study was aimed to find out how SARS-CoV2 IgG antibodies are influenced by demographic and clinical characteristics of donors such as age, sex, ABO/Rh blood group, disease severity, post recovery duration, ethnicity. **Material & Methods:** After approval from the IEC and consent from the study participants, the study was performed in Department of Pathology and Blood Bank of Sri Aurobindo Medical College and PG Institute, Indore (M.P) on a total of 785 COVID-19 recovered patients. **Results:** A total of 785 COVID-19 recovered patients were telephonically contacted for COPLA donation, out of which 103 donor candidates refused for the plasma donation while 82 donors were deferred by blood bank authorities for convalescent plasma donation. 600 donors successfully donated convalescent plasma in the present study. The most common reason for refusal of COPLA donation by the donors was Fear of reinfection (26.2%) followed by diabetes mellitus on insulin (16.5%). Whereas low antibody titre (53.7%) was the most common reason for COVID- 19 COPLA donor deferral in the present study. Majority were in age group 26-35 with higher prevalence of males. Donors' age and COVID-19 severity were positively associated with greater antibody responses. **Conclusion:** The awareness of CP donor characteristics, post-screening deferrals, and correlates of antibody values with age, gender, body weight, severity of COVID-19 disease and blood groups will help improve collection outcomes and give better preparedness for future recurrent waves due to evolution of more virulent SARS-CoV-2 strains and fill treatment gap till availability of more specific treatment.

KEYWORDS : COPLA Donors, SARS-CoV-2; COVID-19; Convalescent Plasma

INTRODUCTION

In December 2019, a novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported from a cluster of patients with pneumonia of unknown cause.[1] The virus primarily causes an acute febrile illness, which can proceed to acute respiratory distress syndrome (ARDS).

The World Health Organization (WHO) named the disease Corona Virus Disease 2019 (COVID-19).[2-4] On 11 March 2020, the World Health Organization declared COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, a global pandemic.[5]

On 24 March 2020, the US Food and Drug Administration (FDA) announced emergency approval for use of convalescent plasma to treat patients with COVID-19.[6] Because there were no known treatments or vaccines available at that time, demand for COVID-19 convalescent plasma (CCP) paralleled the increase of disease in affected individuals.[6-7] As the virus continued to spread and case number continued to rise worldwide,[3] CCP remained the most accessible viral-specific therapy for hospitalized patients.[4,8,9]

COVID-19 has few treatment options, most of which are empirical or experimental. There are no specific antiviral agents targeting SARS-CoV-2.[10] Vaccination is the best approach to control widespread epidemic and its devastating effects on global economy and public health.[11] Despite unprecedented and extensive efforts to make and distribute enough safe and effective COVID-19 vaccine around the world, it seemed time consuming to establish active immunity against the SARS-CoV-2 virus in every person around the world successfully. Therefore, the use of various effective therapies to treat severe cases of the disease to reduce mortality rate until global approach to the COVID-19 vaccines for every individual is achieved, was of substantial importance.

Humoral immune response by targeting the immunodominant SARS-CoV-2 Spike (S) protein seems to be highly correlated with virus neutralization through inhibiting the interaction between S protein and the virus receptor, angiotensin converting enzyme 2 (AEC2).[12] It has been shown that transfusion of COVID-19 convalescent plasma containing these neutralizing antibodies (nAbs) to patients affected with COVID-19 could effectively reduce viral load in the patients' body.[13]

In this regard, this study was aimed to find out how SARS-CoV2 IgG antibodies are influenced by demographic and clinical characteristics of donors such as age, sex, ABO/Rh blood group, disease severity, post recovery duration, ethnicity. This study provided a strategy for selecting individuals possibly with high levels of anti-SARS-CoV-2 IgG antibodies as preferred donors for CCP donation.

Material & Method

After approval from institutional ethical committee the present cross-sectional study was planned in Department of Pathology and Blood Bank of Sri Aurobindo Medical College and PG Institute, Indore (M.P) on a total of 785 COVID-19 recovered patients who were telephonically contacted for COPLA donation, out of which 103 donor candidates refused for the plasma donation while 82 donors were deferred by blood bank authorities for convalescent plasma donation. 600 donors successfully donated convalescent plasma in the present study.

