Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 06, 2023

Original Research

Neutrophil- Lymphocyte Ratio And Platelet- Lymphocyte Ratio: Important Tools In Assessing The Severity Of Illness Of Covid-19 Patients.

Chandrika Sehariya[1], Dr Tina Rai[2]*, Dr Akanksha Jain[3], Dr G.S Rai[4], Dr G.K Sawke[5]

[1]2nd professional M.B.B.S student, ABVGMC Vidisha.

[2]*Associate Professor, Department of Pathology, ABVGMC Vidisha.

[3]Assistant Professor, Department of Community Medicine, ABVGMC Vidisha.

[4]Professor &Head , Department of Radiodiagnosis ,PCMS &RC ,Bhopal.

[5]Professor & Head , Department of Pathology , ABVGMC Vidisha.

***Corresponding Author:-** Dr Tina Rai
[*]Associate Professor, Department of Pathology, ABVGMC Vidisha. Email Id: drtina_rai@yahoo.com

Abstract

Background: On 11th March 2020, WHO declared Covid- 19 as the global pandemic ;affecting over 200 countries world-wide. the clinical features ranges from mild flu like symptoms to seveare illness like ARDS and septic shock . Clinicians are looking for are the reliable prognostic marker that may identify the patients who are at risk & need prior treatment .Neutrophil lymphocyte ratio(NLR) & platelet lymphocyte ratio (PLR) are emerging out to be the important prognostic markers in the developing countries like India where limited resources are available . These markers are the important biomarkers which help in triaging the patients.

Objective:

1. To determine the neutrophil- lymphocyte ratio (NLR) and platelet- lymphocyte ratio (PLR) in COVID 19 patients on day one of ICU admission and before discharge.
2. To correlate neutrophil- lymphocyte ratio and platelet- lymphocyte ratio with the severity of illness in COVID 19 patients.
3. To correlate neutrophil- lymphocyte ratio and platelet- lymphocyte ratio with the respiratory support given to patients during the hospital stay.

Method: It is a retrospective study and included two months data of covid positive patients admitted in ICU . A total of 200 cases that were RTPCR positive or RAT positive recorded with their clinical history. For all cases NLR & PLR were evaluated at the time of admission and before discharge and results were recorded. Clinical complains , age, gender and comorbid conditions were analyzed by cross tabulation to assess their relationship with NLR & PLR.

Result: Out of 200 cases 119cases were males and 81 were females. Maxium deaths were noted in the age group of 40 to 60 years. There was no significant difference between the outcome of the disease in males and females. The most common complaint at the time of admission was breathlessness followed by fever. Hypertension was the most common co-mordidity amongst the

patients . NLR & PLR of the Covid positive patients were raised in the patients who died as compaired to the patients who were discharged from the hospital.

Conclusion :. In this study, it has been found that the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in COVID-19 patients are increasing in diseased individuals and ratios are decreasing in discharged people . NLR and PLR prognostic biomarkers emerged out be cost-effective, readily available biomarker to access the severity of illness in COVID-19 patients, especially in the countries with low medical resources, for the better outcome of the patients .

Keywords: Covid-19, NLR , PLR , Prognostic biomarkers.

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2). It was first identified in December 2019 in Wuhan, China which lead to many cases of pneumonia and hence it was initially called as 'Wuhan Virus'. On 11th February 2020 WHO announced its official name as 'COVID 19' and named the virus as SARS CoV-2 because of its genome resemblance with to SARS-CoV. On 11th March 2020, WHO declared it as a 'global pandemic' affecting over 200 countries world-wide. It is transmitted by respiratory droplets and contact routes. The clinical features are divided into mild (fever, cold and cough, sore throat, breathlessness), moderate (pneumonia, decrease SPO2 level) and severe form (severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock). The diagnosis is perform through molecular assay from nasopharyngeal and oropharyngeal swab. The high risk individual are the older people and those with co-morbidities like diabetes, hypertension, chronic respiratory diseases, cardiovascular diseases or cancer are likely to develop serious illness. Mortality rate in India is of 1.4 %. (1)

