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Original article

Fast-track extubation after orthotopic liver transplant associates with reduced incidence of acute kidney injury and renal replacement therapy: A propensity-matched analysis

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Introduction

Liver transplantation is the only available definitive treatment for end-stage liver disease and subtypes of hepatocellular carcinoma. Patient outcomes have significantly improved alongside developments in surgical technique, peri-operative patient optimisation and post-transplantation management [1]. However, it remains a high risk procedure with significant morbidity and mortality attributable in the short term largely to surgical complications and rejection, and in the longer term to organ dysfunction and malignancy, often related to immunosuppressive medication [2,3]. Due to the challenges inherent to the surgical procedure, traditional post-operative management has been to maintain a period of clinical observation while the patient remains mechanically ventilated. However, several centres have demonstrated that a fast-track approach, with tracheal extubation carried out either in theatre or on arrival to the Intensive Care Unit (ICU), is safe in carefully selected patients, and has benefits of reduced ICU and hospital length of stay and their associated costs [4–7].

It has been hypothesised that there may also be clinical benefits to earlier tracheal extubation, relating to lower requirement for vasopressors to manage sedation-related hypotension and a shorter duration of positive pressure ventilation [8]. Theoretically, fast-track extubation (FTE) with shorter mechanical ventilation, could improve post-operative liver graft and renal perfusion. FTE may also confer a decreased risk of complications relating to mechanical ventilation such as ventilator associated pneumonia and muscle deconditioning [9]. Conversely, it can be argued that patients benefit from remaining intubated until clearly stable and at low risk of post-operative complications or early graft dysfunction [10].

A recent meta analysis of 3,573 patients across 20 studies demonstrated that early extubation associated with a lower rate of pulmonary complications and reintubation [11]. All four studies to date that have assessed the requirement for renal replacement therapy after early extubation have shown an outcome improvement [12,13], although only two were statistically significant [14,15]. Other studies that have addressed renal outcomes in early extubation cohorts have shown a reduction in the incidence of acute kidney injury (AKI) [12,15] although these were unmatched retrospective studies. Our previous work in this area found no difference in AKI outcomes but was not powered for this [16].

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Current evidence regarding patient benefit is limited and confounded by the challenge of retrospectively comparing patients who underwent early extubation to those who did not, with inherent selection bias. Our previous study was the first to investigate whether FTE associated with a direct clinical benefit to patients in a propensity matched study design. This demonstrated a statistically significant reduction in duration of vasopressor therapy in a case-control matched FTE group, with a trend towards reduced requirement for renal replacement therapy (RRT) [16]. The present study aims to investigate whether this trend is a true finding in a much larger patient cohort, and whether there is a reduction in AKI in this patient group.

Methods

Ethics

All data were collected retrospectively and anonymised, hence the need for ethical approval or individualized consent was not required by the Royal Free NHS Foundation Trust Research and Development Office.

Definitions

There is no universally accepted definition of what constitutes ‘early’ tracheal extubation in this patient group, with variation between centres and investigators up to 24 hours post-operatively [11]. In this study, we have defined fast-track extubation as up to 8 hours post-operatively. This is to recognise the challenges of early extubation on the ICU and determine if the benefits of FTE extend to those who may not have been thought appropriate for immediate post-operative extubation.

The Acute Kidney Injury Network (AKIN) criteria were applied for the severity of acute kidney injury. The presence of an AKI was defined as AKIN stage one or greater, using criteria for creatinine clearance and renal replacement therapy, but not urine output. Chronic kidney disease was judged according to estimated creatinine clearance (CrCl), as calculated with the Cockcroft-Gault equation26: CrCl = ([140 - age] $\times$ IBW)/(serum creatinine $\times$ 72) $\times$ (0.85 if female), where creatinine clearance is in millilitres per minute, age is in years, ideal body weight (IBW) is in kilograms, and serum creatinine is in milligrams per decilitre.

Data collection

Data were collected from all adult patients who underwent deceased donor liver transplantation from May 2016 to December 2019 at the Royal Free NHS Foundation Trust. Recipients who received domino or multiple organ transplants, or those who were transplanted for acute (ALF) or acute-on-chronic (ACLF) liver failure were excluded from the analysis. Patients who died intraoperatively or within 24 hours of transplantation were excluded. Patients undergoing re-transplantation were included as over 10% of these patients underwent fast-track extubation.

