A neutrophil-to-lymphocyte ratio higher than 3 may identify inflammation during clozapine titrations: A re-analysis of five published cases of myocarditis

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Objectives: The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation. A NLR≥3 is considered abnormal (and ≥1.8 for benign ethnic neutropenia, BEN). **Methods:** NLR values were added to longitudinal data including c-reactive protein (CRP) in 5 published clozapine-induced myocarditis cases. **Results:** Case 1 had two NLRs with normal values, but on clozapine day 19, the CRP became abnormal (10.0 µg/d, ≤0.9) and the NLR=3.9. Clozapine was stopped on day 26. Case 2 had three normal NLRs before myocarditis, but on day 19 clozapine was stopped due to abnormal CRP (16. µg/dL, ≤0.9) with abnormal NLR (6.7). Case 3 received 25 mg on the first day (on valproic acid and quetiapine) with a NLR=3.4 on day 2. On day 11, CRP and NLR were normal. On day 14, he had chest pain, abnormal CRP (4.9 µg/dL,≤0.9) and abnormal NLR (7.4). Clozapine was discontinued on day 17. CRP and NLR finally normalized on day 35. Skin abscesses led to abnormal CRP and NLR values. On day 148, 12.5 mg of clozapine was restarted leading to a skin rash the next day. On day 155, this dose was stopped. Case 4 had two normal NLRs before myocarditis, but on day 16, clozapine was stopped (abnormal CRP, 15.8 µg/dL, ≤0.5 and abnormal NLR=4.4). Case 5 had BEN. NLR was normal on day 7, but became abnormal (NLR=1.9) on day 11 on 250 mg/day. He died five days later. **Conclusions:** An abnormal NLR during titration may suggest clozapine-induced inflammation and/or infection.

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INTRODUCTION

Clozapine titration that is too rapid for the metabolism of a given patient can lead to clozapine-induced inflammation (de Leon, 2022). The clozapine-induced inflammation releases cytokines which can inhibit several cytochrome P450 (CYP) isoenzymes, including the CYP 1A2 (CYP1A2), the major metabolic pathway for clozapine. If the clozapine dosage continues to be increased during the titration, this leads to positive feedback by further increasing the release of cytokines and further inhibiting clozapine metabolism. Clozapine-induced inflammation can manifest with a wide variety of presentations including: 1) systemic inflammatory processes: fever, isolated c-reactive protein (CRP) elevation, or lupus; or 2) localized signs of inflammation: myocarditis, serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis and dermatological disorders (de Leon, 2022). New forms of localized clozapine-induced inflammation continue to be described (Escobedo-Aedo et al., 2025). This classification is arbitrary since these presentations lie on a continuum with no clear-cut boundary between them; several conditions may co-occur and be associated with eosinophilia, including clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (de Fillippis et al., 2022).

A recent expert group has reached a multidisciplinary consensus on the relevance of rapid titrations in clozapine-induced myocarditis (Wagner et al., 2025). To reduce clozapine-induced inflammation, an international guideline proposed the use of 6 personalized titrations stratified by ancestry groups and the presence/absence of poor metabolizer (PM) status (de Leon et al., 2022). These titrations provide a range from lowest for non-smoking females to highest for males who smoke, as estrogens are weak inhibitors of CYP1A2 and smoking is a weak inducer (Ruan et al., 2019).

CRP is an acute acute-phase protein described as an exquisitely sensitive systemic marker of inflammation. Its synthesis is controlled by the cytokines (Pepys & Hirschfield, 2003). There is a long tradition of using CRP to longitudinally monitor clozapine-treated patients (Shelton et al., 2022). First, Pfuhlmann et al. (2009) proposed using CRP elevations as a marker for the risk that an inflammation may lead to increase in plasma/serum clozapine concentrations. Second, Ronaldson et al. (2011) incorporated CRP monitoring in the Australian protocol to monitor clozapine-induced myocarditis. Third, the international guideline proposed CRP monitoring during titration for early identification of clozapine-induced inflammation, which requires holding the titration or stopping clozapine and restarting it once the inflammation has resolved and clozapine metabolism has normalized (de Leon et al., 2022).

Recently, Onodera et al. (2025) studied another index of inflammation during clozapine titrations. This index is called the neutrophil-to-lymphocyte ratio (NLR). They found that it was correlated with a decrease in clozapine metabolism measured by the clozapine concentration-to-dose (CD) ratio. The NLR was first described by Zahorec (2001) as a marker for systemic inflammation in critically ill patients. Currently, NLR is widely used across many medical disciplines including emergency medicine, cancer and perioperative medicine (Firment & Hulin, 2024). NLR is a reliable and easily available marker for immune response to various infectious and non-infectious stimuli and reflects the online dynamic relationship between innate (neutrophils) and adaptive cellular immune response (lymphocytes). A NLR higher than 3 is considered abnormal (Zahorec, 2021).

The NLR cut score assumes that the patient had a normal absolute neutrophil count but there is a normal variant with lower counts. This variant is called benign ethnic neutropenia (BEN) and occurs in about 25–50% of Africans, in some ethnic groups in the Middle East, and up to 38% of certain Arab tribes (Kelly et al., 2024). On August 1, 2025, a PubMed search using the words "neutrophil to lymphocyte ratio" led to 20,567 articles. The search "neutrophil to lymphocyte ratio and benign ethnic neutropenia" led to only two articles (Bello et al., 2019; Tazeh et al., 2017). Only one of them provided a different NLR cut score. In a study of prostatic cancer in Nigerian men with BEN, Bello et al. proposed a cut score of 1.8.

Koenig et al. (2024) published 4 patients with clozapine-induced myocarditis from two United States (US) hospitals by studying their clozapine C/D ratios, minimum therapeutic clozapine doses and titrations. Chopra and de Leon (2016) had previously published the first case of clozapine-induced myocarditis in the first of these two US hospitals; the case led to the patient's death and autopsy. This study reanalyzed these 5 cases by describing their NLRs during clozapine titration.

