Letters to the Editor

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Low free T_3 levels are related to early mortality in patients with decompensated cirrhosis and acute-on chronic liver failure

To the Editor:

We read with interest the article by Maiwall *et al.* in which serum ferritin along with hepatic encephalopathy, leukocyte count, acute-on-chronic liver failure (ACLF) grades and CTP score predict early mortality in patients with decompensated cirrhosis (DC) [1]. ACLF has recently been recognized as a specific clinical form of liver failure with short term mortality [2,3]. Thyroid test abnormalities in ACLF and their association with survival have not been determined so far.

The plasma thyroid hormone profile in patients with cirrhosis resembles the low T_3 or "sick euthyroid" syndrome, common in many sick patients and normal subjects with caloric deprivation [4,5]. Thus, a low T_3 state in cirrhosis may reflect impairment of hepatic uptake and conversion of T_4 to T_3 due to diminished hepatocellular function or to reduced caloric intake. It may be considered as an adaptive hypothyroid state, which is important for preserving body protein stores [6]. We aimed to better understand the thyroid test abnormalities in patients with (DC) and ACLF compared to those without ACLF.

128 patients (91 [71.1%] males, median age of 61 [interquartile range 53–69] years) with DC were followed for a median of 91 (44–110) days. ACLF was diagnosed in 65 (50.8%) patients according to the CLIFF consortium criteria [2]. No patient had signs or symptoms of thyroid disease. Levels of free T_3 (FT_3) and free T_4 (FT_4) correlated inversely with the severity of liver disease as expressed by the MELD-Na score ($r = -0.482$ and -0.346, respectively, $p < 0.001$). On the contrary, there was no correlation of the thyroid-stimulating hormone (TSH) with the MELD-Na score.

Patients with ACLF compared to those without had significantly lower FT_3 (1.54 [1.18–1.88] *vs.* 2.00 [1.55–2.46], $p < 0.001$) and FT_4 levels (1.00 [0.83–1.19] *vs.* 1.14 [1.00–1.24], respectively, [$p = 0.005$]). TSH did not differ between the two groups. 42 (65%) and 18 (29%) patients had low FT_3 levels in the ACLF and non-ACLF group, respectively ($p < 0.001$). Patients with low FT_3 compared to those with normal FT_3 had significantly higher sequential-organ-failure-assessment (SOFA) (six [5–8] *vs.* five [4–7.25], $p = 0.023$). Patients with low FT_3 had a worse outcome as it is shown by the Kaplan Mayer survival curve (log rank $p < 0.042$) (Fig. 1). On the contrary, only nine patients, seven in the ACLF and two in the non-ACLF group, had low FT_4 levels ($p = 0.09$). Low FT_4 levels were not related to outcome.

It is not the first time that the sick euthyroid syndrome has been related to the prognosis of liver cirrhosis. In the past, low levels of the T_4 variant in the sick euthyroid syndrome were demonstrated to be a good predictor of decreased survival in liver cirrhosis and T_4 levels were inversely correlated with the CTP score [6]. In addition, low FT_3 levels were considered as indicators of poor prognosis in cirrhotics with non alcoholic liver disease [5]. However, the prognostic significance of low T_3 levels in the sick euthyroid syndrome have not been evaluated so far in the ACLF setting.

In conclusion, free T_3 levels are inversely correlated with the severity of liver disease and are significantly lower in patients with decompensated cirrhosis who developed ACLF. Sick euthyroid syndrome with low FT_3 levels was related to early mortality in patients with ACLF.

