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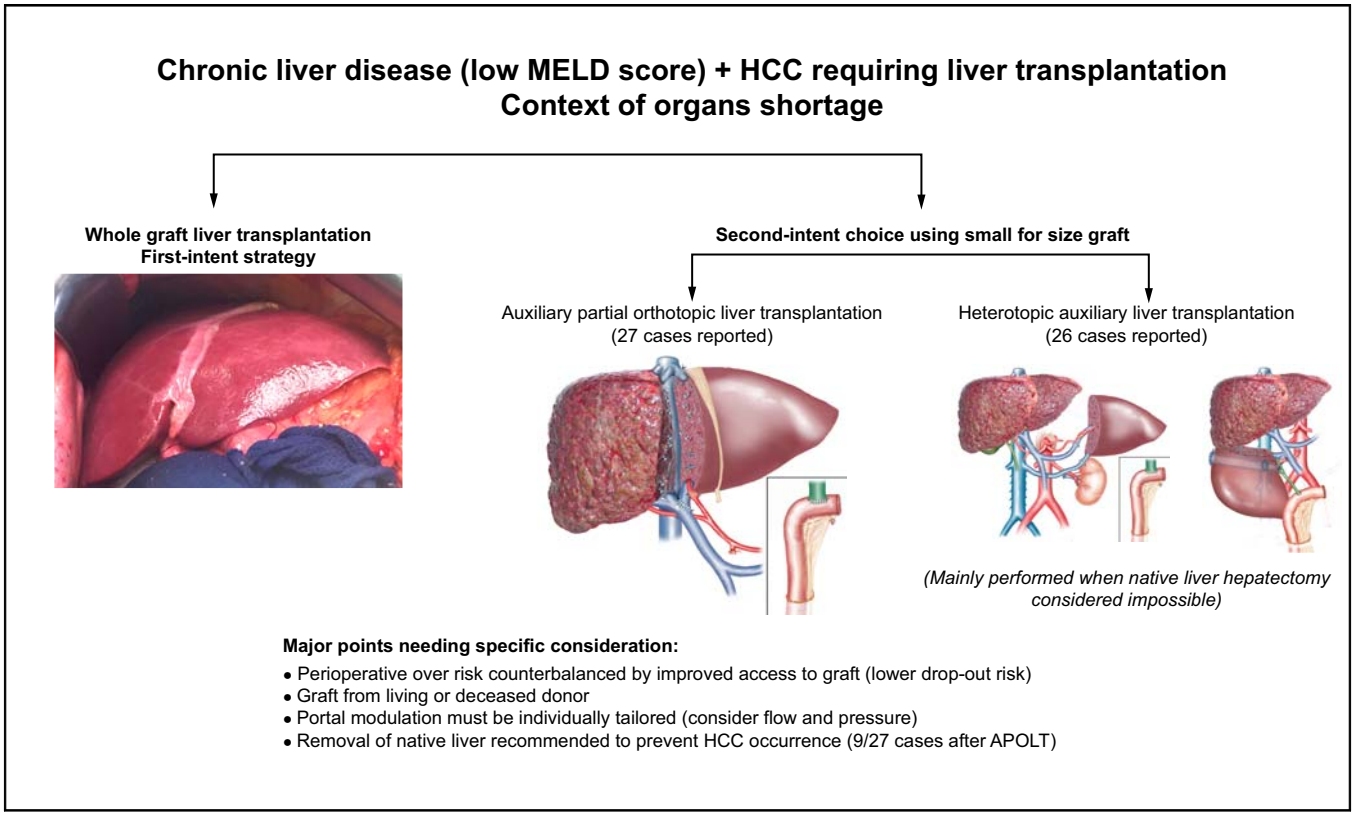
Graphical abstract



Highlights

- Using a small-for-size graft is a risk factor of small-for-size syndrome.
- Auxiliary liver transplantation can be orthotopic or heterotopic.
- In auxiliary transplantation, the remnant native liver prevents small-for-size syndrome.
- Transplantation with a small-for-size graft requires individually tailored portal modulation.
- Auxiliary liver transplantation might substantially increase the number of available grafts.

Lay summary

At the cost of a high postoperative morbidity, the long-term results of APOLT for small-for-size grafts are good. Standardisation of the procedure and of portal modulation remain needed.

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A systematic review of auxiliary liver transplantation of small-for-size grafts in patients with chronic liver disease

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Background & Aims: The shortage of liver grafts continues to worsen. Because the expanded use of small-for-size grafts (SFSGs) would substantially alleviate this shortage, we aimed to analyse the available knowledge on auxiliary liver transplantation (ALT) with SFSGs in patients with chronic liver disease (CLD) to identify opportunities to develop ALT with SFSGs in patients with CLD.
Methods: This is a systematic review on ALT using SFSGs in patients with CLD. The review was completed by updates obtained from the authors of the retained reports.
Results: Heterotopic ALT was performed in 26 cases between 1980 and 2017, none for SFGS *stricto sensu*, and auxiliary partial orthotopic liver transplantation (APOLT) in 27 cases (from 1999 to 2021), all for SFSG. In APOLT cases, partial native liver resection was performed in most of cases, whereas the second-stage remnant native liver hepatectomy was performed in 9 cases only. The median graft-to-body weight ratio was 0.55, requiring perioperative or intraoperative portal modulation in 16 cases. At least 1 complication occurred in 24 patients following the transplant procedure (morbidity rate, 89%). Four patients (4/27, 15%) died after the APOLT procedure. At the long term, 19 (70%) patients were alive and well at 13 months to 24 years (median, 4.5 years) including 18 with the APOLT graft in place and 1 following retransplantation.
Conclusions: Despite high postoperative morbidity, and highly reported technical variability, the APOLT technique is a promising technique to use SFSGs in patients with CLD, achieving satisfactory long-term results. The results need to be confirmed on a larger scale, and a standardised technique could lead to even better results.
Lay summary: At the cost of a high postoperative morbidity, the long-term results of APOLT for small-for-size grafts are good. Standardisation of the procedure and of portal modulation remain needed.