NLR is more available than CRP in clozapine-treated patients. Most countries require hematological monitoring during clozapine titrations so weekly NLR may be available in many of the published cases of clozapine-induced inflammation while they may or may not have data on CRP. NLR ratios have the potential to increase understanding of prior

Table 1. NLR data in clozapine-induced myocarditis: Case 1[a]

Day[b]	CLO		C/D ratio		Laboratory Markers							
	D	C	NCLO		CRP	NLR	N	L	Trop T	ESR	Eosinophil	Clinical status
	mg/day	ng/ml	ng/ml	ng/ml per mg/ day	(0-0.9)	(<3.0) µg/dL	(1.6-6.1) k/µL	(1.2-3.9) k/µL	(<0.010 (0-11) ng/ml		(0-0.5) k/µL	
1	25				0.10	1.7	5.56	3.33	<0.010		**0.75**	
4	50											
8	100					1.6	5.14	3.27	<0.010		**1.06**	First symptoms of myocarditis
13	150											
15	150				**10.0**	**3.9**	**6.23**	1.59	<0.010			
16	200											
19	250											
22	0	603	140	2.62[c]	**18.5**	**3.4**	5.54	1.64	<0.010	**105**	**0.61**	Taken to emergency room
23	250											
24	200										0.37	
25	100											Myocarditis (echocardiogram)
26	0											Symptoms improved rapidly
30	0					2.6	5.49	2.14			0.35	Recovered

C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; ESR: erythrocyte sedimentation rate; L: lymphocyte; N: neutrophil; NCLO: norclozapine; NLR: neutrophil-to-lymphocyte ratio; PM: poor metabolizer; Trop T: Troponin T.
Definitive high laboratory abnormalities possibly explained by CLO-induced myocarditis are described in bold font.
[a]The co-medications and details of the symptoms have been eliminated to simplify the table and facilitate the focus on the NLR data.
[b]Day # is in relation to initiation of clozapine and not total hospital stay.
[c]This C is not steady-state; the average of the last 5 days (230 mg/day) was used to calculate the CLO C/D ratio (603/230=2.62). The average C/D ratio of 340 male non-smokers of European ancestry was 1.18 ng/ml per mg/day (Schoretsanitis et al., 2021), so this CLO C/D ratio is compatible with CLO PM status at the time CLO-induced myocarditis occurred.

published cases of clozapine-induced inflammation. Similarly, in the future NLR monitoring may be easier to implement during clozapine titration than CRP, which requires ordering another laboratory test.

METHODS

A prior article detailed the methodological aspects of how these 4 patients were collected from two US hospitals (one in Lexington, KY and one in Atlanta, GA) under naturalistic conditions using the therapeutic drug monitoring (TDM) from commercial laboratories available at these two hospitals (Koenig et al., 2022). CRP normal values vary according to the quantification method used so the normal values recommended by the laboratory employed in each case were used. In this new study, the charts of these 4 patients were reviewed to obtain their NLR values. Their clozapine C/D ratios were compatible with status as clozapine poor metabolizers (PMs) for the 4 patients after comparing them with published data (Schoretsanitis et al., 2021; de Leon et al., 2025a). The first clozapine-induced myocarditis case in the Lexington hospital occurred in 2005 and led to a fatal outcome (Chopra & de Leon, 2016). This patient's chart was reviewed for NLR, but there was no data on CRP or clozapine TDM.

Cases 3 and 5 received quetiapine. Several more recent studies have indicated that quetiapine co-prescription during titration increases the risk of clozapine-induced myocarditis (De Las Cuevas et al., 2022a;b; Nachmani Major et al. 2020) and clozapine-induced fever (Kikuchi et al., 2024a). Quetiapine co-medication during titration increases the risk of clozapine-induced myocarditis possibly by a pharmacokinetic mechanism, as quetiapine by itself, if overdosed, can cause myocarditis (De Las Cuevas et al., 2022c).

Table 2. NLR data in clozapine-induced myocarditis: Case 2[a]

Day[b]	CLO		C/D ratio		Laboratory Markers						
	D	C	NCLO		CRP	NLR	N	L	Trop T	Eosinophil	Clinical status
	mg/day	ng/ml	ng/ml	ng/ml per mg/day	(0-0.9)	(<3.0) µg/dL	(1.6-6.1) k/µL	(1.2-3.9) k/µL	(<14) ng/ml	(0-0.5) k/µL	
0					0.2	1.8	4.25	2.34	<6	0.14	
1	25										
2	25										
6	50				<0.1	1.7	3.87	2.23	<6	0.16	
9	75										
13	100				0.2	1.5	3.37	2.32	<6	0.16	
16	150										Sinus tachycardia
18	75										
19	0	477	105	4.15[b]	**16.9**	**6.7[c]**	**6.57[c]**	0.98[c]	**30[c]**	0.30	Diagnosis of myocarditis and UTI
20	0										At general hospital
22	0										Back to psychiatric hospital
23	0										

C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; L: lymphocyte; N: neutrophil; NCLO: norclozapine; NLR: neutrophil-to-lymphocyte ratio; PM: poor metabolizer; Trop T: Troponin T; UTI: urinary tract infection.
Definitive high laboratory abnormalities possibly explained by CLO-induced myocarditis are described in bold font.
[a]The co-medications and details of the symptoms have been eliminated to simplify the table and facilitate the focus on the NLR data.
[b]This C is not steady-state; the average D of the last 5 days (115 mg/day) was used to calculate the CLO C/D ratio 477/115=4.15. The average C/D ratio of 218 female non-smokers of European ancestry was 1.48 ng/ml per mg/day (Schoretsanitis et al., 2021), so this CLO C/D ratio is compatible with CLO PM status at the time CLO-induced myocarditis occurred.
[c]At the state hospital Trop T was 30 ng/L. These findings were suggestive of CLO-induced myocarditis. CLO was therefore discontinued and the patient was promptly transferred to the emergency department. She was subsequently admitted to a general medicine service for further evaluation and management. Trop T, collected q 2 hours, decreased from the initial value of 30 to 23 and then 18 ng/L. The NLR at the state hospital was 6.7. Another NLR 5 hours later at the general hospital was 6.8 (7.57/1.12).

