Auxiliary Partial Orthotopic Liver Transplantation for Monogenic Metabolic Liver Diseases: Single-Centre Experience

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Abstract Purpose: Auxiliary partial orthotopic liver transplantation (APOLT) in metabolic liver disease (MLD) has the advantage of correcting the metabolic defect, preserving the native liver for gene therapy in the future with the possibility of withdrawal of immunosuppression.

Methods: Retrospective analysis of safety and efficacy of APOLT in correcting the underlying defect and its impact on neurological status of children with MLD.

Results: A total of 13 APOLT procedures were performed for MLD during the study period. The underlying aetiologies being propionic acidemia (PA)-5, citrullinemia type 1 (CIT1)-3 and Crigler-Najjar syndrome type 1 (CN1)-5 cases respectively. Children with PA and CIT1 had a median of 8 and 4 episodes of decompensation per year, respectively, before APOLT and had a mean social developmental quotient (DQ) of 49 (<3 standard deviations) as assessed by Vineland Social Maturity Scale prior to liver transplantation. No metabolic decompensation occurred in patients with PA and CIT1 intraoperatively or in the immediate post-transplant period on protein-unrestricted diet. Patients with CN1 were receiving an average 8–15 h of phototherapy per day before APOLT and had normal bilirubin levels without phototherapy on follow-up. We have 100% graft and patient survival at a median follow-up of 32 months. Progressive improvement in neurodevelopment was seen in children within 6 months of therapy with a median social DQ of 90.

Conclusions: APOLT is a safe procedure, which provides good metabolic control and improves the neurodevelopment in children with selected MLD.

Introduction

Auxiliary partial orthotopic liver transplantation (APOLT) is a surgical procedure where a portion of native liver is removed and a partial liver graft is placed in the space created (Reddy et al. 2017; Rela et al. 2016). This is in contrast to standard orthotopic liver transplantation (OLT) where the whole liver is removed and replaced with an allograft. APOLT is an excellent option in selected cases of acute liver failure, where the native liver can regenerate and immunosuppression withdrawn; its utility in metabolic liver disease (MLD) is still being criticized due to complexity of surgical technique and a continued need for immunosuppression (Reddy et al. 2017; Rela et al. 2016). Here, we report our experience with APOLT for selected MLD.

Materials and Methods

Clinical data of children who underwent APOLT for MLD over a period of 9 years (July 2009–May 2018) at Institute of Liver Disease and Transplantation was retrospectively analysed. The criteria for patient selection, operative procedure of APOLT and refinements in operative techniques for APOLT for MLD have been described in detail previously (Reddy et al. 2017; Rela et al. 2013, 2016; Kaibori et al. 1998).

Clinical records of these patients were reviewed to collect the following data: indications for performing APOLT, gender, age at onset, symptoms at presentation, type of feeds, mode of feeding, total number of metabolic decompensations, frequency of hospitalizations, need for invasive ventilation, haemodialysis, pre-transplant neurological status and status of metabolic control prior to transplant. Data was also collected about time from onset of disease to APOLT, ABO-blood-type matching, graft types, graft-to-recipient weight ratio (GRWR), donor demographics, postoperative complications, day of initiation of normal feeds, metabolic decompensations in the post-transplant period, immunosuppressive therapy, incidence of rejection and duration of follow-up.

Primary endpoints were patient survival, graft survival and graft function. Secondary endpoints were the improvement of developmental quotient (DQ), the number of episodes of metabolic decompensation in patients with PA and CIT1 and the need for phototherapy in children with CN1. Developmental status was assessed using developmental screening test (DST) and Vineland Social Maturity Scale (VSMS) prior to and 6 months after APOLT (in PA and CIT1). Disease severity (DS), metabolic status (MS), neurological status (NS) and quality of life were assessed by grading scales used previously to compare children with liver-based metabolic disorder as shown in Table 1 (Morioka et al. 2005a, b).