All patients were admitted directly to the intensive care unit post-operatively. The timing of extubation was determined by the anaesthetist in theatre or the intensive care team following transfer, guided by a protocol, as previously detailed [16]. The first line vasopressor intra- and post-operatively was noradrenaline (0.01-1 μg/kg/min) with vasopressor requirements presented here calculated from postoperative day zero. Extubation failure was defined as reintubation for a physiological deterioration (respiratory, cardiovascular, metabolic, neurological) as opposed to a facilitating a return to theatre.

Outcomes

The primary outcome for this study was the incidence of post-operative RRT. Secondary outcomes included the presence and severity of acute kidney injury, duration of vasopressor support, ICU and hospital length of stay, requirement for reintubation, mortality and dependency at three months following transplantation.

Statistical analysis

All patient and outcome metrics were non-normal (Kolmogorov-Smirnov test with Lilliefors significance correction). The Mann-Whitney U and chi-square tests were applied, as appropriate. An *a priori* sample size calculation was performed with a two-tailed Fisher's exact test for a 50% reduction in the primary outcome of post-operative RRT requirement from 21.2% in the non-FTE patients. This RRT incidence is based on our previous study in this patient group [16]. To generate a statistical power of 0.8 with an alpha error of 0.05 a sample size of 216 patients, with 108 in each group, was required. Analyses for renal outcomes excluded those patients on any form of pre-operative RRT and patients requiring post-operative RRT were defined as having AKIN 3.

To minimise the impact of confounding variables that would impact on both the decision to extubate a patient and their post-operative outcome we generated a propensity score for the likelihood that a patient would be fast-track extubated. This propensity score was developed using patient, operative and organ metrics and retained only those that independently associated with patient FTE. Binomial logistic regression analysis was performed using backward conditional elimination with stepwise entry and elimination probabilities of 0.05. The probability of FTE for each patient from this model was used to propensity match patients who underwent FTE after transplantation to those with a similar score, and thereby suitability for FTE, who were not extubated early. Patient matches were performed manually using one-by-one nearest neighbour propensity score matching with all patients matched to within 5% FTE probability. Risk factors included in the development of the propensity model are shown in Table 2.

Results

Data on 415 deceased donor transplant recipients were collected. Of these forty-seven patients were excluded; 33 due to transplantatation for ALF, six for ACLF, three sets of notes were incomplete, three patients died within 24 hours of surgery and two underwent domino transplantation. Of the remaining 368 patients, 157 were fast-track extubated (42.7%), with baseline characteristics shown in Table 1. Of those patients who underwent FTE, 83 were extubated in theatre while 74 were extubated within eight hours of ICU admission. Unmatched patients who underwent FTE were more likely to have a lower MELD and UKELD score, have a viral or cholestatic liver disease aetiology, have an HCC as the indication for the transplant, have a higher pre-operative creatinine clearance, receive an organ donated after cardiac death and undergo caval replacement surgery (Table 1). They were also more likely to have had shorter surgery, received less packed red cells, arrive in ICU during normal working hours and to have a lower APACHE II score.

Fast-track extubation propensity score

Data for the 368 patients were included in the binomial regression model to generate the FTE propensity score. Factors retained in the model, and hence independently associated with the decision to fast-track extubate, were the APACHE II score (OR 0.904, $p < 0.001$), arrival of the patient to the ICU in normal working hours (OR 2.644, $p < 0.001$) and the volume of red blood cell transfusion given