Introduction

The imbalance between the limited number of available grafts and the increasing number of candidates for liver transplantation (LT) continues to worsen worldwide.[1] Inherently to the large implementation of model for end-stage liver disease (MELD) score-based graft allocation systems, candidates with preserved liver function have suboptimal access to LT and are threatened by drop-out owing to disease progression or death. In addition, the current waiting list situation underestimates the reality, as numerous patients with low MELD scores are not listed because, practically, they have no access to LT.

A small-for-size graft (SFSG) is defined by a graft-to-recipient body weight ratio of <0.8 for living-related liver transplantation (LRLT).[2,3] This ratio is probably higher for deceased-donor LT owing to the inherent prolonged preservation time and lower quality of the parenchyma. The small volume, associated with hyper portal flow, is responsible for biological and clinical disorders.[4] Exploiting the regeneration capacities of the liver, the transplantation of SFSGs from living donors or split livers might be a possibility to substantially increase the number of grafts available. The use of these SFSGs has been reported in standard orthotopic LT in patients with advanced end-stage liver disease, mostly in LRLT[5–18] and also in split LT.[19,20] Despite the implementation of versatile portal modulations (aiming to modulate portal pressure and flow per 100 g of remnant liver), small-for-size syndrome (SFSS)[15] still remains the most feared complication after standard orthotopic LT using SFSG[21] and limits the wider use of this type of graft.

A second option would be to use these SFSGs to perform auxiliary liver transplantations (ALTs) in the heterotopic (HALT) or orthotopic (OALT) position in patients with chronic liver

Keywords: Organ shortage; Chronic liver disease; Liver transplantation; Small-for-size graft; Small-for-size syndrome; Auxiliary liver transplantation; Orthotopic liver transplantation; Living-related liver transplantation; Double equipoise; Split liver transplantation; Heterotopic liver transplantation; Systematic review.
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disease (CLD). In ALT, it is the remnant native liver that is auxiliary to the SFSG and obviates SFSS until the graft has sufficiently regenerated to provide full normalized liver function. To be viable, ALT procedures should apply to candidates with CLD that fulfil the following criteria: (1) the native liver function is still relatively preserved to accomplish its auxiliary role, (2) ALT option would provide a sufficient benefit as compared with waiting longer for a sufficient-for-size graft, in practice a whole cadaveric graft.

The present study of the published experience, completed with updated information provided by centres having published their cases, (1) analyses the literature on ALT for SFSG in patients with CLD, (2) discusses the technical options for ALT, and (3) proposes an algorithm to optimise the transplantation output from the available grafts.

Materials and methods

Literature search

A systematic literature review was undertaken of articles reporting ALT in patients (age ≥16 years old) with CLD, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[22] applying the Population, Intervention, Comparison, and Outcome (PICO) framework. An English literature search was performed through PubMed, Embase, and Google Scholar from January 1965 to April 2021.

Only fully published articles were reviewed by 3 senior transplant surgeons, and discrepancies were resolved in a consensus meeting. Any papers that provided insufficient information were excluded. Multiple papers from the same group of authors were considered; the information retrieved from these articles was merged, and the article providing the largest amount of information was retained as the principal reference. The references of the retrieved articles were manually checked for further studies. Cases performed before the study period and studies conducted on animals were not considered. The relevant variables analysed are presented in Tables 1–3.

Data updating

Considering that all reported ALTs performed for SFSG were orthotopic LTs (see the Results section) and that HALT has been practically abandoned, updating of the literature was performed for orthotopic ALTs only. In February 2021, an email was sent to each LT centre that reported at least 1 case of auxiliary orthotopic liver transplantation (AOLT) for CLD identified by the mentioned literature search. The email asked for updates about patients reported to be alive at the time of publication. For each centre, the updating questionnaire included specific questions to complete the available information in the corresponding publications. A reminder email was sent 2, 4, and 6 weeks after the initial distribution to encourage participation.

Results

We identified 645 articles, of which 143 articles remained after duplicate and irrelevant material exclusion. Finally, 16 articles[23–38] met the inclusion criteria and were retained for the present study (Fig. S1). Most of this literature was based on cases reports or small retrospective series (level 4), with limited quality. Eight centres, among those who reported auxiliary partial orthotopic liver transplantation (APOLT) with SFSG, were asked to update their experiences. Seven answered the questionnaire (France [2 centres], Germany [1 centre], Japan [1 centre], China [1 centre], Korea [1 centre], and Turkey [1 centre]).

HALT

We identified 26 cases of HALT in adult patients (≥15 years old) with CLD reported between 1980 and 2017,[23–29] thus excluding recent reports illustrating the use of HALT for unresectable colorectal liver metastases.[39,40] An SFSG was used in 3 (4%) cases, but the option of HALT was not *stricto sensu* applied for SFSG, but, in 1 case each, because the patients were deemed too ill to undergo the total native liver hepatectomy of standard orthotopic LT,[23] during combined liver–small bowel transplantation to protect the latter from rejection,[24] and the native liver hepatectomy was deemed unnecessary.[27] The other 23 of 26 cases of HALT were performed because native liver hepatectomy was deemed impossible or too risky. Considering the above findings, the results achieved with HALT are not discussed here.

Regarding the technical aspects, the graft was implanted in the subhepatic space (20/26 cases) or in the splenic fossa following splenectomy (6/26 cases), leaving the entire native liver untouched in all cases. Figs. S2 and S3 show these 2 options. The relevant characteristics of recipients, donors, and techniques used for HALT and their outcomes are described in detail in Tables S1 and S2.

AOLT

Twenty-seven cases of AOLT in patients with CLD were reported from 1999 to 2021.[30–37,41] The liver graft was implanted orthotopically in the space made up free by partial native liver hepatectomy, a left-sided hepatectomy in most cases. Fig. 1 schematises the operating field after APOLT of a left graft. Table 1 describes the relevant characteristics of recipients, donors, and grafts and the techniques used for APOLT, and Table 2 presents the corresponding outcomes.

