Editorial

The role of platelet-lymphocyte ratio in hepatocellular carcinoma: a valuable prognostic marker

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Primary liver cancer is the fifth most commonly diagnosed cancer and is the third leading cause of mortality worldwide (1). Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancer. Management of HCC requires a multi-pronged approach with consideration for patient factors [co-morbidity, Eastern Cooperative Oncology Group (ECOG) performance status, etc.], tumor factors [tumor size, portal vein tumor thrombosis (PVTT) etc.], and liver function (2,3). Classification systems such as the Barcelona Clinic Liver Cancer (BCLC) and the Hong Kong Liver Cancer (HKLC) staging guide HCC management (2-4). Improvements in local ablative techniques such as radiofrequency ablation (RFA) and locoregional therapies such as transarterial chemoembolization (TACE) or selective internal radiation therapy (SIRT) have revolutionized HCC therapy over the past two decades (5,6). A meta-analysis on the use of RFA and TACE has shown that oncological outcomes were comparable with liver resection (LR) (6).

HCC is a heterogenous tumour with varied prognosis depending on multitude of known and unknown factors. Patient demographics, serological tests, and imaging markers provide prognostic information prior to therapy. For example, large tumor size and PVTT predict inferior oncological outcomes (7,8). Pre-therapy indices are especially important as it can impact decisions regarding choice of therapy. In light of this, serological indices pertaining to the inflammation-carcinogenesis axis are important advances in recent times (9,10). Commonly validated serological indices include platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), prognostic nutritional index (PNI) and albumin-bilirubin index (ALBI) (10). For this editorial, we shall discuss about the utility of PLR in HCC.

PLR is calculated by the platelet count divided by absolute lymphocyte count. The utility of PLR in prognostication of HCC patients has emerged over the past decade (11,12). However, most of the studies are retrospective and include heterogenous study population. The recently published meta-analysis by Li *et al.* is therefore important to consolidate evidence on its use (13). Li *et al.* reduced the bias due to confounding factors through the use of strict exclusion criteria. For example, the authors excluded studies on liver transplantation (LT) and radiotherapy due to their effects on platelet counts. Also, studies on ruptured HCC were excluded in view of relatively poor prognosis of patients with ruptured HCC. Of the 19 studies including 8,269 HCC patients, Li *et al.* showed that elevated PLR was associated with shorter overall survival (OS) [pooled hazards ratio (HR): 1.34, 95% confidence interval (CI): 1.18–1.52, P<0.00001] (13). Elevated PLR was also associated with shorter disease-free survival (DFS) in 8 studies (n=4,387 patients) (pooled HR: 1.35, 95% CI: 1.13–1.63, P=0.001) and progression free survival (PFS) in 3 studies (pooled HR 1.55, 95% CI: 1.09–2.22, P=0.02). The cut-off values for PLR ranged from

75.3–167.7. In view of the heterogeneity of studies and wide range of PLR, the authors performed subgroup analysis for PLR ≥150 and <150 and reported shorter OS with PLR cut-off ≥150 (n=6 studies, 3,748 patients, pooled HR 1.49, 95% CI: 1.33–1.68, P<0.00001).

Using the information presented by the authors, we shall qualitatively summarize and discuss succinct key points and take away messages regarding the clinical utility of PLR as a biomarker for HCC prognostication. To begin, we shall discuss about the role of platelets and lymphocytes in carcinogenesis. Platelets play an important role in tumor angiogenesis (14). Platelet activation results in secretion of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and platelet-derived microparticles (PMPs) which promote angiogenesis (15,16). Activated platelets interact with endothelial cells to induce coagulation and increase adhesion between tumor cells and endothelial cells (17,18). Lymphocytes play a significant role in cancer surveillance. Cytotoxic T cells and natural killer cells are critical mediators of anti-tumor response, and activated B cells activates tumor-infiltrating lymphocytes for anti-tumor activity (19,20). Lymphocyte depletion reflects impairment in anti-tumor response. In the context of cancer, platelets are "bad" and lymphocytes are "good", thus high PLR predicts poor oncological outcomes. We would like to summarize our discussion in four points.