Table 1
Baseline data for all study patients

		Fast Track Extubation		
		No (n = 211)	Yes (n = 157)	Significance
Age (years)		57 (50, 61)	55 (48, 62)	0.421[a]
Body Mass Index (kg/m^2)		27.5 (23.8, 31.6)	26.1 (23.5, 29.1)	0.097[a]
MELD Score		14 (11, 19)	13 (9, 17)	0.013[a]
UKELD Score		53 (50, 57)	52 (49, 55)	0.005[a]
Aetiology	AIH	11 (5.2%)	6 (3.8%)	0.005[b]
	Alcohol	65 (30.8%)	39 (24.8%)	
	Cholestasis	33 (15.6%)	36 (22.9%)	
	NASH	34 (16.1%)	13 (8.3%)	
	Other	33 (15.6%)	17 (10.8%)	
	Viral	35 (16.6%)	46 (29.3%)	
Indication	Cirrhosis	125 (59.2%)	72 (45.9%)	0.008[b]
	HCC	19 (9%)	35 (22.3%)	
	HCC/cirrhosis	32 (15.2%)	24 (15.3%)	
	HPS	4 (1.9%)	6 (3.8%)	
	Other	24 (11.4%)	17 (10.8%)	
	Re-do Transplant	7 (3.3%)	3 (1.9%)	
Preoperative CrCl		92.2 (67.6, 112.9)	100.9 (75.8, 124.7)	0.010[a]
Pre-operative RRT		2 (1%)	1 (0.6%)	1.000[c]
Donor Age		50 (36, 61)	53 (38, 64)	0.162[a]
Organ Type	DBD	175 (82.9%)	117 (74.5%)	0.049[b]
	DCD	36 (17.1%)	40 (25.5%)	
Split Liver Graft		14 (6.6%)	8 (5.1%)	0.658[b]
Cold Ischaemic Time (hours)		8.2 (6.7, 9.5)	8.055 (7, 9.8)	0.993[a]
Caval Replacement Surgical Technique		64 (30.3%)	29 (18.5%)	0.001[b]
Graft Steatosis	None	116 (55%)	99 (63.1%)	0.288[b]
	Mild	77 (36.5%)	46 (29.3%)	
	Moderate	18 (8.5%)	12 (7.6%)	
Operative Time (hours)		7.9 (6.6, 8.9)	7.6 (6.3, 8.3)	0.047[a]
Intraoperative RBC Transfusion (units)		3 (1, 7)	0 (0, 3)	< 0.001[a]
Post-operative APACHE II Score		17 (14, 20)	14 (12, 17)	< 0.001[a]
Day-time ICU Admission		65 (30.8%)	81 (51.6%)	< 0.001[b]

Abbreviations: APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; UKELD, United Kingdom Model for End-Stage Liver Disease; AIH, auto-immune hepatitis; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome; DBD, donation after brainstem death; DCD, donation after cardiac death; RBC, red blood cell.
Values are medians (25%, 75% quartiles) and count (cohort percentage).
[a] Independent samples Mann-Whitney U test.
[b] Pearson chi-square test (two-sided).
[c] Fisher's exact test (two-sided).

intraoperatively (OR 0.823, p < 0.001). These were the same factors as incorporated in our previous model [16]. Therefore, each additional unit of packed red blood cells transfused intraoperatively associated with a 17.7% reduction in the likelihood of fast-track extubation. Similarly, each additional APACHE II score point reduced the likelihood by 9.6% while patients were 2.6-fold more likely to be fast-tracked extubated if they arrived in ICU during normal working hours. 216 patients, 108 in each cohort, were matched to within 5% of their FTE propensity scores. Hosmer and Lemeshow testing demonstrated a good model fit (p 0.774).

Propensity matched outcomes

The 216 patients in the propensity-matched analysis were well matched, with no significant differences between their baseline characteristics other than the time to extubation (Table 2). One patient who did not undergo fast-track extubation died on the ICU while a further two died before hospital discharge. No patients in the FTE cohort died before hospital discharge. A single patient in each cohort was reintubated on the ICU while two non-FTE patients and three fast-track patients returned to theatre during their primary ICU admission (Table 3).

The incidence of acute kidney injury on post-operative day one was significantly lower in the FTE group (36.4% vs. 23.4%, p 0.009) with a comparable reduction in the incidence of more severe degrees of AKI (Table 3). The incidence of AKI of any severity was not different on postoperative days three, five and seven, however. The need for post-operative RRT was significantly lower in the fast-track cohort (16.3% vs. 7.5%, p 0.046). Vasopressor support was needed for a longer period postoperatively in non-FTE patients (2 vs. 1 days, p < 0.001) in keeping with our previous findings [16]. ICU length of stay was shorter in the fast-track cohort by one day (4 vs. 3 days, p < 0.001) but there was no difference in the duration of hospital stay (16 vs. 14 days, p 0.059). Patient dependency at three months following transplantation was no different between the two groups.