Inclusion Criteria

Inclusion criteria:

- Males or nulliparous female.
- Age between 18 to 65 years.
- Prior diagnosis of COVID 19 documented by laboratory test (RT-PCR) with symptomatic disease with at least fever & cough.
- Fourteen days after resolution of symptoms of COVID 19.

Exclusion criteria:

- Age less than 18 years and above 65 years.
- Multiparous female.
- Donors with history of previous whole blood donation in the last 3 months.
- Donors who have had transfusion of blood products in last 8 wks.
- Blood Pressure>140/90 mmHg & Diabetes mellitus on insulin.

Methodology

Suitable COVID 19 recovered patients were connected telephonically and were informed about COPLA donation. Their verbal consent was taken on telephone and willing aspirants were called to hospital's (SAIMS) Blood Bank for written consent, screening and COPLA Apheresis. The procedure of screening and COPLA Apheresis were explained to the donors including its complications and their written

consent was taken for the same. Donors were screened, followed by brief physical examination by the physician. Donors unfit to donate COPLA based on history and examination as well as based on low anti SARS CoV-2 antibody levels were deferred and reason for deferral was explained to them.

Screening of eligible donors by Complete Blood count, Blood grouping, Serological markers – Human Immunodeficiency virus, Hepatitis B virus, Hepatitis C virus, Malaria Parasite, VDRL for syphilis, Serum total protein. Donors negative for all these tests were included. Screening for syphilis and malaria by serology. Negative donors were included.

Presence of Anti SARS Cov2 antibodies to COVID 19 by ECLIA (Electro – chemiluminescence immunoassay) on Roche e411 as per manufacturer's instructions. Donors with Anti SARS CoV-2 antibody COI less than 109 were deferred.

Fig.1. TRIMA® ACCEL™ AUTOMATED BLOOD COLLECTION SYSTEM.

Statistical Analysis

The data was initially captured in the customized proforma and the transferred to Microsoft excel for analysis. Statistically Software IBM SPSS Version 20.0.0.0 was used for calculating the P values. Descriptive statistics was presented in the form of numbers and percentages. Comparison of mean between more than two groups was done using One Way ANOVA followed by Post- hoc Tukey test. The antibody titer and post recovery duration before donation failed the normality test (Shapiro- Wilk), hence the correlation between these two non-parametric variables was evaluated using Spearman Rho test. A p value of <0.05 was taken as statistically significant. The final data was presented in the form of tables and graphs.

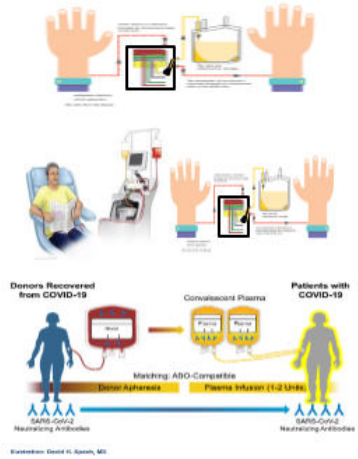


Fig.2. Overview of therapeutic plasmapheresis14

Results

A total of 785 COVID-19 recovered patients were telephonically contacted for COPLA donation, out of which 103 donor candidates refused for the plasma donation while 82 donors were deferred by blood bank authorities for convalescent plasma donation. 600 donors successfully donated convalescent plasma in the present study.

The most common reason for refusal of COPLA donation by the donors was Fear of reinfection (26.2%) followed by diabetes mellitus on insulin (16.5%). Whereas low antibody titre (53.7%) was the most common reason for COVID-19 COPLA donor deferral in the present study.

The results of these 600 COPLA donors are summarized as under: Most of the COVID-19 COPLA donors were in the age range 26-35 years and 36-45 years with mean age 35.16 ± 9.11 years. Youngest donor being 18 years of age and oldest donor being 62 years of age. Most of the COVID-19 COPLA donors were males (97.5%). Only 9 (1.5%) of the COPLA donors were vaccinated for COVID-19 infection. Maximum patients i.e., 37.7% were in 76-85 kg weight group and the mean body weight of the donors was 77.32 ± 10.34 kg.