RESULTS

Case 1

Case 1 was a 46-year-old male of European ancestry with schizophrenia taking omeprazole, a weak CYP1A2 inducer. Clozapine-induced myocarditis was associated with: 1) the co-prescription of valproic acid and aspirin, which increases the effects of valproic acid (Riesselman et al., 2013); 2) rapid titration; and 3) overdose, as the final clozapine dose of 250 mg/day was too high for this patient (Koenig et al., 2022). Table 1 presents a brief summary of the previously published data (Koenig et al., 2022) with the addition of the NLR data. The patient had two NLRs with normal values, on days 1 and 8. On day 15 (7 days after the first symptom of myocarditis), the CRP was abnormal at 10.0 µg/dL (maximum normal was 0.9) and the NLR was abnormal at 3.9. On day 22 (14 days after the first symptom of myocarditis), the CRP continued to be abnormal at 18.5 µg/dL and the NLR was abnormal at 3.4. Clozapine was definitively stopped on day 26 with a rapid recovery. On day 30, the NLR had become normal at 2.6.

Case 2

Case 2 was a 34-year-old nonsmoking female of European ancestry diagnosed with schizoaffective disorder. Clozapine-induced myocarditis was associated with clozapine PM status explained by: 1) obesity, 2) the co-prescription of valproic acid and 3) a urinary tract infection (Koenig et al., 2022). Table 2 presents a brief summary of the previously published data (Koenig et al., 2022), with the addition of the NLR data. The patient had three NLRs with normal values on days 0, 6 and 13. On day 16, she had sinus tachycardia and the clozapine dosage was decreased. On day 19,

Table 3. NLR data in clozapine-induced myocarditis: Case 3[a]

Day[b]	CLO		C/D ratio		Laboratory Markers								
	D[b]	C	NCLO		HS CRP	CRP	NLR	N	L	Trop T	ESR	Eos	Clinical status
	mg/day	ng/ml	ng/ml	ng/ml per mg/day	(<10) µg/L	(0-0.9) µg/dL	(<3.0)	(1.6-6.1) k/µL	(1.2-3.9) ng/ml	(<0.010) mm/hr	(0-11) k/µL	(0-0.5)	
1	25												
2	25						**3.4**	4.46	1.31	<0.010		0.49	
6	50												
7	100												Improvement of psychosis
11	125					0.2	2.9	5.33	1.82	<0.010		**0.66**	
12	150												
14	200												
15	200					**4.9**	**7.4**	**8.25**	1.11	**0.081**		**0.65**	To general hospital due to chest pain
16	50	454	215	2.75[c]		**9.1**	**5.6**	**8.53**	1.53	**0.067[d]**		**0.66**	At general hospital: myocarditis
17	0						**3.5**	5.89	1.68			**0.69**	Back to psychiatric hospital
21	0					**6.6**	**3.6**	**6.69**	1.88	<0.010		**0.65**	
23	0					**2.0**							
28	0					0.6	**5.3**	**6.83**	1.28	<0.010		**0.84**	
30	0					**8.0**	**4.2**	**6.96**	1.66	<0.010		**0.75**	
35	0					**2.9**	**4.1**	**6.21**	1.52	<0.010		0.44	
46	0					**1.6**	2.0	3.41	1.68	<0.010		0.48	
49	0					0.2	2.5	3.63	1.48			0.41	
58	0					**1.5**	2.8	4.10	1.46	<0.010		0.35	
65	0				3.7		2.6	4.00	1.54	<0.010		0.46	
87	0					**3.4**	**7.0**	**6.45**	0.92			0.31	Skin abscess[e]
99	0					**1.8**	1.9	3.07	1.62	<0.010		**0.64**	Skin abscess[e]
100	0				**10.1**								Skin abscess[e]
102	0				4.6								No injections since day 94
109	0					**1.3**	**3.5**	5.29	1.50	<0.010		**0.62**	Skin abscess[e]
112	0					**1.2**	2.7	5.19	1.93	<0.010	7	**0.65**	Skin abscess[e]
114	0					**10.2**	**4.5**	**8.80**	1.97	<0.010	**23**	**0.70**	Skin abscess[e]
121	0					**5.6**	**4.4**	5.67	1.28	<0.010	**44**	0.48	Skin abscess[e]
128	0					**2.2**	**4.4**	**7.62**	1.73	<0.010	**18**	0.40	Skin abscess[e]
137	0					0.4	2.5	4.60	1.84	<0.010	7	0.44	Last injection was given on day 128
148	0					0.1	2.2	4.44	2.03	<0.010	5	0.48	
149	12.5												
151	12.5												Macopapular rash
154	12.5												Headache
155	0					**3.1**	**4.1**	4.01	0.98	<0.010	9	0.22	
157	0												EKG: possible pericarditis
158	0				**39.2**	**2.9**	**3.2**	3.45	1.09	<0.010	**13**	0.34	
161	0				**10.3**	**1.0**				<0.010	7	0.22	
162	0												Diagnosis: Acute pericarditis
164	0												Chest pain
165	0				2.8	0.3				<0.010		**0.58**	Felt fine and no chest pain

