LETTER TO THE EDITORS

Response to Ghinolfi *et al.*

Sebastian Pratschke[1], Andreas Bender[2] & Martin Angele[1]

1 Department of General, Visceral and Transplantation Surgery, Hospital of the University of Munich, Munich, Germany
2 Department of Statistics, Statistical Consulting Unit StaBLab, Ludwig-Maximilians-University, Munich, Germany
E-mail: sebastian.pratschke@med.uni-muenchen.de

Dear Sir,

The authors welcome the discourse presented by Ghinolfi *et al.* [1] and appreciate the opportunity to respond to their comments on the manuscript "Association between donor age and risk of graft failure after liver transplantation: an analysis of the Eurotransplant database" [2].

The aim of our study was to estimate the effect of donor age on the risk of graft failure in liver transplantation. We showed that donor age affects outcomes in a linear manner: Using continuous, noncategorized variables [3], the effect of age has no inflection point and does not increase more rapidly at a certain cut off. As our model includes all available confounders (including the recipients' age), the present results suggest that there is no donor age limit in liver transplantation which can be applied broadly to all patients. Interestingly, these results also demonstrate that using age groups (i.e. octogenarians) may be biologically irrelevant and mathematically misleading. Methods, exclusion criteria and limitations (i.e. a reduced significance because of the many exclusions) are clearly stated and reviewed in the manuscript [4–6] (https://github.com/adibender/liver).

The authors appreciate Ghinolfi's concerns on the exclusion of patients from the data set. In a large multinational dataset, such as the presented database of over 26 000 patients from eight countries, the benefits of multicenter, clinically representative data collection are gained, but some heterogeneity of data quality and completeness is introduced. In addition, the 14-year time span included in the study was witness to changes in the type of data entered in the data base. MELD based allocation was introduced by Eurotransplant in 2006, and so data in the Eurotransplant registry before this time point are incomplete for some values required to retrospectively calculate the score. In order to reflect current allocation practices, donors with missing MELD scores were excluded from our analysis. Further exclusions were made because of abnormal liver function tests (i.e. γGT > 1000 U/l) or prolonged intensive care (i.e. ICU stay >100 days). In our opinion, such extreme values are often implausible and may reflect documentation errors. We do not expect an association with certain donor groups. Although there may be regional differences in organ acceptance, grafts with such properties have not been transplanted at our center. From a statistical point of view, it must be stated that in contrast to univariate, observational data, it is essential for advanced multivariate analyses to exclude such data for the purpose of smooth modeling and these exclusions were also laid down in the manuscript.

Donor comorbidities such as diabetes mellitus or hemodynamic instability are important confounders for the outcome in liver transplantation. Unfortunately, these data were not available in the present Eurotransplant database and the authors agree with Ghinolfi that this information would be a welcome and clinically relevant extension of the database.

The authors greatly appreciate Ghinolfi's statement that "the search for a donor age upper limit to be used in clinical practice is rather controversial, since age should not be viewed as a contraindication *per se*, and age-related co-morbidities should lay the basis for a more granular score to serve for higher-to-unacceptable risk liver grafts". We agree. Our results demonstrate a linear age effect, which suggests that there is no age limit when considering all available confounders. Models as presented in our manuscript are the basis for new risk scores and they are capable to estimate an individual risk for liver grafts as postulated by Ghinolfi. Therefore, they potentially support individual decision-making in liver transplantation.

It is crucial to appreciate the strengths and limitations of statistical methods when applying data from large multivariate analyses. The authors agree that clinical experience varies between centers and that such

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qualitative aspects are difficult to account for in multicenter and multinational data. Therein lies a central challenge of regulating numerous individual centers treating clinically very individual patients. While it is possible to respond to this challenge with regulatory cut offs, such stand-alone cut offs are a relatively blunt tool and do not reflect the complexity of each individual scenario. Multifactorial models are a medically and also statistically appealing alternative, accounting for not just one, but rather many aspects of donor and recipient status.

Unicenter analyses demonstrate a center's experience in transplantation of EDC grafts. In contrast, multicenter analyses may be misbalanced by an inadequate influence of the participating centers. In an attempt to account for this problem, in the present study the center effect was analyzed for 53 transplant centers during the process of modeling indicating the general smooth and linear trends over the years, respectively using a Gaussian frailty term [7].

A propensity score matching analysis would have meant calculating with categorized data which – from a mathematical as well as a biological point of view – may be insufficient because of an imminent loss of information. The current statistical analysis therefore follows a different approach to estimate the effects of donor age on the outcome in liver transplantation using continuous instead of categorized variables thereby estimating an individual risk in liver transplantation. In general, matched analyses (if performed statistically sound) may yield comparable results with covariate adjusted models.

According to the strict exclusion policy of this analysis the number of octogenarian donors was reduced in our analysis. A less strict inclusion policy would have generated a lower quality of the statistical model and the portion of 3% reflects the raw data, which cannot be influenced. This share was also not reduced because of the exclusions and even in the final data set, our manuscript demonstrates one of the biggest series of octogenarian donors in liver transplantation in the literature. Nevertheless, it should be emphasized that categorizations (i.e. age groups, octogenarians etc.) may help to better understand the cohort but are *per se* irrelevant from a biological and statistical point of view.

As a conclusion, the present manuscript demonstrates a linear age effect in liver donors analyzing a large multicentric cohort. Using state of the art statistical methods, the model presented is capable of estimating an individual risk for any recipient/donor matching in liver transplantation.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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