The AOLT option was chosen in all cases because of the small-for-size nature of the graft and to prevent the occurrence of SFSS. The median graft-to-recipient body weight ratio was 0.55 (0.38–0.77) in 25 available cases. In the remaining 2 cases, the graft volume represented 21% and 28% of the standard liver volume and could also be considered an SFSG. The recipient Child class was A or B in 61% of cases, and the MELD score was <15 in 56% of cases that had information available for these variables. Portal hypertension was present and severe in 65% of the cases (17/26 cases with available information). The graft provided from a living donor in 24 (89%) cases[30,32,34–38,41,42] and it was a whole liver in 1 case (graft-to-recipient body weight ratio, 0.77).[33] The graft was a left graft in 23 (85%) cases, a right graft in 3 (11%) cases, and a whole liver graft in 1 case (mentioned above). First-stage native liver hepatectomy was left-sided in 22 (81%) cases and right-sided in 3 (11%) cases.[33,38] In 2 (7%) cases, the left graft could be implanted without left native liver hepatectomy owing to complete left lobe atrophy.[38]

Portal modulation was applied in 16/27 (59%) cases to increase flow into the graft by interruption of the portal flow to the remnant native liver, complete in 13 cases (total of 12[30,38] and partial in 1 case by banding[33]), and to decrease the portal pressure in 3 cases by splenic artery ligation,[37] splenectomy,[37] or a portacaval shunt[36] in 1 case each. Postoperative portal vein embolisation was performed in 1 report to increase the graft portal inflow.[33] (Fig. 2 illustrates the main options to decrease

Table 1. Reported cases of APOLT for SFSGs in patients with chronic liver disease (27 cases): patients, indication graft details.

First author,[ref] year, cases (n)	Liver disease	Severe PHT (other)	Graft	GBWR	First-stage native liver hepatectomy	Portal flow modulation
Ikegami,[30] 2002, 2 cases	PSC Biliary atresia	NA	LD = 2 Left graft	21%, 28%	Left hepatectomy	None
Kasahara,[38*] 2005, 13 cases	Biliary atresia = 4 Cryptogenetic = 3 PBC = 3 Chronic Wilson = 2 PSC = 1	Bleeding = 2 Ascites = 4 (others: encephalopathy, itching, and fractures)	LD = 13 (left graft 11; right graft 2)	Median = 0.55 (0.45–0.72)	Left lobectomy = 9 Right hepatectomy = 2 None (left lobe atrophy) = 2	Native portal flow to native liver interrupted: 10 cases as a result of a dominant artery in native liver
Scatton,[31] 2005, 1 case	Cirrhosis HBV-D	Bleeding and ascites	Left split liver	0.67	Left lobectomy	None
Cho,[32] 2006, 1 case	Alcoholic cirrhosis	Ascites	LD = 1 Left graft	0.46		
Dokmak,[33] 2013, 1 case	Alcohol-NASH with HCC in the right lobe	No	Whole liver	0.77	Right extended hepatectomy	Native portal vein flow banding PVE remnant native liver at POD 15
Scatton,[35] 2016, 2 cases	Alcohol PBC	Ascites = 1 Pruritus = 1	Left grafts from LD = 2	0.39, 0.45	Left lobectomy	None
Wang,[34] 2017, 4 cases	HBV cirrhosis = 4 (with HCC = 1)	Ascites and varices = 4	LD = 3 Split = 1 All left grafts	0.38, 0.47, 0.54, 0.55	Left lobectomy	None
Balci,[36] 2020, 1 case	NASH With HCC in the right lobe	Ascites = 1	Left liver from LD	0.42	Left hepatectomy	Portacaval shunt
Brunner,[37] 2021, 2 cases	PSC-AIH Congenital hepatic fibrosis	Severe = 2	Left lobes from LD	0.43, 0.65	Left hepatectomy	Splenic artery ligation = 1 Splenectomy = 1

Only data for patients with chronic liver disease were retrieved.
AIH: autoimmune hepatitis; APOLT, auxiliary partial orthotopic liver transplantation; GBWR, graft-to-body-weight ratio; HCC, hepatocellular carcinoma; LD, living donor; NA, not available; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PHT, portal hypertension; POD, postoperative day; PSC, primary sclerosing cholangitis; PVE, portal vein embolization; SFSG, small-for-size graft.
* Data merged with Yabe *et al.*,[51] same centre (Kyoto, Japan).

Table 2. Reported cases of APOLT for SFSGs in patients with chronic liver disease (27 cases): short- and long-term outcomes.

First author,[ref] year, cases (n)	Postoperative mortality	Postoperative complications	Second-stage native liver hepatectomy	Long-term outcome
Ikegami,[30] 2002, 2 cases	0	Portal steal ligation shunts, POD 2	Yes = 1 case, prophylaxis cancer PSC, POD 18 No = 1 case	Alive and well = 2, at 2 and 2.5 m
Scatton,[31] 2005, 1 case	0	Ascites	Yes at 3 months, preemptive	Alive and well at 24 years*
Kasahara,[38] 2005, 13 cases	3	Biliary leak = 2 Intraperitoneal bleeding = 2 Gastric bleeding = 1 GI perforation = 1 Portal steal = 1	Yes =1 case (prophylaxis cancer PSC) No = 8/9 survivors	Alive and well = 9 Median = 12 m (6–23 m)
Cho,[32] 2006, 1 case	0	Uneventful	No	Alive and well = 1, at 16 years and then HCC in graft and native liver and lost to FU
Dokmak,[33] 2013, 1 case	0	Uneventful	Yes = 1 case At D30, prophylaxis recurrence HCC	Alive and well = 1, at 8 years*
Scatton,[35] 2016, 2 cases	1	Patient 1: ascites = 1 Patient 2: biliary stenosis	Patient 1: Yes at POD 90, preemptive, death POD 25 post-removal Patient 2: No (biliary stenosis—re-Tx at 1 year)	Patient 2: Alive and well at 6 years post-APOLT (needed re-Tx)*
Wang,[34] 2017, 4 cases	0	Biliary leak = 1 Outflow block = 1 Pulmonary infection = 1	Yes = 1, at 10 m for HCC recurrence (alive and well 16 m later) No = 3	Alive and well = 4 cases, at 13, 20, 26, and 26 m
Balci,[36] 2020, 1 case	0	Uneventful	Yes = 1, at POD 35 because HCC in place	Alive and well at 24 m*
Brunner,[37] 2021, 2 cases	0	Patient 1: Roux-en-Y POD 2 Arterial angioplasty POD 17 Hepatic vein angioplasty POD 20 Biliary leak POD 42 Portal vein stenting at 1 year Patient 2: Portal vein thrombosis surgical desobstruction POD 1 Roux-en-Y at POD 3	Patient 1: Yes, POD 14 Patient 2: Yes, POD 10 Preemptive = 2	Alive and well at 20 and 36 m*