C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; EKG: electrocardiogram; ESR: erythrocyte sedimentation rate; hs: high sensitivity; L: lymphocyte; N: neutrophil; NCLO: norclozapine; NLR: neutrophil-to-lymphocyte ratio; PM: poor metabolizer; T: Troponin T.
Definitive high laboratory abnormalities possibly explained by CLO-induced myocarditis are described in bold font.
[a]The co-medications and details of the symptoms have been eliminated to simplify the table and facilitate the focus on the NLR data.
[b]There are some small discrepancies in days and CLO dose when compared with the prior published version (Koenig et al., 2022). The prior table was developed after chart review by a medical student; this version was developed after careful review from the original records by a very experienced pharmacist with more than 20 years of experience in the hospital and in the management of CLO-treated patients at this hospital.
[c]This C is not steady-state; the average of the last 5 days (165 mg/day) was used to calculate the CLO C/D ratio 454/175=2.75. The average C/D ratio of 340 male non-smokers of European ancestry was 1.18 ng/ml per mg/day (Schoretsanitis et al., 2022), so this CLO C/D ratio is compatible with CLO PM status at the time CLO-induced myocarditis occurred.
[d]Troponine T trended down from 0.067 to 0.062 to 0.059 over the course of the day.
[e]Unfortunately, the patient began to decompensate from the psychiatric standpoint after the discontinuation of CLO. He had to be managed using forced medication with frequent intramuscular injections of chlorpromazine and/or haloperidol and had skin abscesses on his leg. These infections caused CRP to become elevated. On day 92 the court approved a forced order of 10 mg/day of olanzapine and the patient started to take oral medication. The olanzapine dose was increased to 20 mg/day and then changed to haloperidol (from 10 to 20 mg/day) and the number of antipsychotic injections was reduced. CRP normalized once the skin abscesses resolved and intramuscular injections were minimized. Since CLO was the only medication that improved the patient's psychotic symptoms, the decision was made to rechallenge the patient with CLO.

Table 4. NLR data in clozapine-induced myocarditis: Case 4[a]

Day[b]	CLO		C/D ratio		Laboratory Markers					
	D	C	NCLO		CRP	NLR	N	L	Trop T	Clinical status
	mg/day	ng/ml	ng/ml	ng/ml per mg/day	(0-0.5)	(<3.0) µg/dL	(1.8-7.3) k/µL	(0.5-4.5) k/µL	(<0.04) ng/ml	
-1	0					0.7	2.1	3.0		
0	0									
1	25									
2	50									
3	100									
4	150									
5	200				0.19				<0.01	
6	300									
7	400									
8	500									EKG: sinus tachycardia
9	500									
10	500				0.07	0.8[b]	2.0[b]	2.4[b]	<0.01	Psychosis improved
11	500					1.3	2.0	1.6		Discharge from hospital
12	500									
13	500									
14	500									
15	500									Described as sedated
16	0	1637	574	3.27[c]	**15.8**	**4.4[d]**	7.1[d]	1.6[d]	**0.80**	Possible myocarditis
17	0				**22.6**	**3.6**	4.0	1.1	**3.18 & 2.80**	
18	0					**7.3[e]**	5.1[e]	0.7[e]	**1.27 & 0.91**	Diagnosis verified by echocardiogram
19	0					**6.0[f]**	6.0[f]	1.0[f]	**0.55 & 0.43**	
20	0					**4.9**	5.9	1.2	**0.12**	
21	0					**8.4[g]**	6.7[g]	0.8[g]	**0.09**	
22	0					2.2	5.6	2.5		
23	0									
24	0					2.9	7.3	2.5	0.02	No signs of myocarditis

C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; EKG: electrocardiogram; L: lymphocyte; N: neutrophil; NCLO: norclozapine; NLR: neutrophil-to-lymphocyte ratio; PM: poor metabolizer.

Definitive high abnormal laboratory values possibly explained by CLO-induced myocarditis are described in bold font.

[a]The co-medications and details of the symptoms have been eliminated to simplify the table and facilitate the focus on the NLR data.

[b]On the same day there was another NLR=0.9 (1.7/1.8).

[c]This C is steady-state; the D=500 mg/day was used to calculate the CLO C/D ratio (1637/500=3.27). The average C/D ratio of female non-smokers of African ancestry has not been studied but it is expected to be around 1.17 ng/ml per mg/day (de Leon et al., 2025), so this CLO C/D ratio is compatible with CLO PM status at the time CLO-induced myocarditis occurred.

[d]On the same day there was another NLR=4.2 (4.6/1.1).

[e]On the same day there was another NLR=6.8 (6.8/1.0).

[f]On the same day there was another NLR=5.8 (4.6/0.8).

[g]On the same day there was another NLR=2.8 (4.5/1.6).

clozapine was stopped since she had definitive signs of myocarditis. On this day 19, the CRP was abnormal at 16.9 μg/dL (maximum normal was 0.9) and the NLR was abnormal at 6.7, but she was also diagnosed with a urinary tract infection which contributed to the NLR elevation.

Case 3

Case 3 was a 27-year-old non-smoking male of European ancestry with a diagnosis of schizoaffective disorder. The patient had no obesity, nor was he taking any inhibitor of clozapine metabolism. In our prior article, we hypothesized that his clozapine-induced myocarditis was associated with genetic clozapine PM status (Koenig et al., 2022).

For patients of European ancestry taking quetiapine, the international guideline recommends 12.5 mg on day 1 and slow increases to 50 mg/day on day 7 (Schoretsanitis & de Leon, 2022). This patient received a 25-mg dose on day 1 and reached 100 mg/day on day 7. This is much higher than the dosing recommended by the international guideline. The dose of 25 mg on day 1 appeared to be associated with a short episode of clozapine-induced inflammation as, on day 2, the NLR was abnormal with a value of 3.4. On day 6, the patient was on 50 mg/day and the next day it was increased to 100 mg/day, which showed an improvement in psychosis. The response to a low dose of 100 mg/day is compatible with him having a relatively high clozapine concentration for that dose. On day 11, the CRP and NLR were normal. On day 14, clozapine was increased to 200 mg/day. The next day, the patient had chest pain, an abnormal CRP (4.9 μg/dL, maximum normal until 0.9), an abnormal NLR (7.4) and an elevated troponin T. On day 16, the patient had an abnormal CRP (9.1 μg/dL) with an abnormal NLR (5.6) leading to clozapine discontinuation. On day 21, the troponin T had normalized, but abnormal values for CRP (6.6 μg/dL) and NLR (3.6) continued. The abnormal values for CRP and NLR continued until day 35. The next and last set of any laboratory data was drawn on day 46 with a slightly elevated CRP of 1.2 μg/dL.