Discussion

Main findings

This retrospective propensity matched case-control analysis demonstrates a reduction in the incidence of AKI on post-operative day one and a reduced requirement for RRT in patients who underwent fast-track extubation. The findings confirm our previous study, namely a significant reduction in ICU length of stay and duration of vasopressor therapy following transplantation [16]. There was a reduction in AKI of all severities on post-operative day one, but no significant difference in AKI incidence or severity on days 3, 5 and 7.

Discussion

Previous research into the safety and feasibility of FTE has demonstrated a possible link between prolonged post-operative ventilation following liver transplantation, acute renal failure and the need for

Table 2
Baseline data for propensity-matched patients

		Fast Track Extubation		
		No (n = 108)	Yes (n = 108)	Significance
Propensity Score		0.49 (0.37, 0.59)	0.49 (0.37, 0.59)	0.947[a]
Age (years)		57 (50.5, 63)	55 (49.5, 61.5)	0.456[a]
Body Mass Index (kg/m^2)		26.8 (23.4, 31.4)	25.9 (23.4, 29.1)	0.254[a]
MELD Score		14 (10, 19)	13 (10, 17)	0.644[a]
UKELD Score		53 (49, 56)	52.5 (49, 56)	0.307[a]
Aetiology	AIH	5 (4.6%)	4 (3.7%)	0.245[b]
	Alcohol	23 (21.3%)	29 (26.9%)	
	Cholestasis	22 (20.4%)	30 (27.8%)	
	NASH	19 (17.6%)	9 (8.3%)	
	Other	15 (13.9%)	10 (9.3%)	
	Viral	24 (22.2%)	26 (24.1%)	
Indication	Cirrhosis	56 (51.9%)	54 (50%)	0.572[b]
	HCC	15 (13.9%)	22 (20.4%)	
	HCC/cirrhosis	19 (17.6%)	12 (11.1%)	
	HPS	2 (1.9%)	4 (3.7%)	
	Other	14 (13%)	13 (12%)	
	Re-do Transplant	2 (1.9%)	3 (2.8%)	
Preoperative CrCl		94.0 (71.5, 114.8)	96.3 (73.6, 122.4)	0.350[a]
Pre-operative RRT		1 (0.9%)	1 (0.9%)	1.000[c]
Donor Age		51 (39, 61)	53 (38, 63)	0.679[a]
Organ Type	DBD	86 (79.6%)	78 (72.2%)	0.203[b]
	DCD	22 (20.4%)	30 (27.8%)	
Split Liver Graft		7 (6.5%)	4 (3.7%)	0.353[b]
Cold Ischaemic Time (hours)		8 (6.8, 9.2)	7.8 (6.8, 9.33)	0.906[a]
Caval Replacement Surgical Technique		31 (28.7%)	20 (18.5%)	0.078[b]
Graft Steatosis	None	61 (56.5%)	65 (60.2%)	0.631[b]
	Mild	42 (38.9%)	36 (33.3%)	
	Moderate	5 (4.6%)	7 (6.5%)	
Operative Time (hours)		7.6 (6.5, 8.8)	8.0 (6.6, 8.5)	0.970[a]
Intraoperative RBC Transfusion (units)		2 (0, 4)	1 (0, 4)	0.362[a]
Post-operative APACHE II Score		15 (12, 18)	15 (12, 18)	0.690[a]
Day-time ICU Admission		44 (40.7%)	40 (37%)	0.577[b]
Time to Extubation (hours)		16.3 (12.0, 23.5)	0.0 (0.0, 4.5)	< 0.001[a]

Abbreviations: APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; MELD, Model for End-Stage Liver Disease; UKELD, United Kingdom Model for End-Stage Liver Disease; AIH, auto-immune hepatitis; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome; DBD, donation after brainstem death; DCD, donation after cardiac death; RBC, red blood cell.
Values are medians (25%, 75% quartiles) and count (cohort percentage).
[a] Independent samples Mann-Whitney U test.
[b] Pearson chi-square test (two-sided).
[c] Fisher's exact test (two-sided).