B+ve (34.5%) was the most common blood group amongst COVID-19 COPLA donors. 60% of the COVID-19 COPLA donors had hemoglobin between 14.1-16 gm%. Low WBC counts was observed in 50.8% of the COVID-19 COPLA donors had low WBC counts. 12.7% of the COVID-19 COPLA donors had platelets more than 3.5 lac/cumm and rest all (87.3%) had platelets within the normal range (1.5-3.5 lac/cumm). Abnormal serum total protein levels were seen in 52% of the COVID-19 COPLA donors, while 48% had serum total protein levels in the normal range. According to COVID-19 disease severity, 80% had mild disease, 14.5% had moderate disease and 5.5% had severe disease. The mean anti SARS-CoV-2 antibody level in mild disease severity group was 150.83 ± 43.45, in moderate disease group, it was 226.25 ± 58.63 and in severe disease group, it was 217.36 ± 47.11. The mean antibody level was significantly higher in moderate and severe disease severity groups in comparison to the mild disease severity group (P<0.05), while the mean antibody level was comparable between moderate and severe disease severity groups (P>0.05).

The mean anti SARS-CoV-2 antibody level in 18-25 years was 161.09 ± 59.18, in 26-35 years it was 163.34 ± 56.21, in 36-45 years it was 169.44 ± 52.50, in 46-55 years it was 165.96 ± 48.87 and in >55 years it was 170.93 ± 54.92. The mean antibody level did not vary significantly amongst the various age groups (P=0.723).

The mean anti SARS-CoV-2 antibody level in females was 142.00 ± 52.36 and in males it was 166.03 ± 54.54. The mean antibody level was comparable between the males and females (P=0.092). The mean anti SARS-CoV-2 antibody level in A+ve blood group was 164.75 ± 53.55, in A-ve blood group it was 152.75 ± 44.28, in B+ve blood group it was 169.36 ± 56.63, in B-ve blood group it was 170.44 ± 73.32, in AB+ve blood group it was 158.02 ± 47.76, in AB-ve blood group it was 120.00 ± 7.07, in O+ve blood group it was 164.96 ± 54.94 and in O-ve blood group it was 156.89 ± 51.36. The mean antibody level did not vary significantly amongst the various blood groups (P=0.760).The mean anti SARS-CoV-2 antibody level in 55-65 kg body weight group was 154.83 ± 60.91, in 66-75 kg body weight group it was 163.21 ± 54.45, in 76-85 kg body weight group it was 167.77 ± 52.68, in 86=95 kg body weight group it was 169.83 ± 53.67 and in 96-105 kg body weight group it was 178.21 ± 52.24.

The mean antibody level did not vary significantly amongst the various body weight groups (P=0.210). There was no significant correlation between anti SARS-CoV-2 antibody and the recovery duration before donation (r value=0.042, P=0.308). In the present study plasmapheresis related adverse reactions occurred in 1.3% (08/600) of cases, all the reactions were mild and none required therapeutic intervention.

Table 1: Factors contributing to refusal of COPLA donation by recovered COVID-19 COPLA patients

Reasons	Number (No.)	Percentage (%)
Uncontrolled hypertension on medication	07	6.79
Diabetes mellitus on insulin	17	16.5
Asthmatic patients	09	8.7
Fear of reinfection	27	26.2
Nulliparous women with low hemoglobin content	06	5.8
Social / family pressure	11	10.6
Weakness/ bodyache	15	14.5
Patients undergone major surgery within 1 year	02	1.9

Patients with chronic cough	09	8.7
Total	103	100.0

Table 2: Factors contributing to deferral of recovered COVID-19 patients for COPLA donation

Reasons of Deferral	Number	Percentage (%)
Low anti SARS-CoV-2 antibody levels	44	53.7
WBC more than 12000/cumm or platelets more than 4.5lac/cumm	14	17.1
Platelets less than 1.5 lac/cumm	5	6.1
HCV positive	4	4.9
Eosinophilia on peripheral smear	3	3.7
HBV positive	3	3.7
HIV positive	3	3.7
Hemoglobin content less than 12gm%	2	2.4
Poor venous access	2	2.4
Weight less than 55 kg	2	2.4
Total deferral	82	100.0

