Lymphocyte-CRP-ratio and CRP-albumin-ratio as potential inflammation markers in adults with HIV

To the Editors: Lymphocyte-to-C-reactive protein (LCR) and C-reactive protein-to-albumin (CAR) ratios are emerging biomarkers of inflammation, which have been utilised in several areas of clinical medicine [1-3]. C-reactive protein (CRP) and serum albumin are useful prognostic markers for critically ill patients: CRP rises in blood within 6-8 hours of acute inflammation and low serum albumin may indicate malnutrition, chronic disease or inflammation. Lymphocytes are involved in coordinating immune response to infection and indicate inflammatory status. The LCR has therefore been described as a “proxy” for the complex interaction between host and tumour and subsequent systemic inflammation, in the context of malignancy, while the CAR represents nutritional state and acute or chronic systemic inflammatory response [1,2]. Both LCR and CAR may be determined from inexpensive, routinely performed blood tests on admission to hospital. Existing evidence evaluating the significance and role of LCR and CAR is limited to selected hospitalised adults, with either inflammatory (Guillain-Barre syndrome, polycystic ovary syndrome, critical illness) [3-7], malignant (gastrointestinal, liver, renal, lung cancer, or brain metastases) [8-13], and infectious (COVID-19 and appendicitis) [1,4-5,14] conditions.

Despite significant advances in our understanding of HIV infection, there remains a need for further accessible biomarkers of systemic inflammation, which may be associated with longer-term morbidity and mortality for people with HIV (PWH) [15]. Irrespective of sustained antiretroviral therapy (ART) adherence and virological suppression, markers of inflammation including innate and adaptive immune activation remain abnormal for most PWH [16, 17, 18]. This persistent inflammation contributes to disease burden for PWH, including malignancy, cardiovascular disease, chronic obstructive pulmonary disease, type 2 diabetes, renal disease, and frailty, amongst others [19]. Abnormal immune activation likely persists even for PWH who initiate ART early, and there is evidence to suggest that the impact of inflammation on morbidity and mortality is greater for PWH than the general population [15].

Given there is evidence to suggest that CAR and LCR are more reliable long-term indicators of prognosis than CRP or lymphocyte count alone [20, 21], we sought to undertake an exploratory analysis of LCR and CAR as markers of inflammation among PWH. We examined the records of hospitalised PWH to evaluate the frequency of reduced LCR and elevated CAR, and their respective associations with clinical outcome, if any.

Consecutive PWH (≥18 years) admitted, from January 1 2015 to December 31 2017, to the Royal Free Hospital, London were included in this study. An existing database, preceding the COVID-19 pandemic, was used to extract baseline demographics, ART status, diagnosis on discharge from hospital (categorised as: infectious, malignant, cardiovascular, inflammatory, or other) and clinical outcomes including Intensive Care Unit (ICU) admission and mortality at three months post-discharge [22].

Laboratory values analysed included: HIV viral load (virally supressed: <40 copies/mL), CD4 count (immune reconstitution: ≥350 cells/μL), serum CRP (elevated: ≥5mg/L), serum albumin (reduced: <35 g/L) and lymphocyte count (reduced: <800 cells/μL) on admission. A reduced LCR (lymphocyte count (cells/μL)/CRP (mg/L)) was defined as <101[1]. An elevated CAR (CRP (mg/L)/albumin (g/L)) was defined as >0.033, as this cut-off has been associated with shorter overall survival and recurrence-free survival for patients with malignancy[10]. We performed a sensitivity analysis using a different CAR cut-off, >0.19, as this has been predictive of short-term outcome for patients with Guillain-Barre syndrome[6]. Clinical outcomes of those with reduced/normal LCR and elevated/normal CAR, were compared using a two-tailed Fisher exact test. This project was registered locally, with approval granted for audit purposes.

Of 259 PWH, most were male (n=188;73%), median age 47 years (interquartile-range:41-54)[16]. Most patients were admitted with infectious conditions (n=172; 66%), Appendix 1. A reduced LCR was seen in 152 (59%) patients: all had an elevated CRP and 39 had a reduced lymphocyte count, Appendix 2. Elevated CAR was seen in 233 (90%), of whom 192 had an elevated CRP and 61 had reduced albumin. In sensitivity analysis, 180 (69%) had an elevated CAR using the >0.19 cut-off, of whom 177 had an elevated CRP and 55 had reduced albumin. An elevated CAR was more frequently observed than a reduced LCR in this group, irrespective of CAR cut-off; all patients with a reduced LCR had an elevated CAR. The relationship between elevated CRP, reduced albumin and reduced lymphocyte count in those with viraemic or virologically-suppressed HIV are shown in Figure 1. Eight patients died; all had elevated CAR and seven had reduced LCR. Of those admitted to ICU (n=5;2%), four had both elevated CAR and reduced LCR. Reduced LCR and elevated CAR

were not associated with either ICU admission (p=0.65 and p=0.41) or mortality (p=0.15 and p=1.00).

We found that most hospitalised adult PWH had a reduced LCR or elevated CAR. All patients admitted to ICU had either reduced LCR or elevated CAR. All patients who died had elevated CAR. These observations were not significantly associated with clinical outcome, by contrast with studies in the general population [1-14]. It may be that these cut-offs are not appropriate for PWH given the persisting underlying inflammatory state, even among those with viral suppression [15]. The most common biochemical abnormality was an isolated elevated CRP, described in other studies, despite initiation of ART and in matched HIV negative individuals [15]. Low serum albumin was also common in this cohort, with other studies demonstrating that this marker alone associates with adverse longer-term outcomes for PWH [23, 24]. Despite concerns that HIV viraemia or low CD4 count might have been related to an increased inflammatory state, it appeared that the proportion of PWH with reduced/normal LCR and elevated/normal CAR were similarly distributed, irrespective of viral suppression or immune reconstitution.

Interpretation of this data is limited by it being from a single-centre and a relatively small sample size, reducing the statistical power to detect differences or associations. Additionally, information regarding medical comorbidities was limited, and recorded clinical outcomes were restricted to ICU admission and mortality at three months only. Baseline biochemical parameters to estimate CAR and LCR prior to hospitalisation were unavailable. Furthermore, LCR and CAR cut-offs used have not previously been validated in PWH, whether hospitalised or not.

In summary, on admission to hospital most PWH, regardless of virological control, had reduced LCR or elevated CAR and neither appeared to associate with specific diagnoses or clinical outcomes. Future work will need to evaluate use of these novel biomarkers in this patient population and establish cut-off values for hospitalised PWH that associate with adverse clinical outcomes.

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