Clinicians are looking for a reliable prognostic sign or marker that may identify patients who are at risk of acquiring more severe forms of the disease. The neutrophil-to-lymphocyte ratio in peripheral blood has been explored as a systemic inflammatory marker and studies have shown that it is a relevant prognostic factor in a variety of solid tumors and other chronic illnesses such as lung, cardiovascular, and renal disorders.(2)

The majority of leukocytes that activate and go from the venous system to the immunological organ or system are neutrophils. Large quantities of reactive oxygen species are released by neutrophils, which can cause DNA damage in cells and release viruses from their host cells. Consequently, antibody dependent cell mediated cytotoxicity (ADCC) may directly destroy the virus, reveal virus antigen, and induce humoral and cell-specific immunity. Lymphocytes are primarily responsible for the human immune response to viral infection, but systematic inflammation dramatically impairs cellular immunity, causing a considerable decline in CD4+ T cells and an increase in CD8+ suppressor T lymphocytes. Inflammation brought on by a virus so elevated NLR. Increased NLR aided COVID-19 development. Clinical symptoms became more severe, and there was a quick transition from ICU hospitalization to recovery and release or mechanical ventilation. (5)

In moderate to severe cases, early detection of illness development and rapid referral to higher institutions for treatment commencement will reduce mortality. Because of the high cost of COVID-19 in India's healthcare system, many COVID-19 patients are treated in tiny clinics with inadequate facilities for delivering intense care. One of the reasons linked to death is late referral to higher levels of care. As a result, the study's goal was to uncover basic demographic and laboratory indicators that may predict the severity of illness of COVID-19 patients. (3)

A novel inflammatory marker called platelet-to-lymphocyte ratio (PLR) has been proposed to predict the severity of COVID-19 patients. The purpose of this systematic study is to assess the relationship between COVID-19 patient severity and PLR levels upon admission. When compared to patients with non-severe COVID-19, patients with severe COVID-19 had an overall higher PLR value, due to the quick involvement of inflammatory processes in the disease. This shows that, particularly in situations with limited resources, this inflammatory measure may be used to predict the prognosis of COVID-19 patients. (4)

AIM AND OBJECTIVES:
AIM:

To study the Neutrophil- Lymphocyte Ratio and Platelet- Lymphocyte Ratio: Important Tools in Assessing the Severity of Illness of COVID-19 Patients in Tertiary Care Hospital.

OBJECTIVES:

1. To determine the neutrophil- lymphocyte ratio (NLR) and platelet- lymphocyte ratio (PLR) in COVID 19 patients on day one of ICU admission and before discharge.
2. To correlate neutrophil- lymphocyte ratio and platelet- lymphocyte ratio with the severity of illness in COVID 19 patients.
3. To correlate neutrophil- lymphocyte ratio and platelet- lymphocyte ratio with the respiratory support given to patients during the hospital stay.

MATERIAL AND METHODS:

The study was conducted in the Department of Pathology in Government tertiary care hospital after obtaining ethical clearance from the Institute Ethical Committee (IEC) over a time of two months.

Study Type: Retrospective study. (Record based study)

Study Duration: Time period of two months.

Study Population: COVID positive patients admitted in the hospital in past two months. (March and April)

Study Size: Total 200 cases were taken from the records of Intensive care unit (ICU) and Medical records department (MRD).

Inclusion Criteria:
1.RTPCR and RAT positive patients admitted in the hospital.
2.Audit documents of ICU patients were included only after permission grand from hospital authority.

Exclusion Criteria:
1. HIV positive patients
2. Patients who are already suffering from immune-compromised diseases or conditions.

Data Analysis:
The data collection from the medical reports department were documented and analyze.
The statistical analysis was carried out in Microsoft office -excel by applying appropriate tests. The data was maintained in excel itself.

The following formule were used to analyze the indicators from the data source:

1. Calculation of neutrophil and lymphocyte ratio= Absolute neutrophil count/ Absolute lymphocyte count.
2. Calculation of platelet and lymphocyte ratio= Absolute neutrophil count/ Absolute lymphocyte count.
3. Independent t test was applied to compare the neutrophil- lymphocyte ratio and platelet-lymphocyte ratio (before death and before discharge) with the degree of severity of illness in COVID 19 patients.
4. ANOVA test (F test) was applied to compare the group of patients before their death and before their discharge on the basis of neutrophil- lymphocyte ratio and platelet- lymphocyte ratio.