RRT [12–15], but these studies were not matched nor powered for this outcome. This is the first matched study to demonstrate a reduction in the need for RRT following fast-track extubation after liver transplantation. In keeping with our previous work, the reduction in early AKI in FTE patients did not translate to a lower incidence of AKI after post-operative day one [16]. The lack of impact on renal failure beyond post-operative day one may stem from the fact that over 75% of non-FTE patients had been extubated by 24 hours.

While the improvements in renal outcomes in the FTE group are likely multi-factorial, enhanced renal perfusion will undoubtedly contribute. Positive-pressure ventilation, its effects on intra-thoracic pressure and right sided venous return and sedation-related hypotension and consequent need for vasopressor support will all diminish renal perfusion [17]. Our data, showing a one day reduction in the duration of vasopressor and sedation exposure, support this hypothesis. A similar argument can be made for the liver graft and evidence supports post-operative ventilation negatively affecting graft perfusion and oxygenation [18–20]. Hence, we recommend that future studies in FTE should examine markers of hepatic and renal perfusion, function and reperfusion injury.

There is significant heterogeneity between centres in defining what constitutes FTE and there is no universal definition of early extubation. A consensus definition may be valuable in order to improve the comparability between results from different centres. Here, we have included patients who were extubated up to 8 hours post-operatively, showing that outcomes such as reduced length of ICU stay, duration of vasopressors and incidence of AKI and need for RRT hold true in this patient group. This is not an endorsement to routinely ventilate patients for this length of time, especially given that the majority of patients in our study group were extubated within 4 hours. Rather, we propose that the benefits of FTE can be maintained even in patients who may have not been thought appropriate for extubation immediately post-operatively.

Our propensity model showed that arrival to the ICU within normal working hours was a significant predictor for early extubation, which may reflect reluctance to extubate a patient in an environment where there are fewer senior airway-trained staff available should complications arise. In our analysis we have defined a failure of extubation as reintubation for reasons unrelated to need for further operative intervention, which we acknowledge may underestimate extubation failure in those patients whose return to theatre was accompanied by physiological deterioration. However, the rates of reintubation, return to theatre and mortality in both cohorts in this study do not support routinely keeping patients intubated due to concerns over post-operative complications or unplanned return to theatre, as the need for reintubation was low in both groups.

Based on the findings of this study, the reduction in need for RRT, ICU length of stay and duration of ventilation, FTE would be associated with an estimated cost saving of £5,817 per patient [21]. Additional cost savings and patient outcome benefits would be anticipated from the avoidance of acute kidney injury and the need for additional central venous catheters for RRT with the associated complications.

Table 3
Outcome data for propensity-matched patients

			Fast Track Extubation		
			No (n = 108)	Yes (n = 108)	Significance
Reintubated			1 (0.9%)	1 (0.9%)	1.000[c]
Return to Theatre			2 (1.9%)	3 (2.8%)	1.000[c]
AKIN ≥ 1	Day 1 Post-op		39 (36.4%)	25 (23.4%)	0.009[b]
	Day 3 Post-op		18 (17.8%)	17 (16.2%)	0.755[b]
	Day 5 Post-op		11 (10.5%)	17 (15.9%)	0.245[b]
	Day 7 Post-op		16 (15.7%)	13 (12.3%)	0.476[b]
AKIN ≥ 2	Day 1 Post-op		29 (27.4%)	16 (15%)	0.027[b]
	Day 3 Post-op		17 (16.8%)	14 (13.3%)	0.483[b]
	Day 5 Post-op		11 (10.5%)	6 (5.6%)	0.192[b]
	Day 7 Post-op		11 (10.8%)	6 (5.7%)	0.178[b]
RRT Post-op			17 (16.3%)	8 (7.5%)	0.046[b]
Duration of RRT (days)[d]			5 (2, 6)	3 (2, 5)	0.215[a]
Duration of Vasopressor (days)			2 (1, 2)	1 (0, 1)	< 0.001[a]
ICU Length of Stay (days)			4 (3, 6)	3 (2, 4)	< 0.001[a]
Death on ICU			1 (0.9%)	0 (0%)	0.316[c]
Readmission to ICU			11 (10.3%)	14 (13.2%)	0.507[b]
Hospital Length of Stay (days)			16 (12, 23)	14 (11, 19)	0.059[a]
Death before Hospital Discharge			3 (2.8%)	0 (0%)	0.081[c]
Dependency at three months postoperatively		1	66 (64.1%)	59 (58.4%)	0.219[c]
		2	23 (22.3%)	25 (24.8%)	
		3	9 (8.7%)	16 (15.8%)	
		4	3 (2.9%)	0 (0%)	
		5	2 (1.9%)	1 (1%)	