Clozapine had been stopped on day 17 and could not be restarted until day 149. The patient became very difficult to handle and refused oral antipsychotics intermittently but would receive intramuscular injections of antipsychotics with associated skin abscesses. During this period there were 7 abnormal CRPs and 5 of them were accompanied by a NLR>3. On day 99, the CRP was slightly elevated to 1.8 μg/dL (normal until 0.9), but the NLR was lower than 3 (1.9). On day 112, the CRP was slightly elevated with 1.2 μg/dL (normal until 0.9), but the NLR was lower than 3 (2.7). After two normal CRPs on days 137 and 148 (accompanied by normal NLRs), a clozapine dose of 12.5 was restarted on day 148. The next day the patient developed a skin rash. On day 155, the 12.5 mg/day clozapine was stopped. The clinical picture evolved to an acute pericarditis and a diagnosis of clozapine-induced eosinophilia and systemic symptoms (DRESS) syndrome (de Filippis et al., 2022). On day 155, the CRP and NLR were abnormal, respectively 3.1 μg/dL and 4.1. On day 158, the CRP and NLR were also abnormal, respectively 2.9 μg/dL and 3.2. On day 165, the patient was asymptomatic and had a normal CRP.

Case 4

Case 4 was a 34-year-old nonsmoking African-American female diagnosed with schizoaffective disorder. Clozapine-induced myocarditis was associated with clozapine PM status due to: 1) obesity, 2) the co-prescription of valproic acid and 3) a urinary tract infection (Koenig et al., 2022). As the original article described (Cook et al., 2015), the titration was potentially too rapid. Table 2 presents a brief summary of the previously published data (Koenig et al., 2022) and adds the NLR data.

The patient had three normal NLRs, one before starting clozapine, one on day 10 and the other on day 11. On day 16, clozapine was stopped and the CRP was abnormal (CRP=15.8 μg/dL, maximum normal value is 0.5); the diagnosis of possible myocarditis was considered. There were two NLRs on that day (4.4 and 4.2). The NLRs from days 16 to 20 were always abnormal. On day 21 one was abnormal (NLR=8.4) and other was within normal limits (NLR=2.8). On day 22, the NLR was normal (2.2). On day 24, there were no signs of myocarditis and NLR was normal (2.9).

Case 5

Case 5 was a 50-year-old nonsmoking African-American male diagnosed with schizoaffective disorder with a body mass index of 21.4 (kg/m2). Clozapine-induced myocarditis was associated with probable clozapine PM status due to the co-prescriptions of: 1) valproic acid and 2) quetiapine. Table 5 presents the titration, co-medication, and NLR data. A review of the neutrophil values data shows

Table 5. NLR data in clozapine-induced myocarditis: Case 5[a]

Day	Laboratory Markers					
	CLO D mg/day	NLR (<1.8)	N (1.5-7.8) k/μL	L (1.1-4.5) k/μL	Eosinophil (0.05-0.70) k/μL	Clinical status
-21[b]	0					Transferred from another psychiatric hospital
-20[b]	0	0.9	3.27	3.50	0.08	
0[b]	0	1.7	4.78	2.75	0.08	
1[c]	25					No changes in vital signs were reported
2[c]	50					No changes in vital signs were reported
5[c]	100					No changes in vital signs were reported
7[c]	100	0.7	2.44	3.56	0.13	No changes in vital signs were reported
8[c]	150					No changes in vital signs were reported
11[c]	250	**1.9**	5.08	3.62	0.33	No changes in vital signs were reported
12[c]	350					No changes in vital signs were reported
14[c]	350					No changes in vital signs were reported
15[c]	350					No changes in vital signs were reported
16						In early morning: found unresponsive and did not respond to CPR
201						Autopsy: myocarditis with occasional eosinophils and a perivascular infiltrate

C: concentration; C/D: concentration-to-dose; CLO: clozapine; CPR: cardiopulmonary resuscitation; D: dose; L: lymphocyte; N: neutrophil; NCLO: norclozapine; NLR: neutrophil-to-lymphocyte ratio.
Definitive high abnormal laboratory values possibly explained by CLO-induced myocarditis are described in bold font.
[a]The co-medications are presented, as they have never been published in table format.
[b]Divalproex sodium 1000 mg/day, quetiapine 600 mg/day, hydrochlorothiazide 25 mg/day, lisinopril 10 mg/day.
[c]Divalproex sodium 1000 mg/day, quetiapine 600 mg/day, hydrochlorothiazide 25 mg/day, lisinopril 10 mg/day, benztropine 4 mg/day.

compatibility with BEN. Based on Bello et al. (2019), a value of <1.8 was considered normal.

The patient had three normal NLRs, two before starting clozapine and one on day 7 (NLR=0.7). On day 11, when he was taking 250 mg/day, the NLR became abnormal (NLR=1.9). The patient was found dead 5 days later and the autopsy verified that he died of clozapine-induced myocarditis.

DISCUSSION

The NLR appears to behave as a reliable marker for inflammation during the clozapine titrations of these 5 cases of myocarditis previously published.

LIMITATIONS

This study has limitations, as it is a retrospective analysis of the longitudinal NLR data available for previously published cases of myocarditis. A NLR cut score of 3.0 (Zahorec, 2021) was helpful in the context of clozapine titration in the first four cases. In retrospect, this may not be particularly remarkable, as the literature supports the concept that NLR reflects basic physiological processes across multiple illnesses (Buonacera et al., 2022; Firment & Hulin, 2024; Serrano et al., 2022; Zahorec, 2021). Thus, a NLR≥3 appeared to be an index of inflammation during clozapine-induced inflammation in the first four cases and during infection in the absence of clozapine treatment in Case 3.