Ethical Consideration:
Only with the approval of Institutional Ethical Committee the study was carried out.

RESULTS:

Table-1: Distribution of patient according to gender

Gender	Frequency	Percentage
Male	119	59.79
Female	81	40.21

In table 1, total 200 cases have been taken in which males are 119 (59.79%) and females are 81(40.21%).

Table- 2: Distribution of patient according to age

Age	Death	Discharged
Below 40	15	23
40 – 60	49	57
Above 60	36	19

In table 2, the maximum discharge cases were in group 40 to 60 and also this group has the maximum death cases.
Mean Age of admitted patients was 54±14 years.

Table- 3: Relationship of gender with the outcome of cases

Gender	Death	Discharge	P value
Male	59	60	0.888
Female	41	40	

In the table 3, p value is above 0.05 (i.e. 0.888) and it has been found that there is no significant difference in the outcome for male and female.

Table 4: Distribution of patients according to presenting complaints

Complaints	Frequency	Percentage
Cold	55	27.5
Cough	92	46
Fever	115	57.5
Breathlessness	123	61.5
Sore throat	27	13.5
Others	26	13

In table 4, the most common complaint was breathlessness in 123 cases (61.5%) which is followed by fever in 115 cases (57.5%), cough and cold were among 92 (46%) and 55 (27.5%) cases respectively. Sore throat and others as a complaint were low in frequency.

Table- 5: Distribution of co- morbidities

Complaints	Frequency	Percentage
HTN	36	18
Diabetes	26	13
Lung disease	6	3
Heart disease	3	1.5
Kidney disease	3	1.5
Others	3	1.5

In table 5, hypertension is the most common co- morbidity among 36 cases (18%), followed by 23 diabetic cases (13%), lung disease in 6 cases (3%), the heart and kidney disease cases with others were in same frequency of 3 (1.5%).

