Review Article

Alternatives to left lateral sector in paediatric liver transplantation—a systematic review on monosegmental and reduced grafts

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Background: Paediatric liver transplantation (pLT) is the treatment of choice for many liver conditions. However, it still poses relevant challenges, mainly related to the size of the recipients. Unlike in adults, excessive graft volume might represent an issue when the estimated graft-recipient-weight-ratio (GRWR) is significantly disproportionate. In this situation, the traditional left lateral sector (LLS) grafts are too big and other alternatives are required, such as monosegmental or reduced (including hyper-reduced) grafts (RLLS/HRLLS). Results with conventional LLS-pLT are excellent and replicating them with monosegmental or RLLS is challenging given (I) the technical complexity and (II) the need to overcome the large-for-size scenario. This article is to review the existing experience with monosegmental, RLLS/HRLLS grafts and appraise its results.

Methods: Systematic search of the electronic databases, conducted from their inception until May 2020.

Results: After scrutiny of the available literature, 16 studies were included reporting 330 patients transplanted with monosegmental and RLLS/HRLLS grafts. There were 10 re-grafts (6 of them <90 days); 90% of grafts were LDLT. Overall, median recipient's age and weight were 7 months (range, 5 days–22 months) and 5.8 kg (range, 2.6–8 kg) respectively. Median graft weight was 209 grams (range, 124–264 grams) and median GRWR was 3.5% (range, 2.7–5.6%). Hepatic artery and portal vein thrombosis overall incidence were 1.5% and 4.2%; 120 out of the 330 pLT were monosegmental (37%) producing a smaller graft (median of 164 grams) and accordingly a lower GRWR (median 3.2%) compared to reduced LLS. With a median follow-up of 39 months (range, 6–87 months), the overall graft and patient survival were 84% (285/340) and 89% (295/330).

Discussion: Monosegmental and RLLS/HRLLS grafts provide access to liver transplantation for very small recipients with excellent results comparable to the standard LLS.

Keywords: Monosegmental; monosegment (MSG); reduced; hyper-reduced; left lateral sector graft; liver transplantation

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Introduction

Liver transplantation is an established method for treating acute and chronic organ failure. Given the obvious difficulties for obtaining suitable grafts in small recipients, the pool of donors was expanded to facilitate access to the waiting list, initially with reduced organs and later on with split grafts (deceased donors) as well as living donor liver transplantation (LDLT) (1), being the commonest modality of transplant in children the left lateral sector (LLS) (2).

Nevertheless, the Gordian Knot of the paediatric liver transplantation (pLT) continues to be the large-for-size scenario, seen when the volume of the graft exceeds the capacity of the abdominal cavity (2-6). The alternatives are using a standard LLS and delaying abdominal wall closure (4,5) or surgically altering the LLS and aiming for a primary closure. In 1992, to confront this problem, Strong *et al.* (6) published the first monosegmental pLT, implanting the segment 3 from a deceased donor (DD) into a 4-month-old baby [a redo transplant for hepatic artery thrombosis (HAT)]. Larger series with DD appeared later, notably from Srinivasan *et al.* (7). This technique would be further consolidated by Kasahara *et al.* (8), whom produced reduced left lateral sector (RLLS) grafts and mono-segments from LDLT.

The aim of the present study is to interrogate the literature to evaluate the existing experience and outcomes of monosegment (MSG), RLLS/hyper-reduced left lateral sector (HRLLS) transplants in small paediatric recipients. We present the following article in accordance with the PRISMA reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-792/rc).

Methods

This systematic review was carried out in accordance with the guidelines set out in the PRISMA checklist (9).

Literature search

A systematic literature search of articles published from inception until May 2020 performed in Embase, MEDLINE (PubMed), Cochrane library, and Google Scholar databases using free text and MeSH terms (liver pediatric transplantation, monosegments, monosegmental). A grey literature search on www.clinicaltrials.gov was also performed. Bibliographies cited in the retrieved articles were manually checked for further analysis. Disagreements between authors were resolved through discussion.

Search terms, inclusion and exclusion criteria

Studies reporting paediatric liver transplantation, monosegments or monosegmental grafts, reduced or hyper-reduced grafts and left lateral sectors grafts were included in this study. Abstracts (summary of the contents of an article or book) and editorials without original data were excluded.

