~~Novel markers of systemic inflammation among hospitalised HIV-positive adult patients~~

Incidence and significance of elevated platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios among hospitalised HIV-positive adult patients

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Abstract

There is increasing interest in the peripheral blood platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) as markers of systemic inflammation. We audited records of unselected hospitalised HIV-positive adults to identify the frequency of elevated PLR and NLR, potential associations with specific diagnoses, and outcome. Of 259 patients audited, their median age was 47 years (interquartile range=41-54); 188 (73%) were men. An elevated PLR occurred in 87 patients (33.6%); 67 (25.9%) had an elevated NLR; 200 (77%) had an elevated CRP. Elevated PLR and NLR were associated with a variety of infectious, inflammatory and malignant conditions similar to conditions described in the general non-HIV-infected adult population. Additionally, elevated PLR and NLR occurred both in patients in receipt of antiretroviral therapy (with undetectable viral loads), as well as in those with newly-diagnosed and poorly-controlled infection. Fourteen patients with infectious and inflammatory conditions had an elevated PLR and normal CRP, with/without elevated NLR. There was no association between elevated PLR or NLR and ICU admission, p=0.1001 and p=0.605, respectively. Elevated NLR, but not PLR was associated with death, p=0.0405 and p=1.000, respectively: two-tailed Fisher's exact test. The single site nature of the audit and relatively small number of patients limit these observations.

Introduction

The peripheral blood platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are derived by dividing the platelet and neutrophil counts by the lymphocyte count.[1] These ratios are increasingly recognized as markers of the systemic inflammatory response. In the general population elevated PLR and NLR are associated with advanced stage of malignancy, metastatic disease, poor treatment response,[2-4] sarcopenia,[5] and worse prognosis.[6] Elevated ratios are also associated with Psoriasis and its severity,[7] disease activity in systemic lupus erythematosus,[8] Crohn's disease,[9] sepsis in burns patients,[10] and post-surgical acute kidney injury.[11] In patients with pulmonary tuberculosis elevated NLR is associated with malnutrition and cavitatory disease, indicating increased systemic inflammation[12] and in patients with COPD is associated with dyspnoea, lower FEV_1, and poorer survival.[13] In the ageing population elevated NLR is independently associated with all-cause mortality.[14] Among HIV-positive individuals an association between elevated NLR and risk of cardiovascular disease (CVD),[15] thought to be due to systemic inflammation arising from HIV infection and from antiretroviral therapy has been described [16] and elevated PLR and NLR are associated with "all-cause" mortality, independently of CD4 count.[17] In the latter study PLR and NLR appeared to be biomarkers of systemic inflammation.[17] We audited records of hospitalized HIV-positive adults to identify the frequency of elevated PLR and NLR, potential associations with specific diagnoses, and outcome.

Methods

Retrospective audit of electronic records of consecutive unselected HIV-positive adult patients admitted to Royal Free London Hospital, between 01 March 2015 and 30 April 2017. Data collected included: patient demographics (age, gender), CD4 count, HIV viral load, receipt of antiretroviral therapy (ART), admission CRP (elevated: >5 mg/L), platelet, neutrophil and lymphocyte counts, from which PLR (elevated: >200)[12] and NLR (elevated: >5)[6][12] were derived, need for intensive care unit (ICU) admission, outcome: survival, or death, and final diagnosis. Comparison of those with elevated and normal PLR/NLR admitted to ICU, or who died was done using two-tailed Fisher's exact test (GraphPad Prism Version 6.0h: GraphPad Software, La Jolla, CA, USA).

Results

Of 259 patients, 188(73%) were men; median age =47 years (interquartile range: IQR=41-54). Two hundred(70%) were taking ART and 141 had undetectable viral loads (<40 copies/ml); median CD4 count=409 cells/mm^3 (IQR=197-641). Fifty-nine were not taking ART; median CD4 count among these patients=80 cells/mm^3 (IQR=28-280).

Eighty-seven patients (33.6%) had elevated PLR, 67(25.9%) had elevated NLR, and 200(77%) had elevated CRP (Figure 1). Diagnoses in patients with elevated PLR, elevated NLR, or both are shown in Table 1. Several bacterial, viral and fungal infections, non-infectious inflammatory conditions and malignancies were observed. Elevated PLR and/or NLR also occurred in patients with poorly-controlled HIV infection and in those not taking ART. Fourteen patients with infectious and inflammatory conditions had elevated PLR and normal CRP with/without elevated NLR (Table 1).