Table 1 Grading scales to evaluate disease severity, metabolic status and neurological status and classifications of quality of life (used with permission from Morioka et al. 2005a, b)

Severity of the disease (DS):

Grade 4: Many episodes of severe hyperammonemic coma, some with $\text{NH}_3^a > 300 \mu\text{mol/L}$

Grade 3: One to several episodes of hyperammonemic coma, no more than one with $\text{NH}_3^a > 300 \mu\text{mol/L}$

Grade 2: One to few episodes of hyperammonemic coma, none with $\text{NH}_3^a > 300 \mu\text{mol/L}$

Grade 1: Only one episode of hyperammonemic coma, with $\text{NH}_3^a < 300 \mu\text{mol/L}$

Grade 0: No episodes of hyperammonemic coma, no $\text{NH}_3^a > 300 \mu\text{mol/L}$

Metabolic status (MS):

Grade 4: No improvement, severe hyperammonemia and need for constant, full doses of medication

Grade 3: Some improvement, moderate hyperammonemia and need for constant medication

Grade 2: Major improvement, moderate hyperammonemia and need for some medication for control

Grade 1: Almost complete correction, occasional hyperammonemia and with or without need for medication

Grade 0: Completer correction, no hyperammonemia and no need for medication

Neurological status (NS):

Grade 5: Persistent coma or vegetative state

Grade 4: Responds to noxious stimuli, but no social interaction, no ambulation and no communication

Grade 3: Limited social interaction, no bipedal ambulation and limited communication through gestures

Grade 2: Definite social interaction and fair ambulation, though possibly limited by spasticity

Grade 1: Good social interaction and full ambulation but perhaps partially impaired gross and fine motor skills and use of language, mildly delayed development and only modest learning deficits

Grade 0: Seems to be normal spectrum for social interaction, motor skills and language development and learning

Quality of life:

Excellent: Receiving one or no immunosuppressive drugs and all the above grading scales corresponding to a score of 0

Good: Receiving two or more immunosuppressive drugs and all the above corresponding to a score of 0

Fair: Regardless of the number of immunosuppressive drugs each patient received, one or more of the above scales corresponding to a scale to 1

Poor: With any episodes of graft dysfunction to necessitate frequent or long hospital stay regardless of their causes and/or one or more of the above scales corresponding to a score of 2 or more

^a NH_3 serum ammonia level, $\mu\text{mol/L}$ micromoles/litre

Statistical Methods

Chi-square testing was used to compare categorical variables, while comparisons of continuous variables were performed with the *t* test and Mann-Whitney U test. SPSS commercial statistics software was used for all statistical analyses (PASW Statistics ver. 18.0; IBM Co., Armonk, NY, USA). The *p*-values less than 0.05 were considered to be significant. Values were reported as medians and ranges unless stated otherwise.

Results

During the study period, a total of 291 children below 18 years of age underwent liver transplantation (LT), of which 13 APOLT procedures were performed for MLD. The underlying MLD were propionic acidemia (PA) in five, citrullinemia type 1 (CIT1) in three and Crigler-Najjar syndrome type 1 (CN1) in five patients. Details of three patients have been reported previously (Shanmugam et al. 2011; Govil et al. 2015).

Patient Characteristics

Propionic Acidemia (*n* = 5) and Citrullinemia Type 1 (*n* = 3)

These two diseases are grouped together for discussion as both are disorders of amino acid metabolism with elevated ammonia during decompensation and similar medical management during decompensation. The age of presentation ranged from 3 to 6 days after birth, with a median of 3 days. All children with CIT1 and three patients with PA presented with a history of poor feeding, encephalopathy, acidosis and hyperammonemia. Two patients with PA were diagnosed prenatally by genetic assay (patients 2 and 3). Seven patients (58%) had fatal family history due to MLD.

All children with PA and CIT1 were on protein-restricted feeds prior to APOLT. Patients 4 and 8 were on supportive nasogastric feeds. Difficulty in procuring special feeds was a significant concern for Indian patients prior to LT since it had to be imported and was expensive. In the PA subgroup, three were on carnitine, two were on sodium benzoate and all received carnitine and biotin, prior to APOLT. All patients with CIT1 were on arginine and sodium benzoate.

Indications for APOLT in PA and CIT1 were frequent metabolic decompensations, poor quality of life, diet restriction and delayed development in all except one. Patient 3 did not have any metabolic decompensation prior to LT and had normal developmental milestones, but parents opted for LT since caring for the child was restricting the quality of life of the parents and siblings.

Patient 1 with PA had dilated left ventricle (LV) with hypokinesia (LV ejection fraction – 45%) and hypertension.