Data extraction and outcomes

Two reviewers (PG and EH) independently extracted demographic data, operative information and patients' outcomes from the included studies. The data points recorded were: donors' age and weight, donor status (living or cadaveric), recipient indication for liver transplantation, age and recipient weight, donor-to-recipient weight ratio (DRWR), graft-to-recipient weight ratio (GRWR), surgical techniques used for manipulating LLS, segments implanted, postoperative vascular complications, median follow-up, graft and patient overall survival. Row data is presented with mean and media (range) values as well as percentages. Series with <3 cases were not considered to avoid "overweight" their values (6,10,11).

Definitions

The LLS (1) can be modified into: (I) partially reduced grafts, or (II) monosegments. In addition, it can be done before perfusion (*in-situ*) or afterwards (*ex-situ*), from DD or LDLT.

RLLS and/or HRLLS refer to those grafts obtained by transecting along peripheral (horizontal and vertical) section planes of the graft. The references tend to be the outflow, not following the Couinaud's segmentation, hence some authors name them "non-anatomical". Those grafts referred as "reduced to segment…" using peripheral planes for transection, were regarded as reduced (12).

Monosegmental liver transplantation refers to any graft including either segment 2 or 3. This technique is characterised by:

- ❖ Following inflow landmarks as per anatomical Couinaud's segmentation.
- ❖ There is "disruption" of the Glisson capsule.
- ❖ Addresses volume and thickness of the graft.

Query

Two queries were proposed in this systematic review (SR). First, are the overall results of surgically modifying the LLS comparable to the standard LLS pLT? And second, are the different modalities, MSG and RLLS, comparable?

Statistical analysis

The methodological quality of each of the included studies

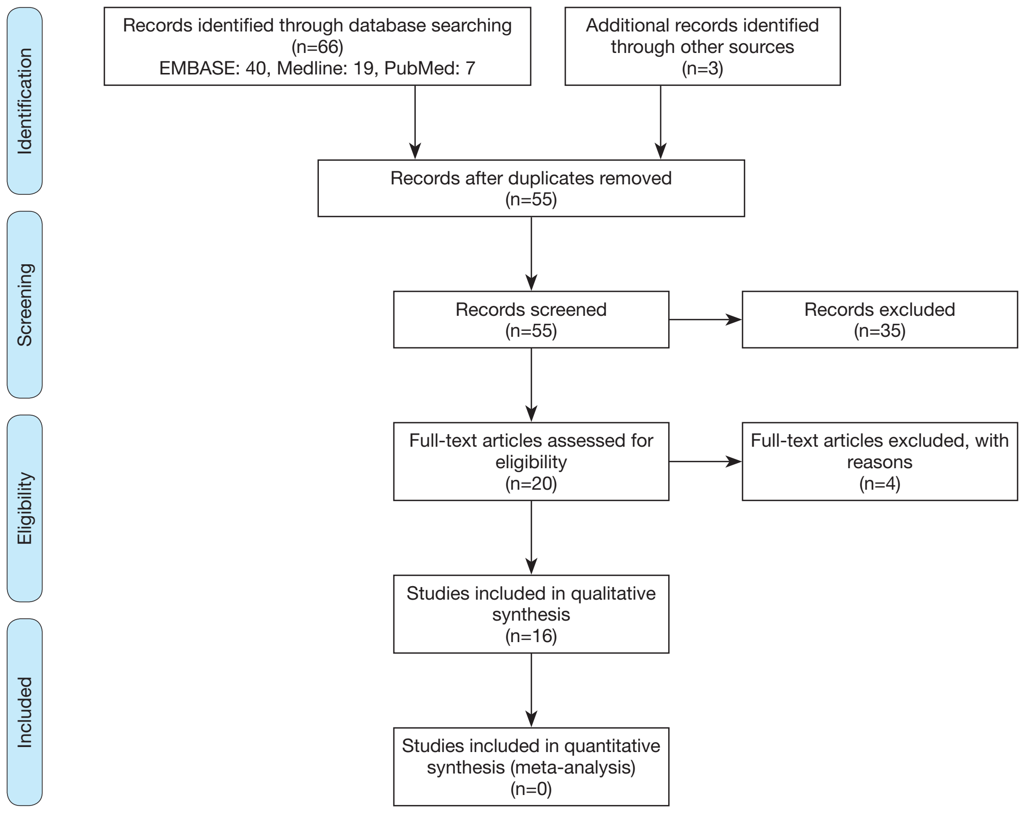

Figure 1 Diagram of the search strategy.

was evaluated for risk of bias using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) which incorporates seven domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of reported results. An important feature of ROBINS-I is the use of signalling questions to detect the risk of bias and facilitate assessment within seven bias domains (13). In all analyses, the point estimate was considered significant at P<0.05.