Table 3: Distribution of COVID-19 COPLA donors according to blood group

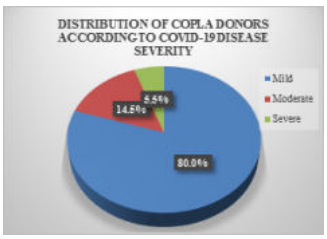
Blood group of COPLA donors	Number of COPLA donors	Percentage of COPLA donors (%)
A+ve	114	19.0
A-ve	4	0.7
B+ve	207	34.5
B-ve	9	1.5
AB+ve	64	10.7
AB-ve	2	0.3
O+ve	191	31.8
O-ve	9	1.5
Total	600	100.0

Table 4: Comparison of mean anti SARSCoV-2 antibody levels in relation to COVID-19 disease severity

COVID-19 Disease severity	No. of donors	Mean ± SD	F value	P value	Post-hoc Tukey		
					Mild-Moderate	Mild-Severe	Moderate-Severe
Mild	480	150.83 ± 43.45	120.504	0.001*	0.001*	0.001*	0.614, NS
Moderate	87	226.25 ± 58.63					
Severe	33	217.36 ± 47.11					
Total no. of donors	600						

Table 5: Correlation between anti SARSCoV-2 antibody level and post COVID-19 recovery duration before donation

Anti SARSCoV-2 Antibody level to Post COVID-19 recovery duration before donation	0.042	0.308, NS



Graph 1: Pie diagram showing the distribution of COPLA donors according to COVID-19 disease severity

Discussion

Understanding the demographic and other characteristics of individuals who were registered and qualified for COVID-19 convalescent plasma donation is very important to understand the epidemiological characteristics of these donors, their clinical and pathological characteristics, severity of the disease, antiSARSCoV-2 antibody levels and the factors contributing to refusal of COPLA donation. Characteristics of COVID-19 COPLA donors reported in the present study are compared with previous similar studies:

Most of the donors were in the age group of 26-35 years, with a mean age of 35.16 ± 9.11 years. This was in concurrence with study done by Datta *et al*.[15] and Ling Li et al.[16] who reported the median age be 32 years (18-55 years) and 37 years (IQR, 25-54 years) respectively. Whereas Lasky *et al*.[17], reported the age range of 55-64 years (21.9%). Jain *et al*.[18] also reported age range of 30-50 years, with mean age of 45 ± 14 years. In the present study, younger donors were more as compared to older donors, while in Lasky *et al*.[17] and Jain *et al*.[18] studies, older donors were more as compared to the younger ones. However, in all studies majority of COPLA donors were of middle age group as young and middle age group was affected most in first two waves of COVID-19 in India. Also affected population below 18 years and above 65 years were excluded as they were not eligible for COPLA donation.

A higher preponderance of males was seen as compared to the females in the present study which was in concurrence with Study done by Korper *et al*.[19] and Ling Li et al.[16] who also reported similar prevalence. Contrary to our findings, Lasky *et al*.[17] and Jain *et al*.[18] showed that female donors outnumbered the male donors. WHO and USFDA guidelines were followed in the present study and multiparous women were excluded.

There were very few nulliparous women willing for COPLA donation, few of them were also deferred due to low weight, low hemoglobin content or low antibody level. Dhiman Y et al.[20] in their study have cited multiparity (38%) as one of the main reasons for deferral among potential female CP donors. Their deferral rates were based on only telephonic recruitment calls made to COVID-19 recovered patients in early phase of the pandemic between May to July 2020. However, as the pandemic progressed the number of eligible donors increased and hence possibly the reason for lower deferral due to multiparity in later phase of pandemic.

Most of the donors were in the weight range of 76-85 kg, followed by 66-75 kg weight range. The mean weight was 77.32 ± 10.34 kg. The results were similar to study done by Datta PK et al.[15] have reported very weak negative correlation (Pearson correlation -0.095) between anti SARS CoV-2 antibody level and body mass index.