Firstly, what should be the universally accepted PLR cut-off? As discussed earlier, platelets are pro-tumorigenic, while lymphocytes are anti-tumorigenic (14,19,20). Hence, a higher PLR cut-off may be more sensitive for prognostication of HCC patients. There is no standardized accepted or agreed cut-off or threshold for "elevated PLR". For example, Kim *et al.* used PLR >132 as the cut-off value and Kabir *et al.* used >155 as the cut-off (21,22). Kabir *et al.* derived 155 as an average of the cut-off values based on receiver operating curves for OS (PLR cut-off 176) and RFS (PLR cut-off 133) (22). However, newer studies conducted are using 150 as a cut-off for PLR, and this seems to be more aligned with majority of published research in HCC (12). Thus, we suggest to use PLR ≥150 as cut-off threshold for poor HCC prognosis. In addition, PLR and other similar biomarkers are dynamic and increasing trends do suggest poor prognosis even if initial levels did not meet threshold cut-offs; however more data is necessary to prove this.

Secondly, what are the implications on the management of patients with high PLR? The meta-analysis by Li *et al.* showed that in both resectable and unresectable HCC, high PLR is associated with worse OS (13). These patients were recommended the treatment based on prevailing clinical guidelines or according to local multi-disciplinary board recommendations. The pre-operative knowledge of poor prognosis due to elevated PLR is important at three fronts:

(I) A clinician may discuss with his/her patient about the value of PLR as a prognostic marker. This may influence the decision making either to select a more aggressive approach (for example combining resection with loco-regional or systemic therapies) or a less aggressive approach (for example a combination of RFA and TACE or SIRT) instead of LR.

(II) Patients with elevated PLR may be considered enrolment in clinical trials for neoadjuvant therapies or post LR adjuvant therapies to reduce risk of recurrence. Selected patients could be considered for translational research as well as immunotherapy regimens.

(III) Patients with elevated PLR may be proposed a closer follow-up interval to detect recurrence.

We however suggest that a clinician considers all possible information and discuss this with his/her patients in making clinical decisions, and PLR should not be the sole biomarker on which bedside clinical decisions should be made.

Thirdly, is PLR reliable in cirrhotic patients? Thrombocytopenia is a common complication of liver cirrhosis. Lymphopenia has also been demonstrated in liver cirrhosis, though the exact pathophysiology has not been clearly described (23). This may affect the cut-off value for PLR used for prognostication of HCC. More than 50% of the patients in the report by Li *et al.* had cirrhosis (13). Hence it is reasonable to conclude that PLR may be used to prognosticate HCC with liver cirrhosis. Yang *et al.* reported 1,174 patients with hepatitis B related HCC and showed similar incidence of liver cirrhosis in patients with low PLR (<150) and high PLR (≥150) [low PLR: n=565/938 (60.23%), high PLR: n=148/236 (62.71%), P=0.486] (11). This implies that there is likely a proportional fall in platelets alongside lymphocytes in cirrhosis, maintaining the validity of PLR use in cirrhotic patients. Thus, PLR may still be useful as a prognostic marker in HCC patients with cirrhosis.

Lastly, what is the role of PLR in special circumstances e.g., after LT? Li *et al.* excluded studies on LT as immunosuppressant treatment may affect platelet counts (13). Previous meta-analysis by Lai *et al.* in 2018 on 5 studies with 899 patients who had HCC and undergone LT showed that elevated PLR was associated with shorter DFS (OR 3.33, 95% CI: 1.78–6.25; P<0.001) (9). Four of the five

included studies used PLR cut-off of 150. Thus, it would not be appropriate to consider LT instead of LR just because a patient has high PLR, as outcomes with both LR and LT are inferior with elevated PLR. Based on the current evidence, PLR also serves as a poor prognosticator of HCC patients treated with LT.

In conclusion, PLR is one of the many inflammatory biochemical indices which have been evaluated for use as a prognostic marker in HCC. Meta-analyses have shown that elevated PLR is a poor prognostic marker for survival outcomes in HCC. Due to emergence of data and proliferation of scientific research in relation to simple, routinely performed, cheap, and accessible serological biomarkers, there is an obvious temptation amongst the scientific community to incorporate them into the existing clinical management guidelines for HCC, and we support this cautiously. The poor outcomes of HCC patients with thrombocytosis as a paraneoplastic syndrome could also be explained due to elevated platelet counts, and role of platelet in inflammation-carcinogenesis axis (24). In closing, the function of lymphocyte is also important issue in anti-tumour activity and simply quantifying the number of cells is not adequate for accurate prognostication (25). Thus, though PLR is a promising biomarker, more research is still necessary to understand the molecular and cellular basis in HCC patients.

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