Results

Sixteen studies from a pool of sixty-two were selected (6,7,10-12,14-24) (*Figure 1* and *Table 1*). Six articles (25-30) were excluded to avoid repetition as more updated publications from the same institutions were identified. This SR includes 330 pLT with a median follow-up of 39 months ranging from 6 to 87 months (composite of each manuscript).

Quality assessment

The overall quality of the studies included varied from moderate to low. Selection, confounding, underpowered sample, detection, national and institutional bias might have influenced the results (Table S1).

- ❖ Overall results (*Tables 1,2*): there were 37% MSG and 63% RLLS/HRLLS grafts. Median recipient age was 7 months (5 days to 22 months) with a median weight of 5.8 kg (2.6 to 8 kg). Ninety percent of the grafts were LDLT. Mean and median donor/recipient weight ratio was 10 (range, 6.25–14). The median implanted graft weight was 209 grams [121–264] generating a median GRWR of 3.5% (2.7–5.6%). HAT and portal vein thrombosis (PVT) overall incidence were 1.5% and 4.2%. Out of 330 patients, 6 underwent re-transplantation within the first 90 days [2 HAT, 1 primary non function (PNF) and 1 PVT, 2 antimicrobial resistant (AMR)] (15,21,24). With a median follow-up of 39 (range, 6–87) months, the overall graft and

Table 1 Study characteristics

Author, (series' span)	Number of patients, status of donor	Donor age (years), median (range)	Donor weight (kg), median (range)	Reduction technique & segment utilised	Recipient weight (kg), median (range)	Recipient age (months), median	Indications
Strong (6) (1992)	1 DD	NR	65	MSG: III (Back-table)	4.7	4	BA-RTx (HAT)
Mentha (10) (1996)	1 DD	22	78	MSG: II (Back-table)	6.9	11	BA -RTx
Srinivasan (7) (1989–1998)	6 DD	8.8 (2 m–14 y)	33.7 [16–60]	RLLS: III (Back-table)	3.45 (2.45–5.46)	1	FHF 5 RTx for HAT: 1
Nujaim (11) (1984–2000)	2 DD	10 [2–53]	65	MSG: II (Back-table)	2.6	NR	FHF: 2
Kasahara (12) (1990–2002)	14 LD	32 [20–48]	61.1 [45–103]	HRLLS *in-situ* S: III (13) HRLLS *in-situ* S: II (1)	5.95 (3.5–7.4)	7	8 BA FHF: 4
Attia (14) (2002–2003)	4 DD	46.5 [6–56]	64.5 [20–78]	HRLLS: III (Back-table)	4.9 (2.9–7.8)	2.8	FHF:1, BA:1 MD:1 RT:1
Grabhorn (15) (1991–2006)	10 DD	5 [1–27]	25 [8–60]	RLLS:5, HRLLS:4, (Back-table)	3.25 [2–4]	0.5	FHF: 10
Enne (16) (2002–2008)	12 LD	NA	NA	MSG: III	6.2 (4.6–9.0)	12	BA
Thomas (17) (1986–2009)	8 DD + 1LD	NA	NA	HRLLS: 9 (Back-table)	7.5	10	BA
Shehata (18) (2000–2009)	44 LD	34 [20–61]	NR	MSG III: 26 Reduced MS III: 18	5.45 (2.78–8.00)	7	BA: 24; FHF: 16; MD: 4
Kanazawa (19) (2005–2011)	31 LD			HRLLS (*in-situ*)	5.8 (2.8–8.5)	7	BA: 18, FHF: 7; MD: 4
Sakamoto (20) (2005–2013)	5 LD	36 [28–36]	66.6 (57.3–84.4)	MSG: II	6.2 (4.0–9.4)	5	BA: 4, MMA: 1
Sanada (21) (2001–2015)	13 LD	NR	NR	MSG II:12 MSG III:1	3.3 (2.6–7.1)	1	FHF: 8; BA: 2; others: 3
Raices (22) (1994–2018)	59 LD	31 [31–38]	69 [63–78]	HRLLS (back-table)	8.0 (7.0–8.9)	14	BA 46; Alagille syndrome 6
Kitajima (24) (2005–2017)	89 LDLT	33 [20–62]	–	HRLLS 47 MSG II :42	5.9 (2.4–9.4)	7.3	BA 50; FHF 17; others 29
Hirata (23)	25 LD	NR	NR	Medial reduction (*in-situ*)	7.1 (6.4–8.0)	10	BA: 25
Overall	330 pts; LD: 298 (90%); DD: 32 (10%)	Median: 31 (5–46.5); mean: 25	Median: 65 [25–78]; mean: 60	a. MSG: 120 (37%) S3: 58 S2: 62 Reduced: 210 (63%) Hyper-R 159 Medial Reduction 25	Median: 5.8 (2.6–8.0); mean: 5.4	Median: 6 months; mean: 6	BA: 197; FHF: 70; others: 63