Seven patients required ICU admission, including four with elevated PLR (one had elevated NLR), and one other with elevated NLR. Six patients died; two had elevated PLR (one also had elevated NLR), one other had elevated NLR. There was no association between elevated PLR or NLR and ICU admission; p=0.1001 and p=0.605, respectively. Death was associated elevated NLR, but not PLR; p=0.0405 and p=1.000, respectively: two-tailed Fisher's exact test.

Discussion

This audit identified that 40% of hospitalised HIV-positive inpatients had an elevated PLR and/or NLR, and these occurred in a variety of infectious, inflammatory and malignant conditions, similar to observed associations reported in the general population.[3-4][7-10] This audit contrasts with previous studies, in that it assessed unselected consecutive hospitalised HIV-positive adults, rather than patients with a specific condition, e.g. Psoriasis, Crohn's disease.[7][9]

Patients with elevated PLR and NLR included those with well-controlled and poorly-controlled HIV infection, and others with newly-diagnosed infection and not in receipt of ART. All patients with an elevated NLR also had either an elevated PLR, and/or elevated CRP

but an elevated PLR, normal CRP, with/without elevated NLR occurred in a small number of patients, with mainly infectious conditions. This potentially infers that the PLR and NLR might be used by clinicians suspecting infection/inflammation in HIV-positive patients when other blood results (e.g. CRP) are not abnormal.

Few studies have considered NLR/PLR in HIV-positive individuals. A retrospective cohort study of 3766 HIV-positive patients showed elevated NLR was a predictor of risk of CVD independently of traditional CVD risk factors.[15] This risk was attributed to systemic inflammation caused by HIV infection and by ART.[16] In the Italian MASTER cohort study of 8230 adult HIV-infected patients recruited before starting ART, elevated PLR and NLR appeared to be biomarkers of systemic inflammation and were associated with "all-cause" risk of death, independently of CD4 count.[17]

In this audit there was no evidence of an association between elevated PLR or NLR and need for ICU admission, and only elevated NLR was associated with mortality. The single site nature of the audit and relatively small number of patients limit this observation, and in part explain the contrast with findings from the MASTER study.[17]

In conclusion, elevated PLR and NLR were commonly identified among hospitalised HIV-positive adults. There was no association with specific infectious, inflammatory, or malignant conditions.

Declaration of conflicting interests

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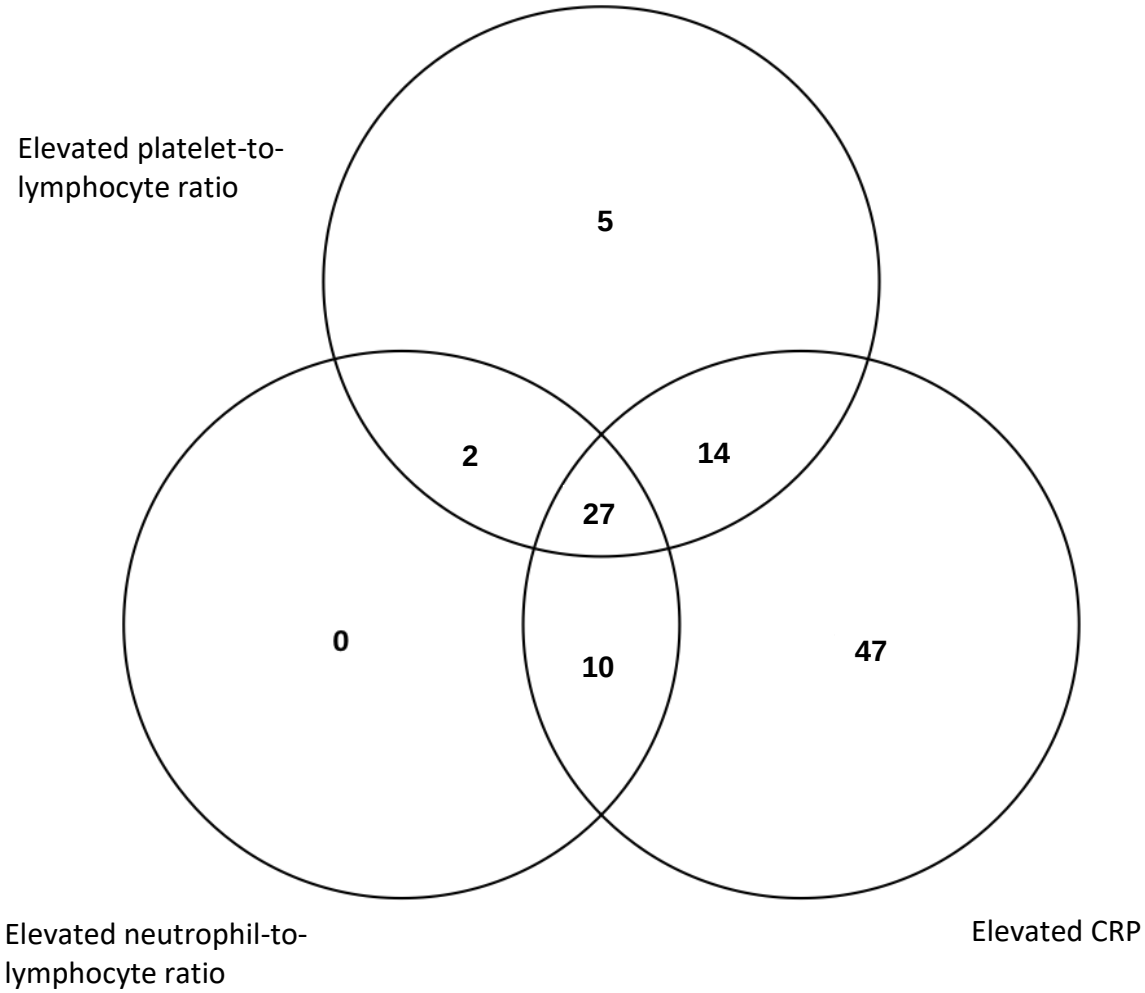
Figure 1. Relationship between elevated peripheral blood platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and elevated CRP among hospitalized HIV-positive adults: (a) 141 with undetectable viral loads, and: (b) 118 with detectable viral loads (59 in receipt of ART).