Crigler-Najjar Syndrome Type 1 (*n* = 5)

The median serum bilirubin value prior to transplantation was 393 µmol/L (range 325–496 µmol/L) in spite of 8–15 h of phototherapy daily. Patients 10 and 11 had normal developmental milestones but were taken up for APOLT because it was difficult to restrict children under phototherapy. Patient 9 had normal milestones while on phototherapy but developed bilirubin encephalopathy at the age of 1.5 years during an episode of intercurrent infection. During that episode, he required mechanical ventilation due to refractory seizures, following which he had developmental delay. Patients 12 and 13 had developmental delay with poor social skills.

APOLT Procedure

The age of patients at APOLT ranged from 8 to 264 months, with a median of 32 months. All transplants were performed as left auxiliary liver transplants. Patient 11 with CN1 received a domino auxiliary graft from patient 5 with propionic acidemia (Govil et al. 2015). All patients underwent intraoperative portal flow modulation as previously described (Reddy et al. 2017; Shanmugam et al. 2011; Rela et al. 2015). None of the patients developed portal steal phenomenon in the immediate post-transplant period. The median duration of hospital stay after transplantation was 18 days (range 14–45 days). The pre-/post-APOLT demographics and follow-up data are summarized in Table 2.

Post-transplant Course

The immediate postoperative period was uneventful with no episodes of metabolic or hepatic decompensation in children with PA and CIT1 except for patient 5. All children received total parenteral nutrition for first 3–5 days with 1 g/kg of bodyweight of protein until enteral feeds were started with close monitoring of serum ammonia and amino acid levels. Enteral protein supplements were gradually increased to unrestricted diet over a period of 5 days with monitoring of ammonia. All children were on normal diet/standard formula intake by the 10th postoperative day. Facilitating oral intake was difficult in many children since they were on enteral tube feeds and were not used to the taste and texture of normal diet. Patient 4 was on nasogastric feeds 6 months after APOLT due to feeding difficulties.

The postoperative recovery was uneventful in all patients with CN1. Serum bilirubin levels normalized within 6 days

Table 2 Characteristics of APOLT for metabolic liver disease

Case	Diagnosis	Sex	Metabolic decompensations (per year)	Pre-transplant complications	Age at APOLT (months)	LDLT/DDLT	Type	Graft weight	GRWR	Donor	Follow-up (months)	DQ Pre/post APOLT	Pre-transplant status ^a (DS/MS/NS)	Status at the latest evaluation ^a (DS/MS/NS)	Quality of life at the latest evaluation ^a	Outcome
1	PA	Male	8–10	Mechanical ventilation (twice) Pancytopenia Septicaemia	55	LDLT	LLS	254	1.7	Uncle	50	44/90	4/4/3	0/0/0	Excellent	Alive
2	PA	Male	4–6	Mechanical ventilation (twice) Pancreatitis Septicaemia	21	LDLT	LLS	231	2.1	Father	31	26/65	4/4/2	0/0/0	Excellent	Alive
3	PA	Male	0	Neutropenia	8	LDLT	LLS	191	1.7	Uncle	34	100/100	0/0/0	0/0/0	Excellent	Alive
4	PA	Female	4–5	Developmental delay	33	LDLT	LLS	355	3.9	Mother	19	56/94	4/4/3	0/0/1	Fair	Alive
5	PA	Male	3–4	Developmental delay Seizures	38	LDLT	LLS (graft reduction)	231	2.3	Mother	36	38/86	4/4/4	0/0/0	Excellent	Alive
6	CTT1	Male	3	Pancytopenia Developmental delay	23	DDLT	LLS	245	2.9	Cadaveric	40	22/68	4/4/3	0/0/1	Fair	Alive
7	CTT1	Female	1	Seizures	39	LDLT	LLS	320	3.7	Mother	20	95/105	0/0/1	0/0/0	Excellent	Alive
8	CTT1	Male	2–3	Developmental delay	32	DDLT	LLS			Cadaveric	19	54/90	4/4/3	0/0/0	Excellent	Alive
9	CN1	Male	NA	Developmental delay Extrapyramidal syndrome	22	LDLT	LLS (graft reduction)	233	2.6	Mother	13	85/100	NA/NA/4	NA/NA/1	Fair	Alive
10	CN1	Female	NA	Nil	26	LDLT	LLS	248	2.4	Mother	21	Not available	NA/NA/0	NA/NA/0	Excellent	Alive
11	CN1	Male	NA	Nil	49	LDLT	Left lobe	233	2.3	Domino auxiliary from patient 5	36	100/100	NA/NA/0	NA/NA/0	Excellent	Alive
12	CN1	Female	NA	Cerebellar involvement Speech delay	264	DDLT	LLS	385	2.6	Cadaveric	99	100/100	NA/NA/1	NA/NA/1	Fair	Alive
13	CN1	Male	NA	Speech delay, hyperactivity	96	LDLT	LLS	247	0.47	Mother	5	Not available	NA/NA/0	NA/NA/0	Excellent	Alive