DD, deceased donor; NR, not reported; MSG, monosegment; BA, biliary atresia; RTx, re-transplantation; HAT, hepatic artery thrombosis; m, months; y, year; RLLS, reduced left lateral sector; FHF, fulminant hepatic failure; LD, living donor; HRLLS, hyper-reduced left lateral sector; MD, medial reduction; NA, not available; MMA, methyl malonic acidemia; LDLT, living donor liver transplantation; pts, patients.

Table 2 Outcome of interests: MSG *vs.* reduced LLS grafts

Outcome of interest	Monosegments (overall n=120)	HRLLS/RLLS (overall n=210)	Significance
Recipient age (months) (6,7,10-12,14,15,19-24)			
N available =330			
Median	6	7	
Mean (range)	5.8 [1–11]	6.5 (0.5–14)	
	(n=120)	(n=210)	
Recipient weight (kg) (6,7,10-12,14-24)			
N available =330			
Median	5	5.8	
Mean	4.9 (2.65–6.9)	5.7 (3.45–8.1)	
	(n=108)	(n=210)	
Donor to recipient weight ratio (6,7,10-12,14-23)			P=0.01
N available =241			
Median	14	9	
Mean	11	9.25 [8–12]	
	(n=78)	(n=163)	
Proportion LDLT/DD (6,7,10-12,14-24)			
N available =330	116/4	182/28	
	(n=120)	(n=210)	
Graft weight (grams) (11,12,14,17-20,22,24-26)			
N available =299			
Median	160	205	
Mean	164 [124–214]	211 [172–264]	
	(n=104)	(n=195)	
Graft recipient weight ratio (%) (12,14,15,18-21,23-26)			
N available =299			
Median	3.3	3.67	
Mean	3.2 (2.7–3.6)	3.89 (2.8–5.6)	
	(n=104)	(n=195)	
Reduction rate (%) (17-21,23-26)			
N available =280			
Median	40	30	
Mean	41 [34–48]	31 [22–39]	
	(n=104)	(n=176)	

Table 2 (*continued*)

Table 2 (*continued*)

Outcome of interest	Monosegments (overall n=120)	HRLLS/RLLS (overall n=210)	Significance
Abdominal wall closure rate (%) (6,7,12,15,17,19,20,23,24)			
N available =177	47/49 (95%)	70/103 (67%)	
		(25/25 in Medial Reduction)	
Hepatic artery thrombosis (6,7,10-12,14-24)			
N available =330	3/120 (2.5%)	5/210 (3%)	
Portal vein thrombosis (6,10-12,14,15,17-24)			
N available =318	4/108 (3.7%)	10/210 (4.7%)	
Overall graft lost (6,7,10-12,14-24)			
N available =330	16/120 (13%)	29/210 (14%)	
Retx cases (6,7,10-12,14-24)			
N available =330	3/120 (2.5%)	7/210 (3.3%)	
Overall patients lost (6,7,10-12,14-24)			
N available =330	13/120 (11%)	22/210 (10%)	

Data are presented with median and mean (including range). Not all the articles provided same amount of data, therefore the size number of each category is shown. MSG, monosegment; LLS, left lateral sector; HRLLS, hyper-reduced left lateral sector; RLLS, reduced left lateral sector; LDLT, living donor liver transplantation; DD, deceased donor.

patient survival were 84% and 89%: a total of 35 deaths were reported throughout all publications, some of them due to delayed causes (*Table 3*).