APOLT, auxiliary partial orthotopic liver transplantation; FU, follow-up; GI, gastrointestinal; HCC, hepatocellular carcinoma; m, postoperative month; POD, postoperative day; PSC, primary sclerosing cholangitis; re-Tx, retransplantation; SFSG, small-for-size graft; TACE, transarterial chemoembolization.
* Updated follow-up questionnaire by 1 April 2021.

Table 3. Postoperative complications following APOLT (26 cases) and second-stage remnant native liver hepatectomy (9 cases).

Postoperative complication	Cumulative data	APOLT (26 cases)	Second-stage remnant native liver hepatectomy (9 cases)
Ascites	2	2	0
Biliary reconstruction *	8	8	0
Portal reconstruction	2	2†	0
Hepatic vein(s) reconstruction	4	4‡	0
Hepatic artery reconstruction	1	1	0
Perforation	1	1	0
Bleeding needing reoperation	2	2	0
Other	4	Pulmonary infection = 1; damage control = 2	Hyperbilirubinaemia§ = 1
Postoperative death	4	3	1

APOLT, auxiliary partial orthotopic liver transplantation.
* Fistula or stenosis.
† One additional case at 1 year post-APOLT.
‡ One leading to retransplantation.[49]
§ Needing repeated plasmapheresis.

[techniques 1 to 5] or to increase [technique 6] the graft portal flow.)

At the time of AOLT, 3 (11%) patients had hepatocellular carcinoma.[33,34,36] The tumour was resected in the specimen at the first stage of partial native liver hepatectomy in 2 cases[33,34] and 35 days after transplantation in 1 case during the second-stage remnant native liver hepatectomy.[36]

Second-stage remnant native liver hepatectomy

Second-stage remnant native liver hepatectomy was performed in nine cases (9/27, 33%): in six cases as prophylaxis for cancer development,[30,31,35,37,38] and for hepatocellular carcinoma in the remnant liver (already mentioned),[36] recurrent hepatocellular carcinoma in the native liver,[34] or during retransplantation for uncontrollable biliary complications[35] in one case each.

Postoperative outcomes

At least 1 severe complication occurred in 24 patients following the transplant procedure (morbidity rate, 89%). The SFSS incidence was nil. Table 3 summarises the postoperative complications following the AOLT procedure and the second-stage remnant native liver hepatectomy. At the graft site, biliary complications were most frequent (8/27, 30%), followed by hepatic vein stenosis or thrombosis (4/27, 15%), portal vein stenosis or thrombosis (2/27, 7%), bleeding requiring reoperation (2/27, 7%), and hepatic artery stenosis (1/27, 4%). There were no complications specific to the first-stage native liver hepatectomy. Mortality occurred in 3/27 (11%) cases at 35, 59, and 22 days post-APOLT,[38] and all were caused by sepsis. Following the second-stage remnant native liver hepatectomy, the postoperative course was uneventful in all but 2 patients: 1 patient developed SFSS with isolated hyperbilirubinaemia and was successfully treated with repeated plasmapheresis,[30] and 1 patient with pulmonary infection died on postoperative day 25 (55 days post-APOLT).[35]

Long-term outcomes

This section combines information from published reports and the updates obtained from 7/8 centres[31–33,35–38] (Fig. 3). Retransplantation was needed in 3 (11%) cases owing to hepatic vein thrombosis,[38] chronic rejection,[38] and uncontrollable biliary complications[35] in 1 case each. Two late deaths occurred owing to colon cancer and sepsis in 1 case each.

At the long term, 19 (70%) patients were alive and well at 13 months to 24 years (median, 4.5 years) including 18 with the APOLT graft in place and 1 following retransplantation. One patient developed hepatocellular carcinoma[32] at 16 years post-APOLT in both native and grafted liver and was controlled by repeated transarterial chemoembolisation.

Discussion

Our main findings are as follows: (1) all reported ALTs for SFSG in patients with CLD were orthotopic (mostly APOLT with left grafts from living donors); (2) despite high postoperative morbidity, the long-term outcomes of AOLT are satisfactory; (3) second-stage native liver hepatectomy as prophylaxis for the development of hepatocellular carcinoma is straightforward and well tolerated; and (4) subsequently, the APOLT procedure offers opportunities to substantially increase the number of grafts available in a large subset of selected patients. The following sections address the main issues of ALT, although they often overlap or have reciprocal influences. Note that only adults cases are reported and commented here. Because of poor literature quality, no strong recommendation may be proposed here.

Identification of candidates for ALT

Inherent to the large adoption of MELD score-based grafts allocation systems, a large subset of candidates with preserved liver function (patients with a MELD score <15 represent 21% of patients listed for LT in France[43] and up to 43 % in the United States[44]) have suboptimal access to LT despite prioritisation systems.

Best candidates for ALT are those with hepatocellular carcinoma developed on compensated cirrhosis with a risk of drop-out as a result of tumour progression (up to 18% at 1 year[45]), refractory ascites (survival <50% at 1 year[46,47]), debilitating encephalopathy (associated 1-year mortality rate up to 64%),[48,49] intractable pruritus (incidence up to 70% in primary biliary cirrhosis),[50,51] and repeated bleeding in patients who are ineligible for transjugular intrahepatic portosystemic shunt.

