

The source of GGT in cystic fibrosis

doi:10.1111/j.1432-2277.2012.01573.x

The authors would like to thank Dr. Alfonso Pompella for initiating this valuable discussion on our manuscript [1]. We agree with Dr. Pompella that recent data support a clinical relevance for the assessment of gamma glutamyl transferase (GGT), exceeding its roles as a marker of liver and biliary disease. In a recent study, Dr. Pompella's group showed that in CF patients, GGT is increased several fold in the lung lining fluid [2]. Moreover, they have identified activated neutrophilic granulocytes as the source of GGT increase; neutrophils in fact contain GGT in their specific granules and may release it upon activation [3]. However, the main source of serum GGT is the liver, indicating a hepato-biliary dysfunction [4]. In terms of prognostic impact on nonhepatic diseases, the threshold of GGT values is much lower; therefore, the significant prognostic relationship of GGT and cardiac events was seen above serum levels of 40 U/l [5].

As our study was focused on the liver and its impact in the outcome of CF patients undergoing DLTX, we did not assess data on granulocyte counts and therefore we are not able to estimate correlation on this specific topic. However, we analyzed our data to support the liver as the main source for GGT, as preoperative GGT ranged from 5 to 513 U/l overall, with a median of 45 U/l in the group of long-time survivors and a median of 150 U/l in the group of patients with early mortality. Thus, most of the patients exhibit pathological elevated serum enzyme levels. Moreover, GGT was significantly correlated with

serum levels of alkaline phosphatase (ALP), with a *P*-value of 0.02 for the entire study population and 0.01 for the early-mortality group (Fig. 1). ALP is an enzyme in the cells lining the biliary ducts of the liver and ALP levels in plasma are known to rise with large bile duct obstruction, intrahepatic cholestasis, or infiltrative diseases of the liver. Neither leukocyte count, nor serum levels of CRP were correlated with GGT or ALP. Thus, elevated GGT serum levels in our cohort are most likely because of liver and/or biliary injury.

We agree with Dr. Pompella that in a cohort of CF patients, the assessment of hyperactive peripheral blood neutrophils to clarify the role of a hyperinflammatory state in outcome and prognosis of DLTX would be an interesting approach. We actually continue to collect data from more patients to validate our model and just recently included more inflammation-related data. Because of the fortunately rare disease, a registry in Europe would enhance the available patient numbers and thus help further improve our understanding and management of these patients.

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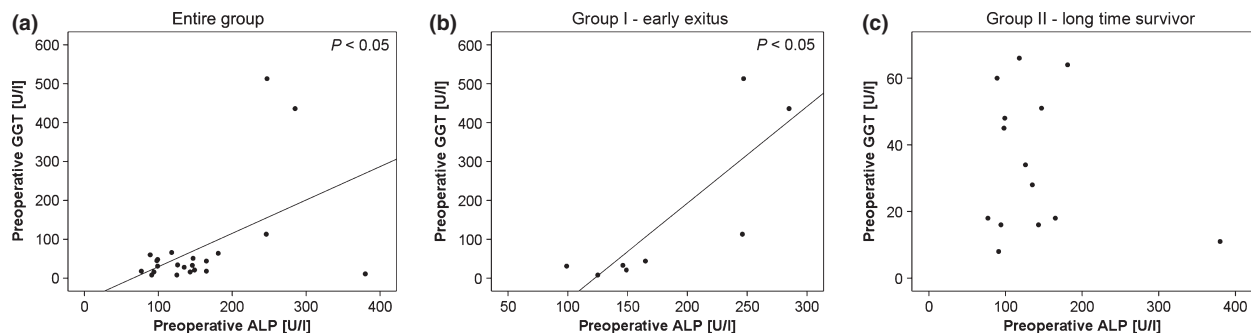


Figure 1 Preoperative elevated GGT levels are associated with ALP levels. (a) preoperative gamma glutamyl transferase (GGT) is associated with alkaline phosphatase (ALP) ($P < 0.05$); Analysis of subgroups revealed that a strong correlation was present in group I – early exitus – (b) and absent in the group of long-time survivors (c). For calculations of significances, Pearson's rank correlation coefficient was applied.

Conflicts of interest

AW, LPB, and AC have no conflicts of interest and are supported by the DFG and Wilhelm-Laupitz Foundation, Germany.

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