Graph- 1: Distribution of co- morbidities

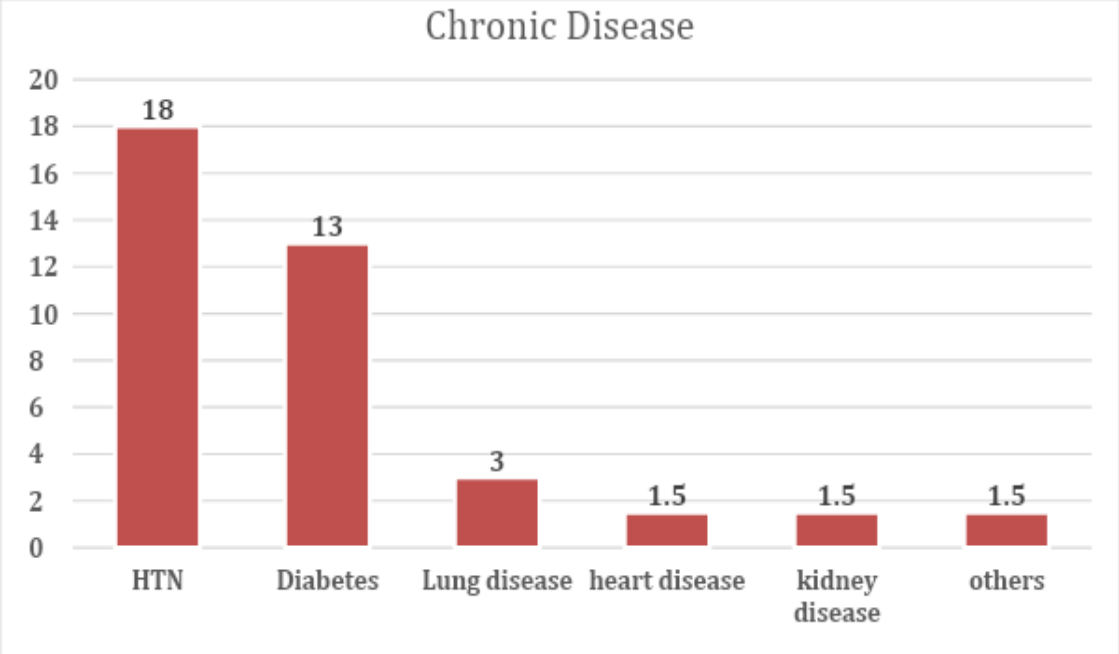

Table – 6: Association of co- morbidities with death and discharged cases

Co- morbidities	Death	Discharged	p value
Present	30	33	0.648
Absent	70	67	

In table 6, the p value is not significant which is above 0.05 (i.e. 0.648)
Mean days of stay in death cases were 8.09 and in discharged cases 10.87

The average NLR of the patients admitted was 5.3 and just before the death were 11.94. The average NLR the patients admitted was 9.6 and before their discharge were 5.40. The mean NLR value dramatically rising with increasing illness severity, with discharged cases the lowest NLR were recorded. The PLR average of the admitted patients was 12.78 and before death 25.37. The average PLR of the patients admitted was 26.23 and before their discharge was 14.43, here also the PLR values increasing with the severity of the illness and decreasing in the discharged cases.

The independent t test is applied for NLR value before death and before discharge and the mean difference obtained as 6.5423, the t test value is 8.21 with df- 198 and p value is <0.0001. For the PLR- independent t test the mean difference is 10.937, the t test value is +5.45 with df- 198 and the p value is <0.0001, here the p value is less than 0.0001 (below 0.05), which is the significant value for both NLR and PLR.

Independent test of SPO2 values in patient who died and the patients who recovered shows the mean difference of 5.01, with t test value of 0.61, df of 198 and the one tailed p value is 0.271

Table- 7: Association between the NLR and PLR values with the mortality- ANOVA

Ratio	Time	Mean	Maximum	Minimum	F test value, p- value
NLR	Before death	6.5087	26.16	0.75	68.15,
	Before discharge	4.2483	15.16	0.21	< 0.0001
PLR	Before death	13.1085	44.63	0.5	29.97,
	Before discharge	12.0005	67.64	0.18	< 0.0001

F test value for the group A, i.e. before death is 68.15 and for the group B, i.e. before discharge is 29.97. Both the values are having p value <0.0001 that means, it is significant in nature.

DISCUSSION:

In this study, it is assessed that how severity and mortality in COVID-19 patients were predicted by NLR and PLR at admission. According to the results of this study investigation, patients with COVID-19 who had higher NLR and PLR levels at the time of admission had a higher probability of developing severe disease, whereas those with higher NLR values had significantly higher fatality rates. This study demonstrates that this straightforward and widely accessible metric can be used to forecast disease progression and prognosis in COVID-19 patients [(7)]. Total 200 cases were confirmed which were retrospectively analyzed in which, 119 (59.79%) were males and 81 (40.21%) were females. They were categorized into diseased and discharged individuals in which out off 119 males, 59 were diseased and 60 were discharged. In females of 81 in total, the 41 were diseased and 40 were discharged. The mean age is 54±14 years, the similar findings were found in the study done by Qin and Zhou the median age was 58 years [(10)]. Further the cases were divided on the basis of age group, in below 40 age group 15 were death and 23 were discharged, in 40-60 age group, 49 were death and 57 were discharged and in above 60 age group 36 were death and 19 were discharged. The p value is 0.888 which is not significant. On the contrary the study done by Yang and Liu they have taken 56 males and 37 female of total 93 patients [(5)]. Also the study of Nair and Maitra they have taken 93 patients with median age of 50 and 61.3% were male with p value of 0.571[(9)].
In this study it is found that there is no significant difference in the outcome for the male and female, which is consistent with the findings from Yang and Liu study that there no significant difference was observed in terms of gender [(5)].

In this study the maximum cases were of breathlessness i.e 123 (61.5%), followed by fever i.e. 115 (57.5%), for cough i.e. 92 (46%), followed by cold i.e. 55 (27.5%). On the contrary in the study of Yang and Liu the fever (83.8%) and cough (70.9%) were the two most common symptoms [(5)].

