# People who survive an episode of severe alcoholic hepatitis should be advised to maintain total abstinence from alcohol.

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Dear Sir,

We read with interest the article published in HEPATOLOGY by Louvet and colleagues (1) highlighting factors influencing outcomes in people with severe alcoholic hepatitis. They found that beyond six months, alcohol relapse, defined using a threshold of ≥30 g/day, was an independent predictor of mortality with a dose-related effect on the hazard ratio (HR). The effect of drinking behaviour on outcome has also been examined in data collected *via* the Steroids and Pentoxyfylline for Severe Alcoholic Hepatitis (STOPAH) trial (2). Patients were classified, in the original published analysis, as abstinent or drinking. A return to alcohol consumption at day 90 conferred significantly greater mortality at day 450 than abstinence (HR 2.77, 95% Confidence Intervals (CI) 1.79–4.29; $p$<0.00001). We have re-examined these data in an attempt to replicate the dose-dependent effect of drinking on mortality observed by Louvet and colleagues (1).

Participants enrolled in the STOPAH trial were treated for 28 days with prednisolone, pentoxifylline, both or placebo (3). Patients categorised their drinking behaviour at day 90 as (i) abstinent; or (ii) drinking daily at low levels: men ≤24g; women ≤16g; (iii) moderate levels: men >24 but ≤60g; women >16 but ≤40g; or (iv) high levels: men >60g; women >40g. The association between drinking behaviour and survival was examined using Cox proportional hazards regression analysis (2).

Data on drinking behaviour were available in 397 patients; of these 84 (9.7%) died by day 450. A total of 138 (35%) had returned to drinking; the distribution within the three drinking categories was reasonably even. There was a clear dose-dependent increased in the HR as drinking levels increased *viz*: low 2.09 (95% CI 1.13–3.88, P=0.02), moderate 3.00 (95% CI 1.69–5.35, P<0.001) and high 3.31 (95% CI 1.86–5.90, P<0.001) (Figure 1).

Thus, while Louvet and colleagues (1) found a dose-related effect on the HR for death above ≥30g/day, we have shown that a return to drinking, *at any level*, confers a dose-related increase in the risk of death. Our use of sex-specific drinking thresholds, based on our previous finding that sex is an independent risk factor for mortality in people with severe alcoholic hepatitis who return to drinking (2), contrasts with the French group's use of a generic drinking threshold; this may explain the difference in our findings.

Whilst alcohol relapse is clearly detrimental, people who survive an episode of severe alcoholic hepatitis and subsequently attain and maintain abstinence from alcohol still exhibit an appreciable mortality. We have shown previously that homozygosity for rs738409:G in *PNPLA3* is an independent risk factor for medium-term mortality in this population (2). Both this genetic variant and sex should be added to the risk factors identified by Louvet and colleagues as determinants of outcome in severe alcoholic hepatitis (1).

## References

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alcohol dependence, alcoholic hepatitis, alcohol-related cirrhosis, *PNPLA3*; survival; mortality, liver-related; alcohol relapse

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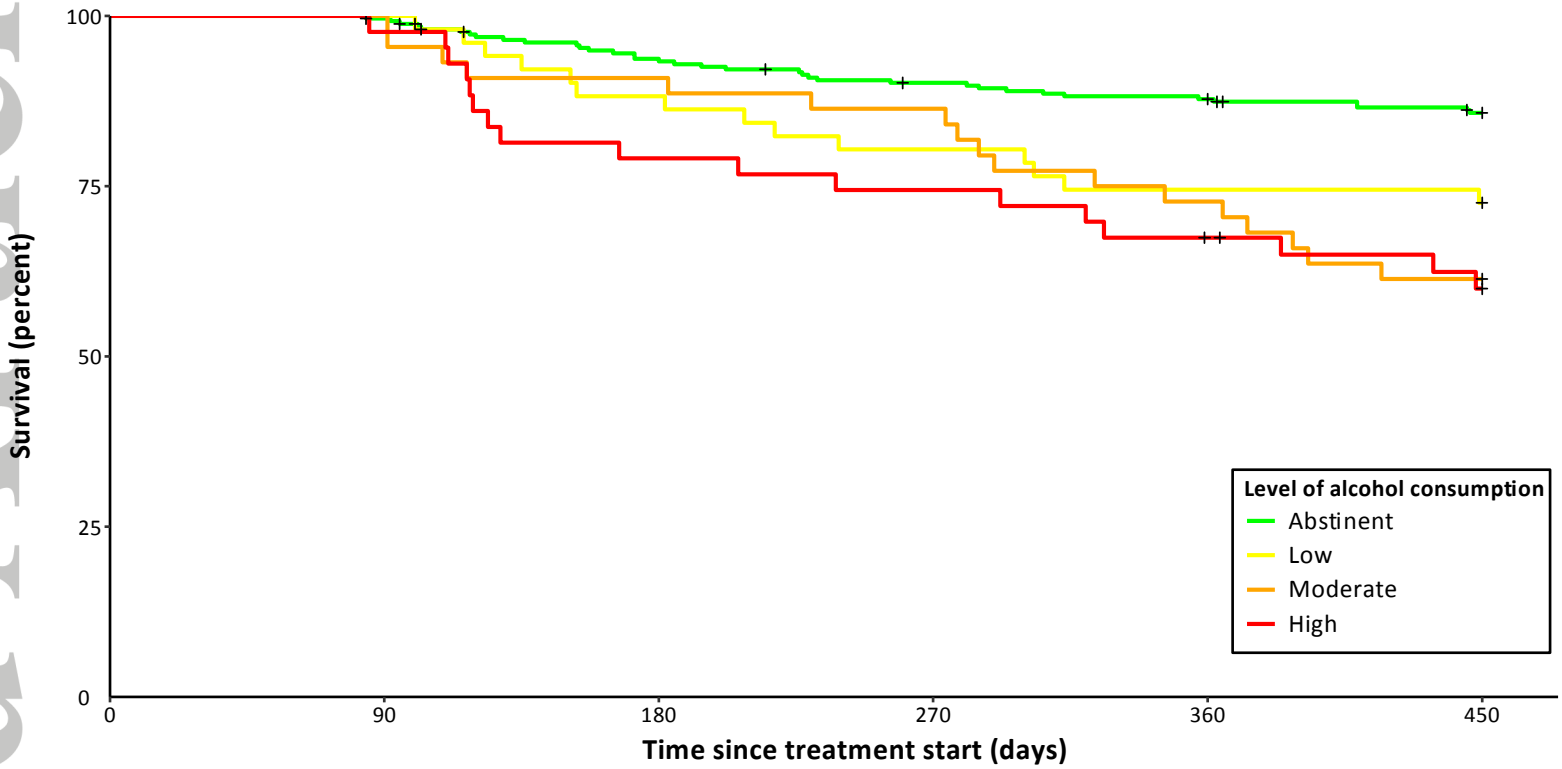
**Conflict of interest**