(a)



(b)

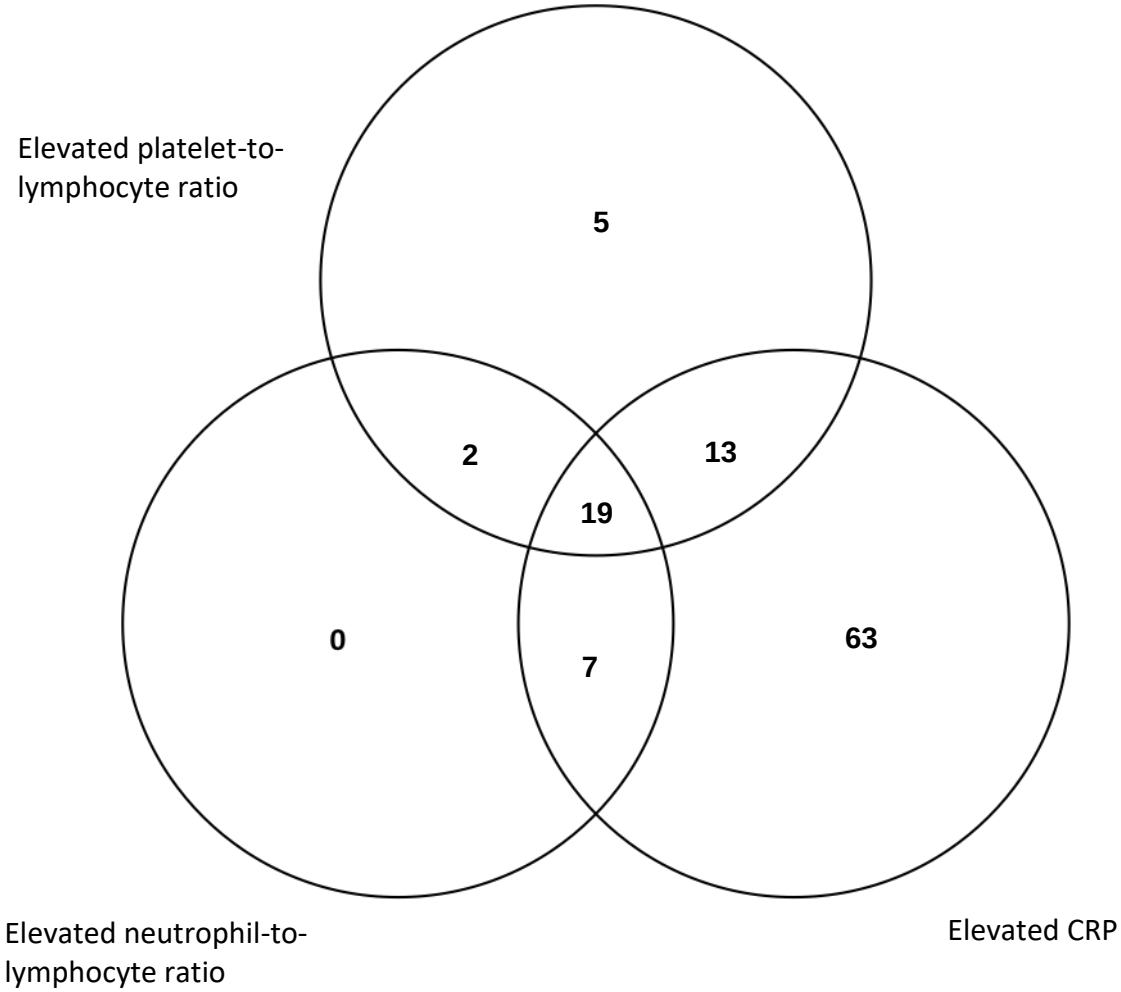

Elevated platelet-to-lymphocyte ratio
5
2
13
19
0
7
63
Elevated neutrophil-to-lymphocyte ratio
Elevated CRP

Table 1. Diagnoses among patients with an elevated peripheral blood platelet-to-lymphocyte ratio, and/or an elevated neutrophil-to-lymphocyte ratio, with or without an elevated CRP.

Elevated PLR, elevated NLR, and elevated CRP (n =46)
7 = CAP (1 also syphilis) 6 = PCP 4 = influenza A 3 = cellulitis (1 also had PE) 2 = bacterial meningitis 2 = TB (1 pulmonary, 1 disseminated) 2 = ESRF (1 also had candidiasis, 1 was post-transplant) 1 each = dMAC, chronic leg ulcer, gastroenteritis, poorly-differentiated neuroendocrine tumour, renal colic, pyelonephritis, UTI, myocarditis, syphilis, CMV colitis, ulcerative colitis, empyema, NHL, *Legionella* pneumonia, peri-tonsillar abscess, MSSA bacteraemia, HSV skin infection, scabies, oral candidiasis, PE + CGD
Elevated PLR, normal NLR, and elevated CRP (n =27)
4 = CAP 3 = PCP 3 = poorly-controlled advanced HIV (1 also had autonomic neuropathy, 1 also had hypothermia/drug overdose) 2 = skin abscesses 1 each = dMAC, recurrent NHL, exacerbation of COPD, ADR to co-trimoxazole, cerebral toxoplasmosis, sinusitis/otitis externa, mycobacterial IRIS , UTI, gastroenteritis, metapneumovirus, hypoglycaemia, colitis, fitting due to ischaemic cerebrovascular disease, *Enteroccoca*l bacteraemia + *Strongyloides* hyperinfestation, ESRF + rash