The co-morbidities in patients in which hypertension is being the most common (18%) followed by diabetes (13%), the same findings are found in study of Ciccullo the 24 patients (32.4%) had hypertension as the most common co-morbidity, 15 (20.3%) had a pre-existing heart condition and 8 (10.8%) had type 2 diabetes mellitus [(2)], in the study of Yang and Liu the severe cases with co morbidities exhibited were hypertension (66.8%) and diabetes (54.2%) [(5)]. Similar findings also

found in the study of Qin and Zhao the 452 patients with COVID-19, 201 (44.0%) patients had chronic diseases (i.e. hypertension, diabetes, chronic obstructive pulmonary disease), and a higher percentage in the severe cases (146 [51.0%]) than in the mild cases (55 [33.1%]). And those patients with severe infection were significantly more likely to have concomitant hypertension and cardiovascular diseases (36.7% versus 18.1%; $P < .001$; and 8.4% versus 1.8%; $P = .004$; respectively) [(10)].

In this study it is found that the NLR and PLR were increasing before the death of the patient, which are consistent with the findings from the study of Ciccullo that higher NLR at hospital admission was associated with a more severe outcome: in particular, a NLR of >4 was a predictor of admission to the ICU. Patients with severe disease presented a significantly higher NLR at admission compared with patients with a milder form of COVID-19, reinforcing the theory of a close association between hyper- inflammatory state and COVID-19 pathogenesis [(2)], study by Maddani and Gupta Higher the degree of the inflammatory state, higher will be the levels of inflammatory markers, and consequently, these markers may help in predicting severity and prognosis [(3)], also in study of Simadibrata and Pandhita patients with severe COVID-19 had a higher PLR value on admission compared to non-severe COVID-19 [(4)], the study of Yang and Liu the evaluated NLR (HR 2.46, 95% CI 1.98–4.569), d-NLR (HR 1.92, 95% CI 0.817–3.496), and PLR (HR 1.023, 95% CI 0.921–1.756) identified by multivariate Cox regression were considered independent factors associated with COVID-19 progression [(5)]. Same findings in the study of Lalani and Seshadri, higher neutrophil indicate a more severe inflammatory response, whereas decreased lymphocytes indicate a greater immunological imbalance and immune escape mechanism on the part of the virus [(6)], also in study of Singh there was increased risk of severe disease was linked to greater NLR and PLR values at the time of admission, whereas increasing NLR strongly indicated worse mortality in COVID-19 patients. This study demonstrates that using this straightforward and widely accessible metric, COVID-19 patients disease prognosis and course may be predicted [(7)] also in the study of Jain and Gopal the mean NLR and PLR were significantly higher in severe patients (NLR = 7.41; PLR = 204) compared with non- severe patients (NLR = 3.30; PLR = 121) [(8)] also in the study of Nair and Maitra they found that sensitivity and specificity of NLR >4.6 were moderately good in predicting the requirement of ventilation within 24 hours and PLR had a 0.56 (0.42–0.69) to predict the requirement of mechanical ventilation, which are associated with increase in NLR and PLR values [(9)] and in the study done by Qin and Zhou, a higher number of neutrophil and a lower number of lymphocytes (i.e. the increase in NLR) were found in the severe group with COVID-19 compared with the mild group. NLR, a well-known marker of systemic inflammation and infection, has been studied as a predictor of bacterial infection, included pneumonia and tuberculosis. To mitigate the potential bias, we acquired reference on the existing international guideline to define the severity of COVID-19 because of its global recognition [(10)]. The result was to be predicted and is consistent with Toori and Qureshi research, which showed a high correlation between mean NLR and serious illness [(11)].

This study is consistent with the study of Toori and Qureshi that in their investigation, they also found a link between elevated NLR and mortality, where their f test value was 164.27 and here it is 68.15 [(11)]. In this study the PLR f test value is also calculated and it is 29.97 which are also correlated with the increase in severity of illness in COVID- 19 patients.