These patients also have a clinical phenotype exposed to the development of acute-on-chronic liver failure.[52] Recent studies show that most patients with acute-on-chronic liver failure had no severe liver dysfunction 3 months before admission to the intensive care unit[53] with a 90-day mortality rate of up to 67%[54,55] and a more than 2-fold increased mortality whenever they underwent transplantion.[56] Finally, the decision to propose an ALT must remain a case-by-case decision between the medicosurgical team and the patient according to the patient's

history/comorbidities and the local specificities of graft allocation, considering the perioperative risk of ALT and the drop-out risk while waiting a whole graft, in an *intention-to-treat* scheme.

Advantages and drawbacks of surgical options

The technical advantages of the APOLT procedure over the HALT procedure are 2-fold. First, the orthotopic implantation of the graft as close as possible to the right atrium optimises its venous drainage. Second, the congruence and coaxiality of the graft vessels, most often short, with the recipient's vessels facilitate their reconstruction. APOLT also has 2 major technical drawbacks. First, a first-stage partial native liver hepatectomy is needed to free up adequate space to implant the graft. This hepatectomy combines the inherent risks of any hepatectomy with those of the diseased native liver decompensation and the subsequent loss of the rationale for ALT. Second, as in the HALT option, APOLT requires a second-stage remnant native liver hepatectomy, a procedure with its own risks in a patient with immunosuppression. However, the present analysis did not confirm these theoretical disadvantages. It should be noted that the second procedure was only performed in a minority of cases, but it is not this strategy that we would recommend.

The poor reputation of HALT is mainly caused by the implantation of the graft at a distance from the right atrium, where the inferior vena cava pressure is slightly higher than that for the APOLT, potentially impairing the graft venous drainage. However, conflicting results have been reported in experimental and clinical models,[39,57,58] and rather than the inferior vena cava pressure *per se*, the pressure gradient between the efferent portal tributary pressure, which can be modulated, and the inferior vena cava pressure seems to play a primordial role.

In HALT, as compared with APOLT, the native liver remains untouched during the transplantation procedure, facilitating second-stage native liver hepatectomy. In addition, when the HALT procedure is performed in the splenic fossa, the required splenectomy to free up space and implant the graft also might

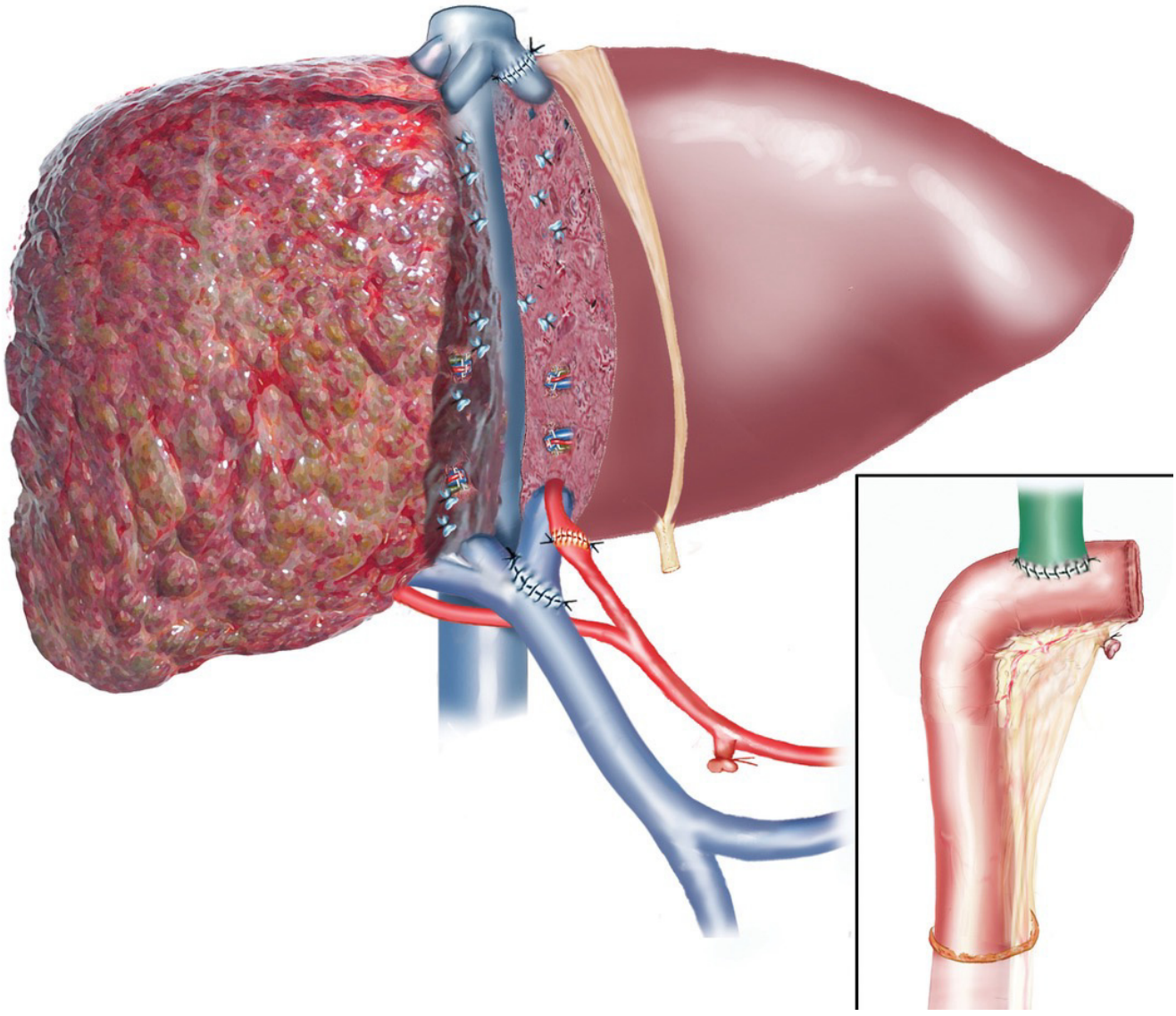

Fig. 1. Illustration of final operative field after auxiliary partial orthotopic liver transplantation of a left graft.