B positive was the most common blood group i.e., 34.5% of the donors had blood group followed by O positive (31.8%), A positive (19%) and AB positive (10.7%). Of the negative blood group donors, O negative (1.5%) was the most common blood group. Our study findings differs from the studies done by Jain *et al*.[18] and He *et al*.[21] Some studies have reported that non O blood group and they have postulated that this is either due to natural antibodies against blood group antigens acting as a part of innate immune response to neutralize viral particles or alternatively, blood group antigens maybe acting an additional receptors for the virus and individual are capable of expressing these antigens on epithelial cells, would possibly have a high propensity to be affected by SARS-COV-2.[22-24]

Most of the donors had Hb levels between 14gm% and 16 gm% with mean Hb 14.70 ± 1.11 gm%, as they were all healthy and not anemic. Our study's findings are comparable to studies done by He *et al*.[21] and Dogra *et al*.[25]

In majority of the donors, the WBC counts were between 4000-7000 per cumm (50.8%), and few had total leucocytes counts greater than 11000 per cumm (3.0 %), while the rest of the donors had WBC counts within normal limits between 7000-11000 per cumm (46.2%). In a study done by Gedda *et al*.[24] the mean total leucocytes count was 6.2 ± 1.4 per cumm which is comparable to the present study's finding.

Platelet count was found to be between 1.50-3.50 lac/cumm (87.3%) while 12.7% donors had platelet count more than 3.5 lac per cumm which were comparable to study done by Gedda *et al*.[24] who also reported the mean platelet count in COPLA donors as 2.32 ± 0.49 lac per cumm.

According to disease severity, 80% COPLA donors had mild disease

severity, 14.5% had moderate disease severity and 5.5% had severe disease severity. Most of the donors have mild disease severity. In Datta *et al*.[17] study, mild symptoms were seen in 57.1% participants, moderate symptoms in 11.1% and severe symptoms were not seen in any of the participants.

The turn up for COPLA donation was high at our hospital, as out of 785 donor candidates only 103 candidates refused for COPLA donation as during second wave a greater number of persons, their family members and close contacts were infected in all the age groups. There was empathetic attitude of persons for COVID-19 patients in the society and majority were coming forward for the COPLA donation considering it as their social responsibilities.

Deferral is a form of rejection and also could be a representation of loss of time for both CP donors and blood banks, and the importance of explaining the status of deferral cannot be ignored. In the present study temporary deferred donors were counselled to increase awareness and to encourage them for future COPLA plasma donation. In our institute, during discharge after COVID-19 disease the awareness program for COPLA donation was conducted, where the patients were counselled and encouraged for COPLA donation after 14 days of hospital discharge. In a study done by Dogra *et al*.[25] the deferral rate was 19.87%. Deferral was more common in male donors (79.57%) compared to 20.43% in female donors. With Absence of detectable / low SARS-CoV-2 antibodies (15.05%) being the most common reason. Rahman M *et al*.[26] reported a deferral rate of 39.1% with highest prevalent reason being Low antibody (18.7%). Sharma *et al*.[27] also reported a deferral rate of 36.8% with highest prevalent reason being low antibody levels (18.7%). Wendel S et al.[28] have reported absence of neutralizing antibodies at the time of screening in 21 of the 271(7.75%) donors screened for CP donation in Brazil as the most common reason.

The mean SARS-CoV-2 antibody level was lowest in donors with mild disease severity (150.83 ± 43.45) and highest in donors with moderate disease severity (226.25 ± 58.63. Datta PK et al.[15] have reported similar findings in their study. The incidence of coagulation function disorder and inflammation in the early stages of disease can influence antibody titer in convalescent plasma, which may help to screen COPLA donors in advance.

The mean antiSARS-CoV-2 antibody levels was comparable amongst the age ranges with highest mean antibody level seen in the age group more than 55 years. Study done by Dogra *et al*.,[25] also found that the median antiSARS-CoV-2 antibody titer was not significantly correlated with age of the donors (P>0.05), which supports the findings of present study.

The mean antiSARS-CoV-2 antibody levels were comparable amongst the males and females and statistically insignificant. In Dogra *et al*.[25] study, the antibody levels were higher in females in comparison to the males. In another study done by Datta *et al*.[15] the mean antibody titer was significantly higher in females as compared to the males. The antibody titers were reported to be higher in females by these two studies, which is contrary to our study's findings. In present study, the mean anti SARS-CoV-2 antibody levels were comparable between the males and the females.