CONCLUSION:

In this study, it is proving that the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in COVID-19 patients are increasing in diseased individuals and ratios are decreasing in discharged people also this study could be used as a innovative, cost-effective, readily available biomarker and as a prognostic tool to access the severity of illness in COVID-19 patients, especially

in environments with low resources, where it is vital to concentrate medical resources wisely and focus on patients with worse prognoses.

IMPLICATIONS:

Neutrophil- lymphocyte ratio and Platelet- lymphocyte ratio could be used as the base line investigation for COVID patients to access their severity of illnesses and for their proper treatment and management- as a prognostic marker.

REFERENCES:

1. Snewastry A. Essential of Medical Microbiology. 3rd ed. new delhi: Jaypee Brothers Medical Publishers; 2021.S

2. Ciccullo A, Borghetti A, Zileri Dal Verme L, Tosoni A, Lombardi F, Garcovich M, Biscetti F, Montalto M, Cauda R, Di Giambenedetto S; GEMELLI AGAINST COVID Group. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line. Int J Antimicrob Agents. 2020 Aug;56(2):106017. doi: 10.1016/ j. ijantimicag.2020.106017. Epub 2020 May 11. PMID: 32437920; PMCID: PMC7211594.

3. Maddani SS, Gupta N, Umakanth S, Joylin S, Saravu K. NeutrophilLymphocyte Ratio in Patients with COVID-19 as a Simple Tool to Predict Requirement of Admission to a Critical Care Unit. Indian J Crit Care Med. 2021;25(5):535-539. doi:10.5005/jp-journals-10071-23801

4. Simadibrata DM, Pandhita BA, Ananta ME, Tango T. Platelet-to-lymphocyte ratio (PLR), a novel biomarker to predict the severity of COVID-19 patients: A systematic review and meta-analysis. 2020;

5. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020 Jul;84:106504. doi: 10.1016/j.intimp.2020.106504. Epub 2020 Apr 13. PMID: 32304994; PMCID: PMC7152924.

6. Lalani, K., Seshadri, S., Samanth, J. *et al.* Cardiovascular complications and predictors of mortality in hospitalized patients with COVID-19: a cross-sectional study from the Indian subcontinent. *Trop Med Health* **50**, 55 (2022). https://doi.org/10.1186/s41182-022-00449-w

7. Singh Y, Singh A, Rudravaram S, Soni KD, Aggarwal R, Patel N, Wig N, Trikha A. Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio as Markers for Predicting the Severity in COVID-19 Patients: A Prospective Observational Study. Indian J Crit Care Med. 2021 Aug;25(8):847-852. doi: 10. 5005/jp-journals-10071-23906. PMID: 34733 022; PMCID: PMC8559739.

8. Jain R, Gopal A, Pathak BK, Mohakuda SS, Tilak TVSVGK, Singh AR. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio and their role as predictors of disease severity of coronavirus disease 2019 (covid-19). Journal of Laboratory Physicians. 2021; 13(01):058–63.

9. Nair PR, Maitra S, Ray BR, Anand RK, Baidya DK, Subramaniam R. Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio as Predictors of the Early Requirement of Mechanical Ventilation in COVID-19 Patients. Indian J Crit Care Med. 2020 Nov;24(11):1143-1144. doi: 10.5005/jp-journals-10071-23663. PMID: 33384528; PMCID: PMC7751036.

10. Chuan Qin, Luoqi Zhou, Ziwei Hu, Shuoqi Zhang, Sheng Yang, Yu Tao, MD, Cuihong Xie, Ke Ma, Ke Shang, Wei Wang, Dai-Shi Tian, Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China, *Clinical Infectious Diseases*, Volume 71, Issue 15, 1 August 2020, Pages 762–768, https://doi.org/10.1093/cid/ciaa248

11. Toori KU, Qureshi MA, Chaudhry A, Safdar MF. Neutrophil to lymphocyte ratio (NLR) in COVID-19: A cheap prognostic marker in a resource constraint setting. Pak J Med Sci. 2021 Sep-Oct;37(5):1435-1439. doi: 10.12669/ pjms.37.5.4194. PMID: 34475926; PMCID: PMC8377926.