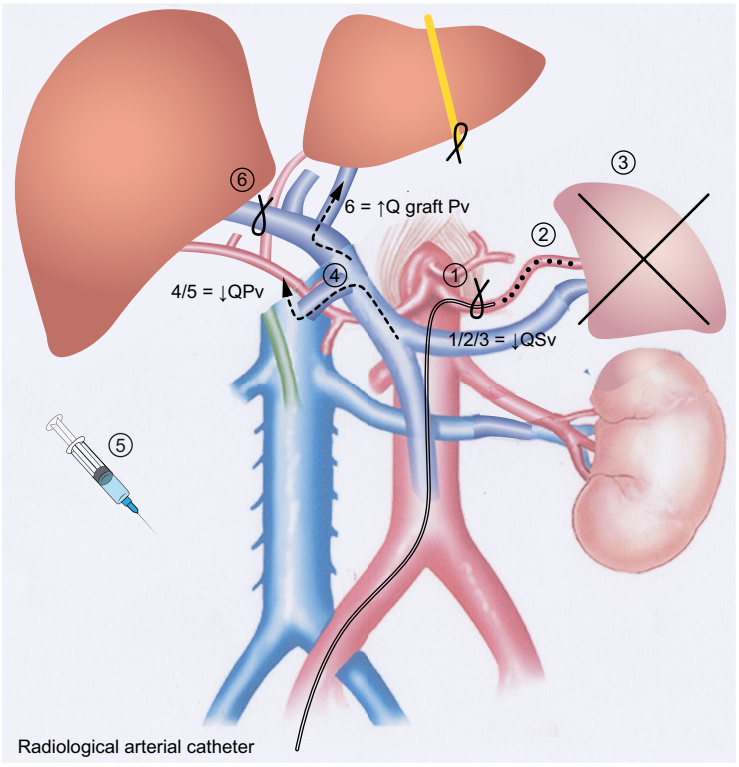

Fig. 2. Portal flow modulation techniques available in the APOLT setting. APOLT, auxiliary partial orthotopic liver transplantation; QPv, portal vein flow; QSv, splenic vein flow.

solve the hypersplenism and portal hypertension whenever present. Finally, if the place of HALT is now very limited, some very selected patients (native liver difficult to explant[29]) or non-validated indications as unresectable metastases[40] could still benefit from a heterotopic graft, even an SFSG.

Management of present hepatocellular carcinoma at the time of ALT

In the setting of hepatocellular carcinoma at the time of LT, APOLT with a left graft is the preferred strategy when the tumour is located in the left liver because this is removed together with the specimen. In cases of hepatocellular carcinoma in the right liver, APOLT might still be performed and combined with local destruction or limited liver resection. HALT combined with the aforementioned local treatment may also be a reasonable option.

Portal modulation to protect the SFSG

Portal flow modulation in the specific setting of SFSG has been reported in 2 different situations, with 2 distinct objectives: (1) protection of the graft from over portal flow is the most common situation and (2) portal flow diversion (rerouting) to promote perfusion of the small graft, and venous deprivation of the native remnant liver, mainly in case of low graft hypertrophy (rare situation). Fig. 2 illustrates these 2 distinct situations.

Although the use of an SFSG carries a risk of SFSS,[21] no cases occurred following AOLT in the present analysis. One can assume that this resulted from the auxiliary remnant native liver providing a sufficient proportion of liver function to mask the clinical expression of SFSS combined with the portal modulation used in most cases.

In the most frequent situation, portal modulation aims to prevent SFSS subsequent to the SFSG and must take into account that (1) portal pressure higher than 20 mmHg is a risk factor,[59,60] (2) the contribution of the portal flow to parenchymal perfusion increases with worsening reduction of the hepatic vascular bed,[61] and (3) there is no direct correlation between portal pressure and portal flow.[62] In this field, the level of evidence is low owing to the heterogeneous definitions of an SFSG, SFSS, the modulation types used, their timing, the small sample size, and the absence of a control group in most reports, as well as the absence of objective metrics to assess their effects (no available flowmetry in the published series). Tables S3 and S4 describe the portal modulation means. Portal modulation, reversible or not, can be performed preoperatively, intraoperatively, or post-operatively using medical, surgical, or radiological approaches. So far, pharmacological reduction of splanchnic flow[63,64] was not reported in the setting of ALT.

In 2017, the international guidelines[65] encompassed the recommendation for portal modulation but not for splenectomy to prevent SFSS. The latter might be nuanced by a recent series[66] that reported improved outcomes after simultaneous splenectomy with living-donor LT. In practice, portal modulation might be considered in recipients with severe portal hypertension, that is, with portal pressure >15–20 mmHg and/or portal flow >300/ml/100 g graft weight.

Portal modulation can also consist in the rerouting of the global portal flow towards the graft, to the detriment of the native liver. This technique, particularly reported in the context of APOLT, allows promoting the hypertrophy of the graft and atrophy of the diseased liver. Technically, it consists of a ligation