The mean anti SARS-CoV-2 antibody levels in relation to blood groups showed no statistically significant comparison (P=0.760) and it was comparable amongst the various blood groups. The mean anti SARS-CoV-2 antibody level was highest in B+ve donors and lowest in B-ve donors. In Dogra *et al*.[25] study, the median SARS-CoV-2 antibody titer was highest in AB donors followed by B, then A and last was O in both centers. In Datta *et al*.,[15] study, a significant variation in the mean antibody titer amongst the blood groups with the mean antibody titer highest in A+ve donors and lowest in B+ve donors. The results of Datta *et al*.[15] study are contrary to our study's finding.

The mean anti SARS-CoV-2 antibody levels in relation to body weight showed no statistically significant association (P=0.210). The mean antibody level increased with the increase in the body weight. Datta PK et al.[15] have reported similar findings.

The mean duration between recovery and convalescent plasma donation among the COPLA donors in the present study was 24.59 ± 5.03 days (range: 19 to 48 days). In Del Fante *et al*.[29] study, the mean duration between symptom recovery and convalescent plasma donation was 36.6 ± 20 days. He *et al*.[21] had reported the duration of disease onset to donation, as 52 ± 12 days in their study, with a range from 17 days to 85 days. Most of the donors had donated their convalescent plasma between 43 days to 56 days. The duration of disease to donation was longer in their studies. The probable reason is that they had calculated the duration from the onset of disease, while we had calculated this duration from recovery of the disease.

Higher antibody levels always appear within 4-6 weeks after symptom onset, which can be thus be considered the best time to donate CP. No significant correlation was seen between antibody titer and the post recovery duration before COPLA donation. This parameter was not assessed by other studies; hence we could not compare this variable. Datta PK et al.[19] have reported no correlation between time from RT-PCR positive date to anti SARS CoV-2 antibody titer date (Pearson correlation -0.012) and time of RT-PCR positive date to RT-PCR negative date (Pearson correlation -0.253) of COVID-19 patients in their study. There was no statistically significant association between time from RT-PCR positive date to anti SARS CoV-2 antibody titer date (p value-0.094) and time of RT-PCR positive date to RT-PCR negative date (p value 0.102) of COVID-19 patients in their study.

In the present study plasmapheresis related adverse reactions occurred in 1.3% (08/600) of cases, all the reactions were mild and none required therapeutic intervention. However, Del Fante C et al.[29] have reported plasmapheresis related adverse reactions in 2.6% (13/504) of COVID-19 COPLA donors in their study which were also mild in severity.

The present study had following limitations: It focused on the procurement of convalescent plasma donors, but not on the effectiveness of the plasma therapy. Another limitation was that our analysis for correlates of anti SARS CoV-2 antibody values are retrospective only and single point evaluation which requires follow up to evaluate the dynamics of antibody levels and their symptom-wise dynamics and also to re-assess those cases who were deferred due to absence of detectable/low SARS CoV-2 antibodies. Further, we could not perform the neutralization assay that requires virus culture which need to be conducted in laboratories with higher biosafety levels. We could only detect anti SARS-CoV-2 antibodies by CLIA and could not measure the anti-S-RBD and anti-spike antibody titer.

Conclusion

It can be concluded that Recruitment of CP donors process includes not only education but also motivation to overcome the perceived stigma of infection and the fear of repeat RT-PCR test. The pattern of donor deferral is an important tool for blood safety and also provides key areas to focus on a demographic region or policy formulation for donor selection as well as to ensure donor safety. All RT-PCR positive COVID-19 patients subsequently may not develop antibody. Although antibody levels among hospitalized symptomatic patients was significantly higher, further study is needed to recommend optimal convalescent plasma donor criteria. The awareness of CP donor characteristics, post-screening deferrals, and correlates of antibody values with age, gender, body weight, severity of COVID-19 disease and blood groups will help improve collection outcomes and give better preparedness for future recurrent waves due to evolution of more virulent SARS-CoV-2 strains and fill treatment gap till availability of more specific treatment.

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