The cutoff score ≥1.8 for NLR in patients with BEN proposed by Bello et al. (2019) in a Nigerian study of cancer worked well for clozapine-induced myocarditis in Case 5. In retrospect, if clozapine had been stopped or the dose held to 150 mg/day on day 11, when the NLR was 1.9, this might have saved the life of that patient.

Table 6. Three-phase model of CLO-induced inflammation

	Phase I	Phase II	Phase III
ACTIVATION	**Cytokine**	**Extensive neutrophil**	**Lymphocyte**
Cytokines	Start	Severe	Severe
Neutrophils	Start	Extensive	Extensive
Lymphocytes	No	No	Yes
METABOLISM[a]			
CYP1A2	Main but starts inhibition	Starts saturation	Saturated
CYP3A4	<10% CLO-N-oxide C	↑ as CYP1A2 saturated	↑ ↑ of CLO-N-oxide
UGT	Minimal	↑ unless VPA inhibition	↑ unless VPA inhibition
TISSUE DAMAGE	No	No	Yes
Reactive oxygen species			↑ as CLO-N-oxide
Autoimmune damage	No	No	Yes
↑ BLOOD MARKERS			
↑ CRP	Mild	Yes	Yes
↑ NLR	Mild	Yes	Yes
↑ Troponin[b]	No	No	Possible
↑ Liver[c]	No	No	Possible
↑ Pancreatic[c]	No	No	Possible
↑ IgE	No	No	Yes

C: concentration; CLO: clozapine; CRP: C-reactive protein; CYP1A2: cytochrome P450 1A2; CYP3A4: cytochrome P450 3A4; Ig E: immunoglobulin E; NLR: neutrophil-to-lymphocyte ratio; UGT: uridine diphosphate glucuronosyltransferase.
[a]CYP1A2 is the main metabolic pathway in normal circumstances. In high CLO Cs, CYP1A2 may become saturated and CYP3A4 may become more important. UGT is usually a minor pathway and may be influenced by VPA. During titration VPA may be an inhibitor, but after longer time it may become an inducer leading to lower norclozapine C.
[b]Many psychiatrists monitor troponin during titration so this elevation is easily identified.
[c]Liver and pancreatic markers are rarely monitored during CLO titration. Inflammations other than myocarditis (including hepatitis, pancreatitis, pericarditis in the absence of myocarditis, colitis, interstitial nephritis, pleuritis or pneumonitis) tend to be diagnosed later than myocarditis (Ertuğrul et al., 2022; de Filippis et al., 2024).

Timing of the onset of abnormal NLR values during clozapine titrations

This retrospective review of 5 cases is seriously limited by the available data, as only weekly values of NLR were available before the onset of clozapine-induced myocarditis. Case 3 has very interesting NLR data. On the first day a clozapine dose of 25 mg/day was administered to a male of European ancestry taking quetiapine. This is the double the dose recommended by the international guideline (Schoretsanitis & de Leon, 2022). One could hypothesize that this single dose could lead to a mild case of clozapine-induced inflammation. On day 2, a NLR of 3.4 was observed and is compatible with that hypothesis. In retrospect, this NLR could have led to stopping the clozapine until the NLR had normalized, restarting with a slower titration (dose of 12.5 mg/day), and close monitoring with CRP, NLR and troponin. Thus, use of the NLR might have prevented this case of clozapine-induced myocarditis and this patient, who appeared to respond to clozapine, might have been able to continue clozapine use for the rest of his life.

Comparison of the onsets of CRP and NLR abnormalities

Case 5 has no CRP data. In cases 1 to 4 the data is too limited to explore whether the CRP or the NLR is the earliest marker for inflammation. In Case 1, the first available abnormal value for both markers was on the same day, day 10. In Case 2, the first available abnormal value for both markers was on the same day, day 19. In Case 3, there is an abnormal NLR on day 2, but CRP was not measured. On day 15 both were abnormal. After the rechallenge, the first day

with laboratory studies was day 155 and both the CRP and NLR were abnormal. In Case 4, the first available abnormal value for both markers was on the same day, day 16.

Comparison of the resolution of CRP and NLR abnormalities

Our limited data suggest that CRP may take a little longer to normalize, at least in some patients. In Case 3, the delayed normalization happened during clozapine-induced myocarditis and during infection in the absence of clozapine. During the episode of clozapine-induced inflammation on day 46, the NLR had become normal at 2.0, while the CRP was slightly elevated at 1.6 μg/dL (normal up to 0.9). On day 49 both the NLR and CRP were normal. On day 58, the NLR continued to be normal at 2.0, while the CRP was slightly elevated at 1.5 μg/dL (normal up to 0.9). During the infection, in the absence of clozapine, twice the NLR appeared to normalize before the CRP. On day 99, the NLR had become normal at 1.9 while the CRP was slightly elevated at 1.8 μg/dL (normal up to 0.9). On day 112, the NLR had become normal at 2.7 while the CRP was slightly elevated at 1.2 μg/dL (normal up to 0.9).

In Case 4, on day 21 one NLR was very abnormal at 8.4, and the other NLR was normal at 2.8. On day 22, the only NLR available was 2.2, normal. It is unfortunate that the CRP was not available on days 21 or 22 in this patient in order to compare the NLR values.

There is need for studies comparing the resolution of CRP and NLR in clozapine-treated patients, but our limited data suggest that the NLR may normalize faster than the CRP. This would be compatible with the shorter half-life for neutrophils than for CRPs, which is what the literature describes. Pepys and Hirschfield (2003) described the half-life of CRP as 19 hours, while Summers et al. (2010) described the half-life of neutrophils as 6-8 hours.