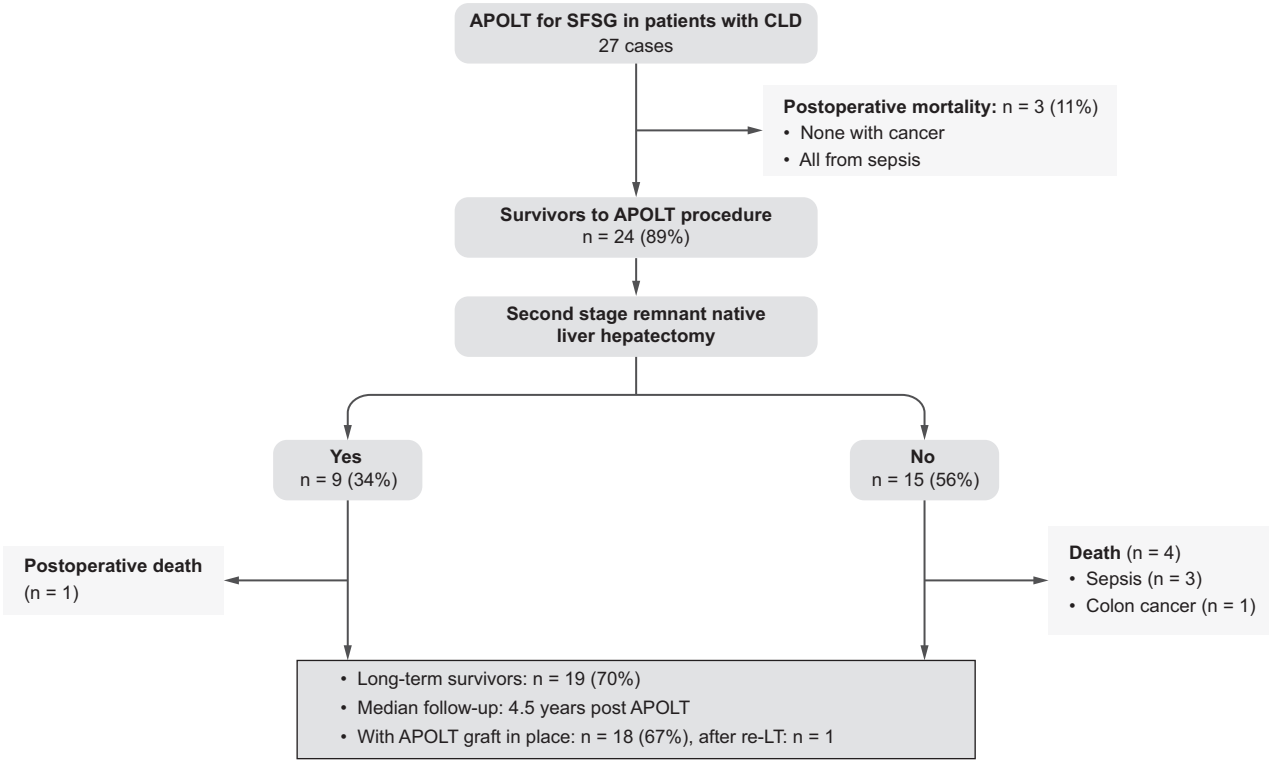

Fig. 3. Long-term outcomes after APOLT. APOLT, auxiliary partial orthotopic liver transplantation; SFSG, small-for-size graft; CLD, chronic liver disease; LT, liver transplantation.

(if necessary, associated with sectioning) of the right portal branch.

Second-stage native liver hepatectomy

The rationale for the second-stage remnant native liver hepatectomy relies on the risk of hepatocellular carcinoma development in the remaining cirrhotic liver, in the region of 10% of survivors following ALT in the present analysis,[25,28,32] consistent with the 5-year cumulative incidence of 8 to 21% of hepatocellular carcinoma development in a cirrhotic liver. When the second-stage native liver hepatectomy is considered, this should be performed when the graft has achieved sufficient regeneration to sustain the major part of or all the normalised liver function.

Dynamic hepatobiliary scintigraphy remains the only method that can noninvasively distinguish the functional performance of both the graft and the remnant native liver. Recent refinements in magnetic resonance imaging using hepatospecific contrast agents might be useful in this setting.[67] In the near future,[68,69] preoperative modelling of the post-LT hemodynamic status might help anticipate the need for portal flow modulation.

Potential grafts for ALT

In living-donor LT

Although a graft-to-recipient body weight ratio <0.8 increases the risk of graft loss by SFSS in the recipient, an inadequate residual volume in the healthy donor is not an acceptable option.[70] In clinical practice, this double requirement is often conflicting: although debated,[71–73] the risk of inadequate remnant volume in the donor was in most series reported as one of the main causes for donor disqualification, ranging from 13 to 54%,[74–78] and the potential left-lobe grafts for adult recipients often tend to be too small. This explains why left-lobe donations for adult recipients have been almost abandoned, especially in Western countries. The development of ALT for SFS left grafts in the field of LRLT might help to cut this Gordian knot. Roll *et al.*[5] showed that shifting from an adequate right graft to a SFS left graft would increase the ratio of recipient lives saved at 1 year per donor death from 40 to 150.

*After split LT (*in situ *or* ex situ*)*

As 9% of livers from optimal donors are split-able for 2 adults,[19,79,80] the potential for the use of the left graft including SFSG should increase this rate to 15–20%. This objective is attainable provided multicentric cooperation.[19,81,82] Such a programme has been accepted by the French regulation of organ sharing, including some prioritisation for patients embarking on this endeavour.

Two approaches might be implemented to alleviate as much as possible the ischemia injury to the left graft: first, the development of *in situ* splitting and, second, the split performance on machine, hypothermic or normothermic.[83,84] Further, normothermic machine perfusion could even favour graft regeneration, which might have a major impact on post-APOLT outcomes.[85]

Within the IDEAL framework (which describes the stages through which surgical therapy innovation normally passes, and the characteristics of each of 5 stages: Idea, Development, Exploration, Assessment, and Long-term follow-up),[86] the programme proposed here qualifies for a stage 2b study (novel technique investigated in a prospective multicentric cohort).