- Reduced grafts (*Table 2*): 210/330 were reported as reduced grafts (7), including hyper-reduced (12,14,15,17-19,22,24) and medial (23). Shehata's (18) and Kitajima's (24) series comprise MSG and RLLS. Only three of the ten authors performed the reduction *in situ* (19,23,24) although it represented 49% of the series. Actual median graft weight and GRWR obtained were 205 grs [172–264] and 3.67% (2.8–5.6).
- Monosegmental grafts (*Table 2*): 120/330 were reported as monosegmental grafts (6,10,11,16,18,20,21,24). The vast majority were LDLT. Recipients were younger and there was a higher DRWR mismatch. Nevertheless, the actual graft weight and GRWR (3.3%) obtained were smaller than RLLS allowing to go below the 4% GRWR mark. Vascular complications (HAT and PVT) were no different nor was overall mortality. Only nine publications reported data regarding abdominal wall closure (177 patients). Primary closure was more frequent in MSG (47/49) (6,12,20,24) than in RLLS (70/103) (7,15,17,19,24), being the medial reduction (25/25) an exception (23).

Discussion

This is the first systematic review that evaluates the existing evidence with monosegmental and reduced LLS grafts in paediatric liver transplantation over the last 25 years. There is a former manuscript published in 2005 focusing on 7 papers and including 27 MSG, arguably labelled as a meta-analysis (29,31-36).

The studies evaluated were quite heterogenous, including single case reports (6,10) and large series. Five of the sixteen studies (18,19,22-24) represented 82% of the total population (*Table 1*). In addition, the age ranged from 5 days to 22 months. Some studies included only neonates (7,15) while the rest included infants as well.

The overall median weight of this cohort was 5.8 kg (2.6–8 kg) and it clearly represents a complex group of recipients where a significant DRWR mismatch can be expected. This might result not only in a compartment syndrome but can also compromise the inflow and outflow of the graft. Some authors refer to this scenario as a large-for-size syndrome (2-6).

Are the results of surgically manipulating the LLS comparable to the standard LLS?

This cohort of 330 modified LLS, albeit heterogenous, provided an overall graft and patient survival of 84% and 89% with a median FU of 39 months (3 years). The incidence of HAT and PVT were 1.5% and 4.2%. Direct comparison with standard LLS is difficult given historical bias and large series will include a wide range of age and weights. In fact, the comparison should be made against recipients with similar weight (5 kg) receiving a standard-whole LLS. A significant consequence in this later approach would be the need for delayed/secondary abdominal wall closure, bridging the gap with a prosthetic or biological mesh (4,5).

Table 4 presents graft and patient overall survival from large series for comparison. Figures reported are not dissimilar to those in MSG and RLLS.

Table 3 Causes of patients' death

Deaths (overall)	ALL	Monosegmental	Reduced LLS
• Sepsis	• 15	• 4	• 11
• HAT	• 2	• 1	• 1
• PVT	• 1	• 1 (after retx)	• -
• GVHD	• 1	• -	• 1
• Pulmonary haemorrhage	• 1	• -	• 1
• Pulmonary hypertension	• 2	• 1	• 1
• Pneumonia	• 1	• 2	• -
• CVA	• 4	• 1	• 3
• MOF	• 2	• -	• 1
• Rejection	• 3	• 3	• -
• Not specified	• 3	• -	• 2
			• 1
	35/330	13/120	22/210
RETX (<90 days)	6	1 (PVT)	3 (1 PNF + 2 HAT)
RETX (>90 days)	4	1 PVT + ACR	2 ACR + sepsis

LLS, left lateral sector; HAT, hepatic artery thrombosis; PVT, portal vein thrombosis; GVHD, graft *vs.* host disease; CVA, cerebral vascular accident; MOF, multi-organic failure; PNF, primary non function; RETX, retransplantation; ACR, acute cellular rejection.