Comparison with other indexes of inflammation during clozapine titrations

In our patients, the absolute count of eosinophils appeared to be a much less accurate marker for inflammation than CRP or NLR. Case 1, before the onset of clozapine-induced myocarditis, had two abnormal values and, during myocarditis, one normal and one abnormal. Case 2 had four normal absolute counts of eosinophils before myocarditis and one during clozapine-induced myocarditis. Case 3 had a normal value during the short episode of clozapine-induced inflammation on day 2; then one abnormal value on day 11 with normal CRP and NLR. During clozapine-induced myocarditis, 6 values were abnormal and 5 were normal. During clozapine-induced DRESS, three values were normal. On day 165, when the CRP and the NLR were normal, the absolute eosinophil count was abnormally high. Case 5 had 4 normal absolute eosinophil counts, 3 before clozapine-induced myocarditis and one on day 11 when the NLR was elevated. Two prior clozapine studies (Kikuchi et al., 2024b; Mohammadzadeh et al., 2024) also suggested that the absolute eosinophil count is not a good marker for clozapine-induced inflammation. Kikuchi et al. (2024b) observed that 50% (27/54) of the patients who experienced inflammatory adverse drug reactions (ADRs) on clozapine and 11% (21/187) of those without inflammatory ADRs developed eosinophilia. Mohammadzadeh et al. (2024) observed that 10% (7/72) taking clozapine for Parkinson's disease developed transitory eosinophilia without any other inflammatory signs.

The erythrocyte sedimentation rate (ESR) is another inflammation marker. Case 1 had a very abnormal value on day 22, when CRP and NLR were abnormal. In Case 3, the ESR appeared to take longer to become abnormal than the CRP and NLR. In some early articles, German authors studied ESR elevations during clozapine-induced fever. In an article written in German, Blum and Mauruschat (1972) first reported that during clozapine titration patients can develop fever in the absence of any concomitant infection. They found that 55% (11/20) of their patients had fever. In these 11 patients, 63% (7/11) had elevated ESR on day 10 and 100% (11/11) on day 20. Later, Helmchen (1989) described this fever as a transient phenomenon occurring between the 5th and the 20th treatment days and was frequently associated with increased ESR. The ESR was not included in: 1) the Australian protocol to monitor myocarditis (Ronaldson et al., 2011), 2) a US survey on protocols for screening clozapine-induced myocarditis (Goldsmith & Cotes, 2017) and 3) more recent clozapine guidelines (Correll et al., 2022; Qubad et al., 2024; Richardson et al. 2021; Wagner at al., 2025). In a PubMed search, we found that the ESR has been mentioned in: 1) a case of clozapine-induced colitis (Karmacharya et al., 2005), 2) a fatal case of clozapine-induced inflammation (Li et al., 2018) and 3) a review of clozapine-induced pericarditis (Yakubu et al., 2025).

Recent guidelines (Correll et al., 2022; Qabad et al., 2024; Richardson et al., 2021; Wagner at al. 2025) do not describe the potential of increased values of immunoglobulin E (Ig E) to be a marker for inflammation during clozapine-induced inflammation. Five case reports described abnormal Ig E values during clozapine titration (Dimitri Valente et al., 2018; Körtner et al., 1998; Lucht & Rietschel, 1998; Noh & Ryu, 2025; Shnoda et al., 2023). An Ig E elevation should be suspected if clozapine-induced inflammation is a hypersensitivity reaction (de Leon et al., 2015; Freudenreich, 2015). Case 4 would have greatly benefited from the measurement of Ig E values before clozapine was restarted. The patient had a hypersensitivity reaction during the first clozapine titration and then had a chronic infection. Once the inflammation had disappeared, clozapine was immediately started, but in retrospect it would have been wiser to measure Ig E before restarting clozapine to verify that the hypersensitivity reaction had disappeared, too. Future studies should explore the value of Ig E measurement on the clozapine rechallenge after any clozapine-induced inflammation.

Update of the three-phase model of clozapine-induced inflammation

Table 6 presents an updated version of the three-phase model of clozapine-induced inflammation which has been described in prior articles (de Leon, 2022; de Leon et al., 2022; 2025a). The first phase leads to cytokine activation, the second to extensive leukocyte activation and the third to lymphocyte activation and tissue damage. Psychiatrists tend to pay attention to troponin during clozapine titration, which makes myocarditis easier to diagnose, but local inflammations other than myocarditis tend to take longer to diagnose (Ertuğrul et al., 2022; de Filippis et al., 2024).

This model tries to simplify for educational purposes a very complex clinical phenomenon. If the titration is not increased or clozapine is stopped, the inflammation may not progress beyond phase I. Case 2 received a dose that was too high on day 1 (25 mg); then on day 2 the patient had a mild inflammatory response. The same dosage was maintained through day 5 and then increased on days 6 (50 mg) and 7 (100 mg); thus, at day 11 there were no signs of inflammation according to the CRP or NLR, so the initial inflammation was not only mild, but transitory. Unfortunately, the dose was further increased on day 12 (150 mg) and day 14 (200 mg), which led to a massive inflammation with heart tissue damage that was evident on day 15 when laboratory markers were available. If the dose increase is massive, all three phases can happen very rapidly. Case 5 was reported as having no relevant changes in vital signs until he was found dead on day 16.

Potential of the NLR to improve the safety of clozapine titrations

Safe clozapine prescribing (de Leon et al., 2020a) is becoming more and more important (de Leon, 2024a), as the benefits of clozapine are becoming more evident in patients with 1) schizophrenia that is treatment-resistant (McCutcheon et al., 2025) or includes suicide risk (De Las Cuevas et al, 2025), 2) first psychotic episode (Taipale et al., 2025), or 3) off-label indications (de Leon et al., 2025b).

Most countries require hematological monitoring during clozapine titration so the NLR has the advantage of being automatically available during titration. A recent recommendation of European experts (Verdoux et al., 2025) has led the European Medicines Agency to propose the elimination of the need for the lymphocyte count, which would preclude the possibility of calculating the NLR.

The package insert in China does not require hematological monitoring (Ruan et al., 2024), so the NLR may or may not be available, depending upon the setting. There is no doubt that clozapine-induced myocarditis and other clozapine-induced inflammations are severely underdiagnosed in China (de Leon et al., 2020b; Ruan et al., 2024). Obtaining the NLR during titration in China will help to identify clozapine-induced inflammation and the frequent concurrent infections (Ruan et al., 2020).