The authors have no conflicts of interest to declare

**Authors' contribution**

SRA performed statistical analyses and with MYM drafted and revised the manuscript. AQ, MYM and MRT recruited participants; all authors critically appraised the final manuscript.

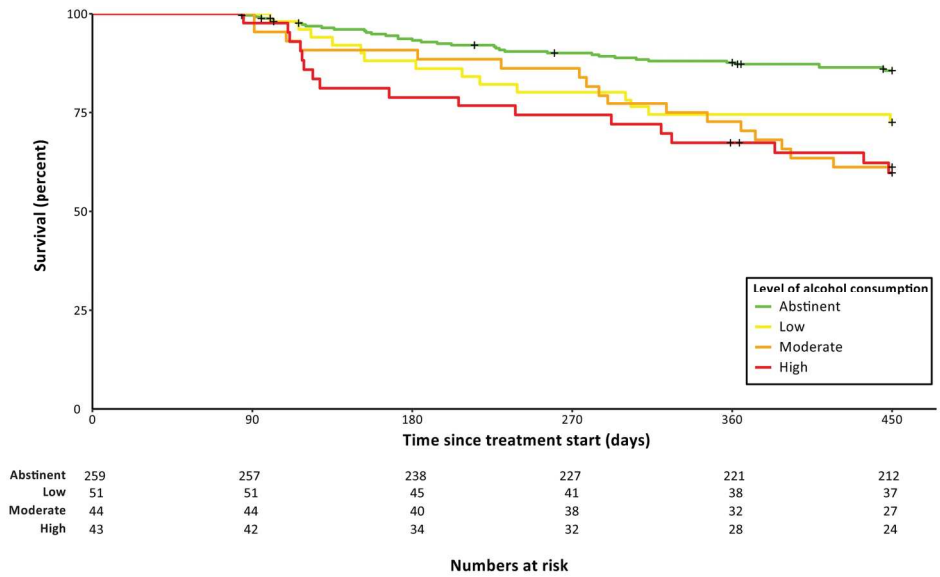



| | | | | | | |
|---|---|---|---|---|---|---|
| Abstinent | 259 | 257 | 238 | 227 | 221 | 212 |
| Low | 51 | 51 | 45 | 41 | 38 | 37 |
| Moderate | 44 | 44 | 40 | 38 | 32 | 27 |
| High | 43 | 42 | 34 | 32 | 28 | 24 |

**Numbers at risk**

## Figure legend

Figure 1. **Survival in patients with severe alcoholic hepatitis alive at 90 days, by subsequent drinking behaviour. Survival times, and mortality endpoints, were calculated with respect to the treatment start date or, if not recorded, the date of randomization; cases were censored at the time of liver transplantation, the limit of follow-up or day 450, whichever occurred first. Compared to abstinence a clear dose-dependent increase in the risk of mortality at day 450 is seen with low (HR 2.09, 95% CI 1.13 – 3.88, P=0.02), moderate (HR 3.00, 95% CI 1.69 – 5.35, P<0.001) and high-level alcohol relapse (HR 3.31, 95% CI 1.86 – 5.90, P<0.001).**

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