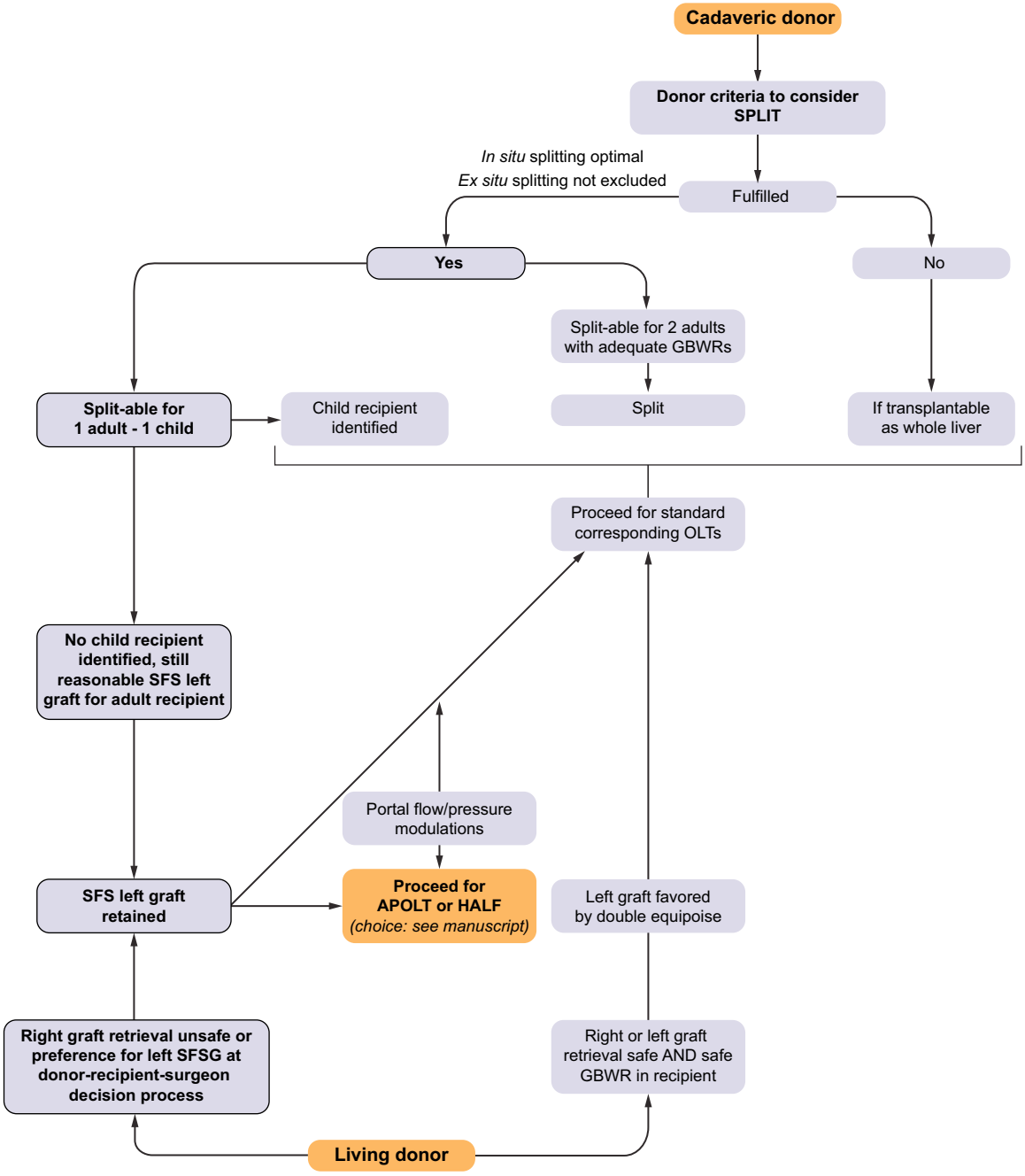

Fig. 4. Decision tree algorithm to select grafts and recipients for APOLT or HALT (proposal algorithm). APOLT, auxiliary partial orthotopic liver transplantation; GBWR, graft-to-body-weight ratio; HALT, heterotopic auxiliary liver transplantation; OLT, orthotopic liver transplantation; SFS, small-for-size; SFSG, small-for-size graft.

These complex procedures must be undertaken exclusively by experienced transplant surgeons in high-volume centres.[87–89]

Limitations of the study

Despite our efforts to provide a detailed and most comprehensive analysis of the literature, this systematic review is subject to multiple possible biases, including a huge heterogeneity in the techniques reported, the decisional algorithms, the clinical settings, and the quality of the data provided. This is an undeniable limitation for which there is no possible methodological improvement. However, we have contacted the authors to clarify the missing data concerning the follow-up, and we have tried to provide the most meaningful analysis of the literature. Finally, we have enriched the interpretation of published data with our own experience in partial graft LT and particularly in SFSS.

Proposition of a decisional algorithm

Fig. 4 summarises the potential place of ALT for SFSGs in the overall management of liver grafts from a cadaveric or a living donor among the other technical options and how this might increase the overall output of LT.

Conclusions

APOLT might increase the grafts pool by allowing transplantation of SFSG still preventing the occurrence of SFSS. To be viable, APOLT for SFSG should be considered in patients with a low MELD score. APOLT for SFSG might increase the use of left grafts from living donors and decrease the risk in the latter. In the field of split LT, the use of SFSG increases the LT output without penalising the recipient of the right graft. Evidence-based portal modulation remains needed. A multicentre prospective evaluation of APOLT is underway to make the technique simpler and more reproducible, because evidence remains low as huge heterogeneity in surgical practice is encountered so far.

Abbreviations

ALT, auxiliary liver transplantation; AOLT, auxiliary orthotopic liver transplantation; APOLT, auxiliary partial orthotopic liver transplantation; CLD, chronic liver disease; HALT, heterotopic auxiliary liver transplantation; IDEAL, Idea, Development, Exploration, Assessment, and Long-term follow-up; LRLT, living-related liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; PICO, Population, Intervention, Comparison, and Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SFSG, small-for-size graft; SFSS, small-for-size syndrome.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: DA, CF, NG. Acquisition of data, analysis, and interpretation of data: DA, CF, EV, NG. Drafting of the manuscript: DA, NG. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the manuscript: All authors.

Data availability statement

This review is based on published data, updated by information obtained from authors of these data. The data associated with this paper (literature review) is available without any conditions.

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Supplementary data

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