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Implausible algorithm output in UK liver transplantation allocation scheme: Importance and implications of transparency in model-based decision making

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Algorithm-based allocation of resource-limited healthcare interventions is growing, however, concerns over transparency and bias have restricted its use.[1] Transparent algorithms can be readily explained, allowing patients and clinicians to clearly understand the basis for decision making.[2] In 2018, the Transplant Benefit Score (TBS) was introduced in the UK to allocate deceased donor livers to patients with chronic liver disease and primary liver cancer (hepatocellular carcinoma). Patients may also undergo transplantation for acute liver failure, although these patients are allocated organs via a different process. The TBS algorithm uses 7 donor and 21 recipient parameters to predict the difference in survival without transplantation (Need) to that after transplantation (Utility) for each potential recipient (TBS=Utility–Need).[3]Balancing the risk:benefit between patients with chronic liver disease (CLD) and patients with cancer, which typically arises on a background of CLD, is challenging.[4] National reports show that for the first three years of the TBS scheme (excluding the period when TBS offering was suspended due to COVID) patients with cancer were rarely allocated livers by the TBS model and that waiting list removals for death/deterioration were significantly increased compared to patients with CLD alone (relative risk = 1.58, 95% CI [1.22, 2.06]); Appendix 1).[5] We aimed to understand TBS-derived allocation decisions using deterministic simulation methods.

We simulated a cohort of CLD patients using rule-based methods which ensured plausible parameters for each individual (Appendix 2). Simulated patients meeting transplant criteria were analysed using three cancer scenarios (small (2cm), large (5cm), and multiple cancers). We compared TBS predictions, as well as US and EuroTransplant allocation scores, using repeated measures analysis.

17,046 simulated patients with CLD had similar characteristics to real world patients with chronic liver disease eligible for the liver transplantation waiting list (Supplementary Figure 1). Taking these simulated patients with CLD alone and adding cancer, counterintuitively reduced the probability of an organ offer being made. This resulted from the TBS prediction that cancer *improves* survival without transplantation (relative cancer effect (IQR): small= 2.08 (1.38-5.05); large=1.49 (1.00-3.78); multiple=2.07 (1.38-5.01)) (Figure 1A-C). The effect of cancer on survival prediction persisted across a range of donor parameters (Appendix 3). With increasing waiting time, patients with cancer were further disadvantaged (Figure 1D). In contrast USA and Eurotransplant models prioritised patients with cancer (Figure 1E-F).

The liver transplantation allocation algorithm used in the UK for over 4 years produced implausible predictions: that patients with chronic liver disease survive longer if they develop cancer. In so doing, the algorithm actively deprioritised patients with cancer. Under the USA and Eurotransplant models patients with cancer are given additional points (exception points), reflecting the fact that their liver disease severity markers (MELD-Na and MELD respectively) do not accurately predict the risk related to their cancer).[6, 7] Assumptions made by the Cox regression model used for TBS and biases within the data set may have contributed to the counterintuitive survival predictions seen in the UK liver allocation scheme (Appendix 4).

Concerns over allocation of livers to patients with cancer have been recognised by the UK liver transplant community and in October 2022 algorithm weightings were revised. The impact of these changes is not yet clear. Modelling survival of waiting list patients to generate allocation algorithms is challenging due to unmeasured confounding and the high frequency non-random censoring that occurs as patients are selected for transplantation. In addition, different timepoints for key variables included in

the TBS model and shorter follow-up for patients with cancer may have overestimated their survival (Supplementary Table 1). Simulation facilitates interrogation of algorithms and can identify limitations and errors ahead of clinical application. The addition of cancer resulting in a survival benefit, contrary to real-world experience, reflects limitations in the model rather than a novel insight. Algorithm-based allocation systems should not be introduced without extensive exploration and a deep understanding of the model. Comprehensive simulation of scenarios is essential to ensure a trustworthy and transparent algorithm that avoids implausible predictions directly impacting on patient care.

Author statement: All authors contributed to the design, analysis of results, drafting and revisions, and final approval of this letter.
Conflicts of interest: None
Funding received: None
Acknowledgements: Lisa Norman and Kelsey Pearson, Data Team, Edinburgh Transplant Centre