PA propionic acidemia, CTT1 citrullinemia type 1, CN1 Crigler-Najjar syndrome type 1, NA not applicable, APOLT auxiliary partial orthotopic liver transplantation, LDLT living donor liver transplantation, DDLT deceased donor liver transplantation, LLS left lateral segment, GRWR graft-to-recipient weight ratio (%), DQ developmental quotient, DS disease severity, MS metabolic status, NS neurological status

^a Assessed by grading scales or classified into subgroups as shown in Table 1 (used with permission from reference) Morioka et al. 2005a, b

after APOLT (range 3–7 days), and none of the children required phototherapy after surgery.

Immunosuppression Post-APOLT

All patients were on standard immunosuppression with tacrolimus and steroids as per our unit protocol. Trough tacrolimus levels were maintained between 10 and 12 nanogram/millilitre (ng/mL) in first 3 months, 8–10 ng/mL for next 6 months and 5–7 ng/mL later on. Steroids were started at 2 mg/kg and then tapered to 1 mg/day (same dose for all patients) over the next 3 weeks. Children were monitored for rejection based on aminotransferase level elevation. Any elevated levels were evaluated with tacrolimus level, Doppler ultrasound to evaluate preferential graft portal perfusion and biopsy of the native and graft liver. Rejection confirmed by biopsy was treated with intravenous methyl prednisolone for 3–5 days followed by oral taper to 1 mg/day.

Post-transplant Complications

Four children had six episodes of histologically proven steroid-responsive acute cellular rejection. The first episode of rejection occurred after a median of 35 days (range 22–70 days). Patient 5 had two more episodes of steroid-responsive rejection 114 days and 180 days after APOLT. None of the rejection episodes were associated with metabolic decompensation.

One child with PA (patient 5) was diagnosed with hepatic artery thrombosis on the 6th postoperative day. He underwent immediate surgical revascularization and made a complete recovery. Over a follow-up period of 30 months, his graft function remains good.

Patient 3 with PA had an episode of high ammonia without encephalopathy during an episode of intercurrent illness 9 months after APOLT. A segmental portal vein embolization of the native liver was performed to cause segmental atrophy of the native liver and facilitate compensatory hypertrophy of the graft. This rapidly corrected the metabolic abnormality, and the child has remained asymptomatic without further episodes of decompensations with good graft function over 29 months of follow-up.

Patient 8 with CIT1 developed gastrointestinal post-transplant lymphoproliferative disorder 6 months after APOLT. He was managed with immunosuppression withdrawal and rituximab. There were no episodes of rejection or metabolic decompensation during the time period. He recovered well, immunosuppression was reintroduced 6 months later and he is presently on regular follow-up with good graft function and disease in remission.

Follow-Up

We have 100% graft and patient survival at a mean follow-up of 32 months (range 5–99 months). All children with PA and CIT1 had metabolic cure of hyperammonemia and are on unrestricted diets. Carnitine supplementation was stopped in patient 1 resulting in low serum-free carnitine and elevated acyl carnitine levels and so was restarted. All other children with PA were continued on carnitine and biotin supplementation. Cardiomyopathy and hypertension in patient 1 did not progress after liver transplantation, and the patient has remained stable on follow-up of 50 months. He continues to take digoxin for cardiac problem and lisinopril for hypertension.

All three children with CIT1 had serum citrulline levels of more than 2,000 $\mu\text{mol/L}$ before transplant that has reduced to 300–800 $\mu\text{mol/L}$ after transplant on a median follow-up of 20 months. CIT1 patients continued to receive arginine supplementation. CN1 patients have normal bilirubin values without phototherapy.