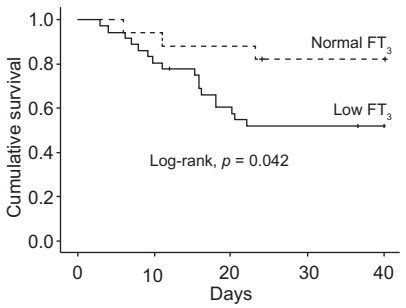

Fig. 1. Probability of survival in patients with low compared to normal FT_3 in ACLF group.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Low free T_3 levels are related to early mortality in patients with decompensated cirrhosis and acute-on chronic liver failure"

To the Editor:

We would like to thank Agiasotelli *et al.* for taking a keen interest in our recently published manuscript where we showed that serum ferritin is a predictor of early mortality in patients with decompensated cirrhosis [1]. Agiasotelli and colleagues demonstrate that low T_3 levels in patients with ACLF are associated with an increased mortality. We would like to clarify that our patient population was comprised of decompensated cirrhosis and not ACLF patients. Further, we did not use the CLIF definition for the diagnosis of ACLF [2,3].

We have looked into our cohort of patients with decompensated cirrhosis (n = 318, 257 males) and patients with ACLF (n = 148, 109 males), defined according to the APASL criteria [2] for abnormalities in thyroid function and their relationship to predictors of mortality [1]. Median (IQR) free T_3, free T_4, and TSH concentration were 2.3 (1.98–2.69) pg/ml, 1.04 (0.9–1.23) ng/L, and 2.47 (1.28–4.27) μIU/ml, respectively in the decompensated cirrhotic group. A significant inverse correlation of T_3 was noted with predictors of early mortality i.e. the MELD ($p = 0.0004$, −0.36) and CTP score ($p < 0.00001$, −0.43), hepatic encephalopathy ($p < 0.0001$, −0.46) and leucocyte counts ($p = 0.002$, −30). Interestingly, low T_3 levels also correlated with an increase in ferritin ($p = 0.007$, −0.27). Similar to the observation by Agiasotelli *et al.*, low T_3 was associated with decreased survival (log rank $p = 0.0003$), which was not observed for T_4 ($p = 0.5$) and TSH levels ($p = 0.6$) (Fig. 1 A–C). On multivariate analysis, however, low T_3 was not a significant predictor of mortality in our cohort.

On the contrary, median (IQR) free T_3, free T_4, and TSH concentration in patients with ACLF [2] were much lower as compared to patients with decompensated cirrhosis i.e. 1.9 (1.6–2.2; $p < 0.0001$) pg/ml, 0.96 (0.73–1.12; $p = 0.001$) ng/L, and 2.1 (0.65–3.5; $p = 0.01$) μIU/ml, respectively. Low free T_3 was noted in 89% *vs.* 64% ($p < 0.0001$), low T_4 in 16% *vs.* 4% ($p < 0.0001$) and low TSH was noted in 18% *vs.* 3.5% ($p < 0.0001$) of patients with ACLF, as compared to patients with decompensated cirrhosis, respectively. Interestingly, serum ferritin showed an inverse correlation with both free T_3 (r −0.18, $p = 0.012$) and TSH (r −0.234, $p = 0.03$). Also, in these patients, a significantly lower survival was noted with low T_3 (log rank $p = 0.005$), low T_4 ($p = 0.014$) as well as low TSH ($p = 0.001$) (Fig. 1D–F). This could be possible because within the first few hours of the critical illness, T_3 concentrations decrease due to decreased peripheral deiodination, while T_4 and TSH concentrations may increase or remain normal. However, if the illness becomes more protracted or severe, a decrease in the concentration of T_3, T_4, and TSH is caused by a decrease in TRH-release from the hypothalamus [4]. Our patients with ACLF, diagnosed as per APASL definition, have characteristically an acute liver failure–like presentation (not just acute decompensation) on a background of underlying chronic liver disease with a sudden and massive loss of functional hepatocytes and activation of the systemic inflammatory response syndrome that probably puts extra stress on the thyroid [2]. In our cohort, we also found patients with hepatorenal syndrome (HRS) with significantly lower free T_3 as compared to those with no HRS (2.19 ± 0.47 *vs.* 2.42 ± 0.62; $p = 0.04$). This is because the 5′-monodeiodinases, which produce T_3, the biologically active hormone, are also present in the kidney apart from the liver. Thus, our data suggest that low T_3 levels are frequent in patients with advanced