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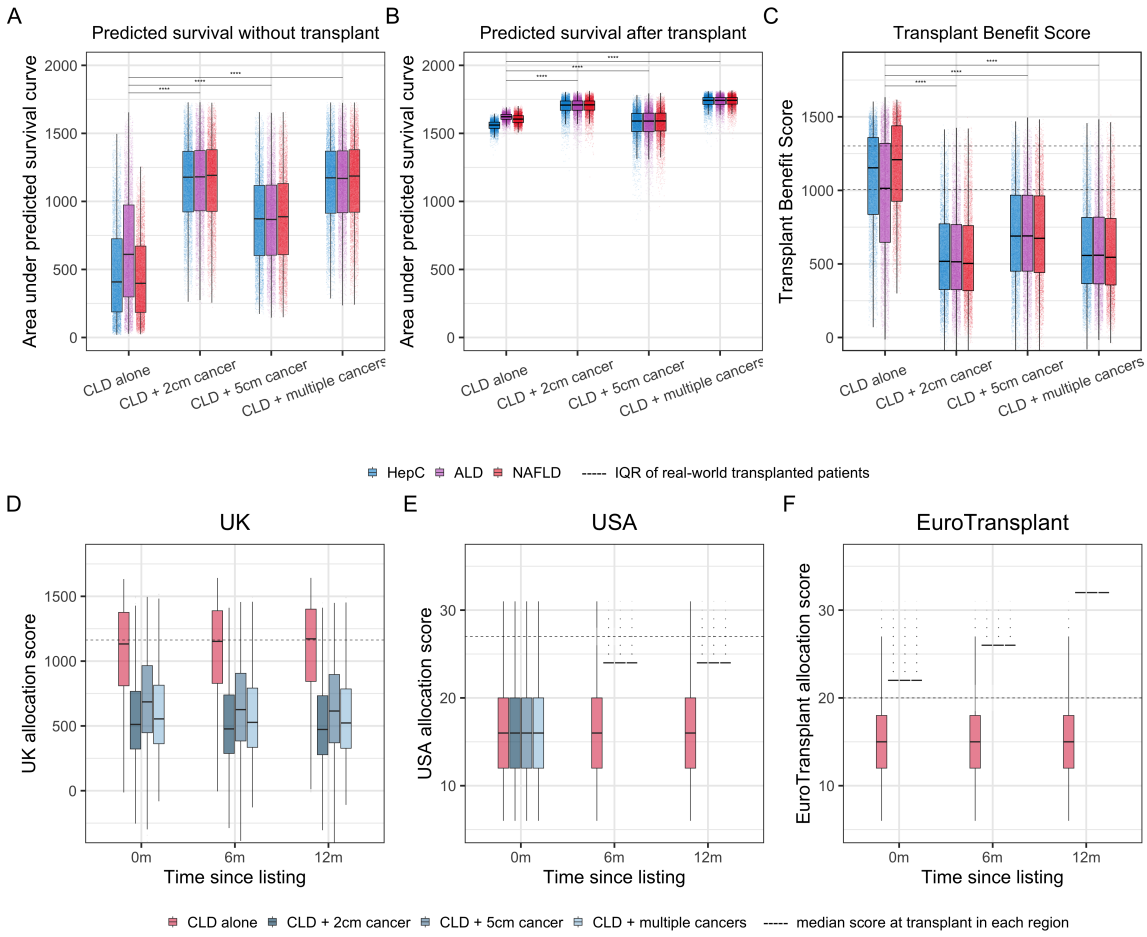

Figure 1: A-C: Boxplots showing area under predicted 5 year survival curve without transplant (Need), after transplant (Utility) and the Transplant Benefit Score (TBS = Utility – Need) for simulated patients (n= 17,046) with CLD alone and the same simulated patients with additional cancer. Interquartile range for real-world patients selected for transplantation by the TBS model are shown on **C)** as dashed lines. Overall repeated measures comparisons shown for CLD alone group versus cancer scenarios (Friedmann test). CLD disease types (HepC (n= 5744), ALD (n=5641), NAFLD (n=5661)) had significantly different Need, Utility and TBS scores in the CLD alone scenario ($p<0.001$), but no significant differences existed between disease types (HepC, ALD, NAFLD) for the cancer scenarios ($p>0.4$ for all comparisons). **D-F:** Comparison of scores for SimPatients subjected to CLD alone and cancer scenarios according to **D)** UK liver allocation model (Transplant Benefit Score), TBS reduced for simulated patients with cancer over 12 months (small cancer: -8%; large cancer: -10%; multiple cancers: -6%; $p<0.0001$), but increased over 12 months with CLD alone (+3.4%, $p<0.0001$); **E)** USA liver allocation model (MELD-Na + exception points for cancer and **F)** EuroTransplant liver allocation score (MELD + exception points for cancer for SimPatients with chronic liver disease and liver cancer (hepatocellular carcinoma) (see Appendix 2 for details). Median allocation score of real-world patients transplanted in each region is shown as dashed lines (UK: Transplant Benefit Score = 1155; USA = MELD-Na = 29; EuroTransplant MELD = 20). NB: the horizontal lines in the boxplots for the cancer scenarios in E and F are generated as patients with cancer in the US and Eurotransplant regions are awarded exception points up to the same level, so flattening the boxplot (see Appendix 2). ****$p<0.0001$. CLD= chronic liver disease; HepC= Hepatitis C; ALD = alcohol related liver disease; NAFLD = non-alcohol related fatty liver disease