Development and Quality of Life

Patients with PA and CIT1 had a mean social developmental quotient (DQ) of 49 (<3 standard deviation) as assessed by VSMS prior to APOLT. Progressive improvement in developmental scores was seen in children within 6 months of therapy with a median social DQ of 90. Disease severity, metabolic status, neurological status and quality of life prior to APOLT and at the last follow-up are shown in Table 2.

Discussion

Metabolic liver diseases are a group of liver-based monogenic inherited disorders that cause disruption in normal metabolic pathways due to the absence of specific protein, which could be an enzyme or a receptor (Fagioli et al. 2013; Sokal 2006). MLD could be grossly divided into cirrhotic and non-cirrhotic (Fagioli et al. 2013; Sokal 2006). Non-cirrhotic could be further divided into those with primary defective hepatic enzyme expression, such as CN1, or defective hepatic and extrahepatic expression such as PA and CIT1 (Fagioli et al. 2013).

APOLT is primarily indicated in non-cirrhotic MLD where the gene defect leads to a deficiency or lack of a specific enzyme or protein such as CN1, urea cycle defects, etc. (Reddy et al. 2017). APOLT should not be offered in cirrhotic metabolic disorders as there is a potential risk of development of malignancy in the remnant native liver (Reddy et al. 2017). This procedure is also not recommended for MLD such as primary hyperoxaluria and primary hypercholesterolemia where an excess of toxic

substrates such as oxalate crystals and cholesterol, respectively, are produced (Reddy et al. 2017; Trotter and Milliner 2014). The retained native liver in primary hyperoxaluria will continue to produce oxalate crystals, which will continue to damage the kidneys, while continued production of cholesterol in primary hypercholesterolemia would result in progressive atherosclerosis (Reddy et al. 2017; Trotter and Milliner 2014).

APOLT in the setting of LT for MLD has several distinct advantages. Most MLD need only small amount of enzyme activity to be completely symptom-free. This could range from 20% for PA to just around 5% for CN1 (Fagiuoli et al. 2013). Replacing an entire, otherwise normal liver in these children is unnecessary. A small graft is usually sufficient for these patients; hence, a split left lateral segment may be sufficient even for an adult, while a smaller graft can improve donor safety in the setting of LDLT. Since there is no need for a total hepatectomy during APOLT, the stress of the anhepatic phase and the risk of intraoperative metabolic crises are sharply reduced. APOLT also decreases the cardiac stress associated with LT (Blankensteijn et al. 1990). In MLD with defective hepatic and extrahepatic expression, whether OLT or APOLT, there is only partial correction of the defect, and in theory, these children could have metabolic crisis during an intercurrent illness (Baba et al. 2016).

Domino liver transplantation involves the use of a genetically defective liver as a graft for a second recipient and can be used in the setting of MLD when the extrahepatic organs of the recipient are able to compensate for the deficient gene in the allograft liver (example: maple syrup urine disease). We have expanded this concept further and used liver graft from a child with PA in a child with CN1 (Govil et al. 2015). Patient can survive with two hemilivers, each with a different metabolic defect without clinical or biochemical manifestation, because each genetically defective hemiliver cancels the metabolic defect of the other (Govil et al. 2015).

Domino liver transplantation between MLD patients requires a basic understanding of the disease pathology and the complications. For example, it is not feasible for primary hyperoxaluria liver to be used as domino graft because the allograft will continue to produce oxalate which will damage the recipient's kidneys and could lead to renal failure (Popescu and Dima 2012). The other important considerations include the informed consent of both the domino recipient and the donor, compatible blood groups and size-matched liver grafts.

Living donor liver transplantation with heterozygous donors has been documented to be safe and effective in CN1, CIT1 and PA (Morioka et al. 2005a, b). The effectiveness of genetic evaluation in MLD other than ornithine transcarbamylase deficiency is uncertain

(Morioka et al. 2005a, b). In a large series of LT for MLD, neither mortality nor morbidity related to the heterozygous state was observed for the recipient or the donor (Morioka et al. 2005a, b). No differences were noted between the cadaveric and related grafts in our study. Based on the analysis of data from a large group of urea cycle disorder patients who underwent LDLT, it has been postulated that neurological impairment is more likely to remain in deceased donor LT than in those who underwent LDLT, but the difference was not of statistical significance (Morioka et al. 2005a, b).