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; RRT, renal replacement therapy; ICU, intensive care unit. Dependency: 1, able to carry out normal activity without restrictions; 2, only restricted in physically strenuous activity; 3, can move freely, capable of self care, but unable to do any form of work; 4, only capable of limited self care, confined mostly to bed or chair; 5, completely reliant on nursing/medical care.
Values are medians (25%, 75% quartiles) and count (cohort percentage).
[a] Independent samples Mann-Whitney U test.
[b] Pearson chi-square test (two-sided).
[c] Fisher's exact test (two-sided).
[d] Duration of RRT within subgroup of patients who received RRT.

Strengths and limitations

Due to the volume of transplants performed at our centre each year (141 in 2019-2020 [22]), patients in our study had a wide range of indications for orthotopic liver transplantation. As a result, our findings are likely to be widely applicable to other centres, including patients transplanted for HCC and re-transplantation. Patients were operated on using both widely used surgical techniques (traditional caval replacement and piggyback) and received liver grafts from either donation after brain or cardiac death of which some were split prior to implantation.

This was a retrospective observational study, limiting the authors' conclusions to association and not causation. In addition, only 108 of 157 patients in this cohort who were extubated within the defined timeframe could be matched to 108 control patients, reducing the total number of patients in the case-control analysis. Although the comparable baseline characteristics of our matched populations indicates that our modelling has resulted in two well matched groups (Table 2), we acknowledge that there may have been other variables which were not accounted for in this model. However, our model goodness-of-fit measures suggest we have accounted for a large proportion in the outcome variability.

The analysis of post-transplant AKI is limited by the use of serum creatinine measurements only to define the degree of kidney injury, and does not account for definitions of AKI based on hourly urine output. As a result, the numbers of patients with different stages of AKI in both the conventional and fast track groups may have been underestimated. The decision not to use urine output in this setting is based on its poor of reliability as a marker of AKI acutely post-transplant.

This study was designed to investigate immediate post-operative outcomes; we are limited in our ability to comment on long term outcomes in this patient cohort from the data we have presented. The reduction in post-operative AKI, vasopressor requirements and ICU length of stay did not confer any statistically significant reduction in overall hospital length of stay or dependency at 3 months. We note the vast majority of patients from both cohorts had a dependency level of 1 or 2 at 3 months, as one might hope if patients have been appropriately selected and pre-assessed for an elective operation. However, there were a small number of patients, largely in the non-FTE group, that had a dependency of 4 or 5, which did not reach statistical significance. Future research is needed to further investigate outcomes in these cohorts with respect to need for re-hospitalisation and long term renal outcomes.

Due to a lack of living donor liver transplants performed at our centre these patients were not studied, and whether our results hold true in this population may be an area for future research. Our results are unlikely to be applicable in patients undergoing status 1 or 'superurgent' transplantation due to ALF or ACLF, due to the high probability of high-grade hepatic encephalopathy and organ dysfunction immediately prior to surgery in this patient group, which would make FTE inappropriate.

Conclusion

This work reinforces the findings from our previous study that FTE is as safe as conventional ventilatory weaning following liver transplant in appropriately selected patients. It also associates with significant clinical benefits to patients and reduced resource utilisation due to reduced organ support requirements and therefore a reduction in the length of ICU stay. Further trials are needed to investigate other potential benefits for this intervention, such as effects on early graft function.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.liver.2022.100137.

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