Elevated PLR, normal NLR, and normal CRP (n =10)
3 = PCP (1 also *Pseudomonas* bacteraemia) 2 = toxoplasmosis (1 had seizures), 1 each = dMAC, prostatitis, constipation, ophthalmic VZV, neurocognitive decline + CMV retinitis
Normal PLR, elevated NLR, and elevated CRP (n =17)
7 CAP (1 also had influenza B) 3 cellulitis 1 each = prostatitis, gastroenteritis, bacteraemia, hepatitis, epididymitis, MRSA osteomyelitis + endocarditis, *Campylobacter* enteritis
Elevated PLR, elevated NLR, and normal CRP (n =4)
1 each = VZV skin infection, influenza A & B, cellulitis + perforating collaginosis, HSV skin infection

Key: PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; CAP: community-acquired pneumonia; PCP: *Pneumocystis* pneumonia; TB: tuberculosis; ESRF: end-stage renal failure; dMAC: disseminated *Mycobacterium avium* complex*;* UTI: urinary tract infection; CMV: cytomegalovirus; NHL: non-Hodgkin lymphoma; MSSA: methicillin sensitive *Staphylococcus aureus*; HSV: herpes simplex virus; PE: pulmonary embolus; CGD: chronic granulomatous disease; COPD: chronic obstructive pulmonary disease; ADR: adverse drug reaction; IRIS: immune reconstitution inflammatory syndrome; ADR: adverse drug reaction; MRSA: methicillin resistant *Staphylococcus aureus*; VZV: varicella zoster.