None of the children with PA and CIT1 in our series had intraoperative or perioperative decompensation necessitating the need for dialysis (Baba et al. 2016). The highest recorded ammonia and lactate were 76 $\mu\text{mol/L}$ and 2.2 mmol/L, respectively, during intraoperative period. APOLT provides intraoperative and perioperative stability as there is no anhepatic phase during surgery, potentially eliminating the risk of metabolic crisis during the time period in these disorders (Fagiuoli et al. 2013). Carnitine supplementation in PA and arginine in CIT1 is indicated even after transplantation, the reason being allograft donor liver is the only source of missing enzyme, while the metabolic defect continues to persist in the rest of the body.

In CN1, high unconjugated bilirubin fraction can cross the blood-brain barrier and damage the brain, resulting in neurological sequelae. CN1 requires intense phototherapy for 12–16 h a day to keep unconjugated bilirubin under danger levels. As these children get older, the efficiency of phototherapy declines due to increase in thickness of the skin and increased mobility. Restriction under constant phototherapy affects the quality of life and interferes with the attainment of normal developmental milestones.

Allograft dysfunction due to any cause such as rejection, surgical complications, etc. after OLT could present with metabolic crises and liver failure which could be life-threatening and difficult to manage. On the contrary, graft problems in APOLT manifest as a metabolic crisis which can be medically managed as the native liver would support the liver function.

Technical complications including portal steal with early graft dysfunction and long-term graft atrophy have been a major problem with this operation previously (Kasahara et al. 2005). LFT or even disease-specific markers may not be sufficient to diagnose graft atrophy at an early stage (Reddy et al. 2017). We perform 6 monthly Doppler ultrasound to confirm preferential graft portal perfusion in all patients on follow-up. Volumetric computed tomography (CT) to quantify the graft and native liver volume was done 6 monthly in the first year of follow-up and then as per clinical indication. Recurrence of original symptoms in patient 3 was evaluated with Doppler ultrasound, volumetric CT, graft and native liver biopsy.

With technical refinements and careful intraoperative portal flow modulation, this is uncommon as evidenced in our present series (Reddy et al. 2017; Rela et al. 2015, 2016). Sze et al. also reported outcome of APOLT in 11 children with metabolic disease, with no significant difference in patient or graft survival when compared with standard OLT at 1-, 5- and 7-year follow-up (Sze et al. 2009).

Finally, APOLT preserves a part of the patient's native liver for future gene therapy. While this goal may take decades to achieve, it is important to note that most patients undergoing LT for MLD now are small children and will still benefit immensely as young adults from an immunosuppression-free life when gene therapy becomes available.

APOLT is a safe procedure in selective cases of MLD providing adequate metabolic control with improvement in developmental and neurological state. Apart from the added benefit of preserved native liver, it provides greater intraoperative and postoperative stability due to the absence of anhepatic phase during LT. This study shows that APOLT provides adequate metabolic control in selected MLD.

Synopsis

Auxiliary partial orthotopic liver transplantation provides good metabolic control and improves the neurodevelopment in children with selected metabolic liver diseases while retaining a part of the native liver for future gene therapy.

Compliance with Ethics Guidelines

Conflict of Interest

Naresh P. Shanmugam, Joseph J. Valampampil, Khoula Julenda Al Said, Khalid Al-Thihli, Nadia Al-Hashmi, Emtithal Al-Jishi, Hasan Mohamed Ali Isa, Anil B. Jalan and Mohammed Rela declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

This article does not contain any studies with animal subjects performed by the any of the authors.

Contributions of Individual Authors

Naresh P. Shanmugam and Joseph J. Valampampil – collection of clinical information, literature review and manuscript writing. Khoula Julenda Al Said, Khalid Al-Thihli, Nadia Al-Hashmi, Emtithal Al-Jishi, Hasan Mohamed Ali Isa and Anil B. Jalan – literature review and review of manuscript. Prof. Mohammed Rela oversaw all aspects of the manuscript preparation and edited the manuscript. Prof. Mohammed Rela will be the guarantor for the article.

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