Using the NLR may have greater impact on improving clozapine safety in several countries with inadequate titration models (de Leon, 2024b). Japan (Kikuchi et al., 2024c) and South Korea (Kang et al., 2024) have major problems with clozapine ADRs during titration due to the use of titration models following US dosing recommendations, although Asians need lower doses (de Leon and Tandon, 2025). The Australian titrations are too aggressive for many of their patients (de Leon, 2024b); thus, it is not surprising that in 2025 some Australian psychiatrists still think that a 7% level for clozapine-induced myocarditis is normal (Paul et al., 2025). These Australian psychiatrists need to learn to use NLR monitoring during clozapine titrations.

Using the NLR may even have benefits in

Finland, the world leader in clozapine prescription (Bachmann et al., 2017) and possibly in managing clozapine ADRs (Partanen et al., 2024). There is definitive room to improve Finnish titration. In 2659 patients less than 5 cases (<0.19%) of myocarditis were described; however, other localized clozapine-induced inflammations not associated with troponin elevations were more frequent, 0.48% with colitis (13/2659), 0.38% with intestinal nephritis (10/2659), and 0.31% with pancreatitis (8/2659). Our article did not explore the use of the NLR to manage pneumonia in clozapine-treated patients, which is associated with the greatest burden in clozapine-treated patients in Finland, at 30% (408/2659) incidence (Partanen et al., 2024). Moreover, pneumonia may be the ADR that kills more clozapine-treated patients worldwide than any other ADR (De las Cuevas et al., 2024; de Leon et al., 2024).

More studies are needed during clozapine titration; until they are available, we recommend that the increase of NLR to ≥3 (or ≥1.8 in patients with BEN) may indicate the possibility of an infection or clozapine-induced inflammation associated with a rapid titration. Close monitoring of NLR, CRP and troponin will be beneficial and the titration should be slowed (clozapine dose should not be increased) until the NLR and CRP normalize. If there is any doubt, clozapine should be stopped and only restarted after eliminating other risk factors of clozapine-induced inflammation and with an extremely slow titration and very close monitoring of inflammation markers.

CONCLUSION

In the last 20 years, there has been a progressive understanding of the very important role of infection and inflammation in the management of clozapine-treated patients (Clark et al., 2018; 2025; de Leon, 2004; de Leon & Diaz, 2003; de Leon et al., 2020c; Leung et al., 2023; Raaska et al., 2002; Ruan & de Leon, 2019; Ruan et al., 2020); therefore, the NLR, as an easily available marker of inflammation, appears to have major potential to help in the management of clozapine-treated patients. Future studies need to verify what we found in the first 4 cases which suggested that a NLR ≥ 3 during titration should lead to consideration of the differential diagnosis of a clozapine-induced inflammation and/or infection (Verdoux et al., 2019). Future prospective studies during titration need to explore the NLR cut score in patients with BEN ≥1.8 as Case 5 suggested. Future prospective NLR studies during maintenance need to explore its role in the management of infection in clozapine-treated patients.

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A 3 feletti neutrofil-limfocita arány gyulladást jelezhet a klozapin adagjának titrálása során: öt publikált szívizomgyulladásos eset újbóli elemzése

Célkitűzések: A neutrofil-limfocita arány (NLR) a szisztémás gyulladás egyik markere. Az NLR≥3 értéket abnormálisnak tekintik (≥1,8-at a benignus etnikai neutropénia, BEN esetében). **Módszerek:** Az NLR értékeket hozzáadtuk C-reaktív fehérjét (CRP) is tartalmazó longitudinális adatokhoz, 5 publikált, klozapin által kiváltott miokarditiszes esetleírás esetben. **Eredmények:** Az 1. esetben két NLR-érték normális volt, de a klozapinszedés 19. napján a CRP abnormális lett (10,0 µg/d, ≤0,9), az NLR=3,9. A klozapin adagolását a 26. napon abbahagyták. A 2. esetben három normális NLR volt a miokarditisz előtt, de a 19. napon a klozapint abnormális CRP (16, µg/dL, ≤0,9) és abnormális NLR (6,7) miatt abbahagyták. A 3. eset az első napon 25 mg-ot kapott (valproinsav és kvetiapin mellett), a 2. napon az NLR=3,4 volt. A 11. napon a CRP és az NLR normális volt. A 14. napon mellkasi fájdalmat, abnormális CRP-t (4,9 µg/dL, ≤0,9) és abnormális NLR-t (7,4) észleltek. A klozapint a 17. napon abbahagyták. A CRP és az NLR végül a 35. napon normalizálódott. A bőr tályogai eredményeztek abnormális CRP- és NLR-értékeket.. A 148. napon újra elkezdték a 12,5 mg klozapin adagolását, ami másnap bőrkiütéshez vezetett. A 155. napon ezt az adagot abbahagyták. A 4. esetben a miokarditisz előtt két normális NLR-érték volt, de a 16. napon a klozapint abbahagyták (abnormális CRP, 15,8 µg/dL, ≤0,5 és abnormális NLR=4,4). Az 5. esetben BEN alakult ki. Az NLR a 7. napon normális volt, de a 11. napon 250 mg/nap adag mellett abnormális lett (NLR=1,9). Öt nappal később a páciens meghalt. **Következtetések:** A titrálás során abnormális NLR a klozapin által kiváltott gyulladást és/vagy fertőzést jelezhet.

Kulcsszavak: klozapinadagolás és -dózis, klozapinmellékhatások, klozapin vérszint, klozapinmetabolizmus, klozapin farmakokinetika, gyógyszerkölcsönhatás, gyógyszerfigyelés, gyulladás, kémiailag indukált miokarditisz, miokarditisz etiológia, miokarditisz megelőzés és kontroll, szkizofrénia