

Reply:

We read with interest the letter of Slieker et al. providing data from a cross-sectional evaluation of risk factors for cystic fibrosis liver disease (CFLD). The issue is controversial, and there is no agreement in the literature among the results obtained at different CF centers. One could even extend the list of conflicting data provided by Slieker et al. by mentioning the results from 2 recent reports on retrospective assessment of CF patients with end-stage liver disease undergoing liver transplantation^{1,2}: in both series there is a striking male predominance and transplantation had been performed in the pediatric age, making it unlikely that over-representation of males due to their survival advantage is the main explanation. In addition, in the series by Molmenti et al., frequency of a history of meconium ileus was as high as 80%.¹

Besides the effects of genetic or environmental factors that may condition different susceptibility for liver involvement in CF patients, heterogeneity of study design is another source of substantial disagreement in the ascertainment of risk factors for CFLD. For example, inconsistent identification of male sex as a risk factor, which Slieker et al. cited in their letter, may well result from biases inherent in retrospective designs that prevent any meaningful comparison between the available studies. As far as the role of history of meconium ileus is concerned, the concurrent effects of patient susceptibility and of the different approaches to assess risk factors may be even more difficult to disentangle.

Our long-term, prospective study³ was specifically aimed at evaluating the incidence and risk factors of CFLD in consecutive patients enrolled at time of CF diagnosis or of referral to the CF Center. Such design was chosen to overcome several flaws affecting studies that employed different, less robust formats—be they retrospective, retrospective-prospective, cross-sectional, or case-control ones. Results clearly show that, at least in CF populations similar to the Italian one, patients with a history of meconium ileus, male sex, or a severe genotype are exposed to higher risk of developing CFLD. Therefore, such patients should be considered for preferential inclusion in studies aimed at preventing this complication. The presence of substantial differences in the risk factors for CFLD among patients with different

genetic or environmental backgrounds seems of major interest and, if confirmed by properly designed studies, may foster our understanding of the disease.

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References

1. Molmenti E, Squires R, Nagata D, Roden J, Molmenti H, Fasola CG, et al. Liver transplantation for cholestasis associated with Cystic Fibrosis in the pediatric population. *Pediatr Transplant* 2003;7:93-97.
2. Gridelli B, Colledan M, Melzi ML, Adam R, Callegaro A, Valsecchi MG, Assale BM, et al. Liver transplantation for cystic fibrosis: preliminary results of a European survey. *Transplantation* 2002;74:190.
3. Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, Giunta A. Liver disease in Cystic Fibrosis: a prospective study on incidence, risk factors and outcome. *HEPATOLOGY* 2002;36:1374-1382.

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