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Archives of Gastroenterology Research Commentary

Prognostic Utility of Ferritin Transferrin Ratio in Hepatocellular Carcinoma

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Abstract

Prognostic factors for hepatocellular carcinoma (HCC) has been a dynamic study section. Different staging systems like TNM (tumor size, node status and metastasis) staging, Barcelona staging, Okuda staging, as well as albumin- bilirubin score, alfa fetoprotein (AFP) and many more are evaluated for prognostication of HCC patients. This is an invited commentary on our previously published paper, where we explored the role of the ratio of serum ferritin and transferrin level (FTR). We concluded that FTR >7.7 is associated with better overall survival and outperformed the Barcelona staging system.

Commentary

There is growing body of literature to identify novel prognostic markers in hepatocellular carcinoma (HCC), including serum ferritin (SF), transferrin levels, alfa fetoprotein (AFP), and neutrophil to lymphocyte ratio (NLR) [1-7]. Chronic inflammation and fibrogenesis are considered quite essential in the oncogenesis of HCC. The trigger for this inflammation could range from viral hepatitis, alcoholic cirrhosis, to non-alcoholic fatty liver disease [8-10]. Also, iron overload as in hereditary hemochromatosis is linked to one of the factors for HCC oncogenesis [11].

SF is a positive marker of inflammation and a marker of iron stores [12]. Prior studies using SF as a prognostic factor in HCC have been listed in Table 1 [1,2,13]. SF measured in 103 HCC patients treated with radiofrequency ablation (RFA) were found to predict overall survival and time to recurrence with a cut off value of 244 ng/ml [1]. Similar study done on 427 HCC patients undergoing curative hepatic resection showed SF to predict overall survival and recurrence free survival [2] with cut off being 267 ng/ml. A recent study done in 2018 contradicted the idea. This study evaluated 578 HCC patients undergoing RFA, with SF not able to significantly predict the survival [13]. Serum ferritin and iron stores vary according to race [14,15]. The mean ferritin among the patients in this study [13] was lower than other above-mentioned studies [1,2]. To note, the study was done in Japan where prevalence of hereditary hemochromatosis and SF and iron stores are very low. At the same time, most of the HCC patients studied were secondary to HCV [13]. So, this does not support SF as an inflammatory marker to predict the survival. SF has inflammatory and iron storage properties which can confound or exaggerate the predictive value of it as a survival parameter. In our study, the serum ferritin was significantly lower in survivors with mean SF of 193 ng/ml [16]. Further studies need to be done to build up the support for SF independently as a prognostic factor.

Another inflammatory marker and marker of iron stores is serum transferrin which is negative acute phase reactant [17]. Transferrin has also been studied to find its prognostic value in HCC survival. A retrospective study done in 44 HCC patients receiving hepatic arterial infusion therapy was found to correlate higher serum transferrin level to higher survival rates [3]. Another study supporting the idea found high ferritin along with low transferrin saturation independently predicted the mortality; it was done in 328 patients with end stage liver disease, out of which only 17% had HCC [4]. Not enough

evidence is there to support serum transferrin alone to predict the survival rate. Prior studies evaluating the role of transferrin as a prognostic factor in HCC are shown in Table 2. SEPT6 mainly regulates actin dynamics, cell shape and microtubule dynamics, cytokinesis, cell proliferation, cell cycle progression, cell apoptosis and cell migration. But the role of SEPT6 and its mechanism in liver fibrosis has not been studied before. Therefore, in the manuscript entitled "Effect of SEPT6 on the biological behavior of hepatic stellate cells and liver fibrosis in rats and its mechanism", we explored the role of SEPT6 in liver fibrosis and elucidated the underlying mechanism [22].

We did not use SF and transferrin individually in the multivariate analysis due to the multicollinearity with ferritin transferrin ratio (FTR). An FTT cut off value of 7.7, yielded sensitivity and specificity of 87% and 88%, respectively, based on receiver operating curve analysis [16].

In literature, studies have shown AFP to independently predict the risk of pathological grade of HCC, its progression and survival. Halazun et al., addressed AFP cut off of 200 ng/ml while Bai et al., used AFP positive or negative without using a discrete value to show relation of AFP to lower survival [5,6]. A metanalysis of 4,726 HCC patients showed that post treatment AFP response was significantly associated with overall survival, progression free survival and recurrence free survival [7]. In our study, AFP >350 ng/mL was associated with lower overall survival with hazard ratio (HR) of 2.58, P=0.018 (CI 1.68-2.95) on multivariate analysis [16].

	Study	**Number of Patients**	**Result of Study**	**P value**	**Patient Population**
1.	Facciorusso et al., 2014 [1]	103	SF below 244ng/ml predicted significantly better overall survival		HCC patients treated with RFA
2.	Uchino et al., 2018 [13]	578	SF did not predict the OS (SF cut off 244ng/ml)	0.45	HCC patients treated with RFA
3.	Wu et al., 2019 [2]	427	SF below 267ng/ml predicted significantly better overall survival	0.001	Patients received curative hepatic resection
Abbreviations: HCC: Hepatocellular Carcinoma; SF: Serum Ferritin; RFA: Radiofrequency Ablation					

Table 1: Summary of studies with use of ferritin as prognostic factor.

	Study	**Number of HCC Patients**	**Result of study**	**P value**	**Patient population**
1.	Zaitsu et al., 2014	44	Transferrin level 190mg/dl or above with better overall survival rate	0.001 [CI], 0.132-0.603;	Patient undergoing RFA
2.	Weismüller et al., 2011	56 (out of 328 patients with chronic end stage liver disease)	Transferrin saturation (TS) less than 55% along with high SF >=365 mg/dl has lower survival rate than transferrin saturation more than 55% and high SF >=365 mg/dl.	0.003	SF higher than 365 independently predicted survival but TS did not independently show any survival benefit.
Abbreviations: HCC: Hepatocellular carcinoma; CI: Confidence Interval; RFA: Radiofrequency ablation; SF: Serum Ferritin; TS: Transferrin Saturation					

Table 2: Summary of studies using transferrin as prognostic factor.

Cox regression analysis showed that FTR, advanced liver disease with Barcelona liver staging D and AFP had significant impact on mortality. Area under curve (AUC) for FTR is greater than that of Barcelona staging for HCC [16]. This further emphasizes the prognostic importance of FTR, making it better than Barcelona staging for HCC. FTR is an easily available tool that can be used to predict survival in HCC.

Contributions

I) Conception and design: Ishaan Vohra; (II) Administrative support: Bashar Attar; (III) Provision of study materials, collection and assembly of data: Vatsala Katiyar; (IV) Manuscript writing: All authors.

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