Are the different modalities for surgically manipulating a LLS comparable?

We found sixteen articles presenting several institutions' strategies to address the issue of a severe GRWR mismatch. Out of 330 pLT, 37% were MSG and 63% RLLS.

At birth, the liver represents close to 3.5% of our Total Body Weight (range, 2.1–4.7), to then gradually become 2–1.5% (range, 1.8–2.8) in individuals >17-year-old (42). An adult LLS might represent 16% (±4) of the Standard Total Liver Volume (1,518±353 cc), averaging 242±79 cc (31). Accordingly, a 5 kg child receiving a LLS graft, will likely face a GRWR close to 5% (1:1 equivalence between cc and grams). It is well documented that GRWR is a strong predictor of graft survival and the vast majority of reports concur that those grafts exceeding 4% will likely generate a conflict with the abdominal cavity's capacity (4,5,12,16-20,23,25,43-45). Hence, some groups advocate for altering the LLS, reducing or converting it into a monosegment. One should however avoid adopting a very dogmatic view based only on volume, since several other factors (ascites, sarcopenia and specially graft thickness) will have a role in deciding (the myth of 4?) (46). Even though the first MSG was reported by Strong in 1992, there is a clear preference for this technique in Japan, whereas

Table 4 Graft and patient overall survival in paediatric LT

Study	Period	Age	Graft	Patient	Total
ELTR (37)	1988–2015	2–18 years	71% at 3 years	82% at 3 years	n=5,886
SRTR (38)	1897–2018	<18 years	75% at 5 years	88% at 5 years	n=13,442
JLTS (39)	1989–2010	NR	NR	88% at 1 year	n=2,224
UCLA (40)	2007–2015	<18 years	73% at 1 year	86% at 1 year	n=1,000
SRTR (41)	2014–2016	<18 years	88% at 3 years	93% at 3 years	August 2020 report
Current SR	1995–2019	NR	88% at 3 years	90% at 3 years	n=241

ELTR, European Liver Transplant Registry; SRTR, Scientific Registry of Transplant Recipients; JLTS, Japanese Liver Transplant Society; UCLA, University of California LA; SR, systematic review; OS, overall survival; NR, non-reported.

reduction seems more prevalent in western countries. When both techniques were compared, some differences were encountered (*Table 2*). Recipients of MSG were younger and lighter with a bigger DRWR mismatch and yet, MSG produced smaller grafts (median of 160 grams), finally achieving a GRWR below 4%. Primary abdominal wall closure was more likely too. The lines of transection for MSG are clearly different from reducing a graft and hence "off-sets" volume and thickness, the only exception being the Medial Reduction described by Hirata *et al.* (23). Several authors (20,21,23) factor on the direct thickness measurement of the graft (median value 6 cm in this SR) or the GRDR (cm from left hepatic vein to PV bifurcation on preop CT imaging) (21) to select their surgical strategies. Results, in terms of vascular complications and overall survival, were similar (*Table 3*). In addition, one must take into consideration that MSG were by and large obtained in-situ from LDLT (94%), with all the technical complexity added, in particular shorter and smaller arteries compared with RLLS in DD, where often the celiac axis is left with the LLS.

Limitations

The results of the present study should be interpreted in the context of its limitations. Assessment of bias within the included studies using ROBINS-I tool demonstrated that the overall quality varied from moderate to low and confounding, selection and detection bias might have affected the results. Furthermore, seven out of sixteen studies included less than 10 patients (6,7,10,11,14,17,20). Five studies (three from Japan, India and Argentina) represented the 67% of the total sample (18,19,22,23). The time span of the included studies extended over 25 years period. Therefore, institutional, national, underpowered sample, selectional, detection and learning curve bias might have influenced the results.

Conclusions

The large majority of reports included in this SR would recommend aiming for a GRWR <4% to reduce the risks of a large-for-size scenario. RLLS and MSG are both optimal options to facilitate pLT to a very small recipients with results comparable to standard LLS despite the technical complexities. MSG will be able diminish volume and thickness providing the smallest possible graft, in particular Segment 2. Special mention deserves the Medial Reduction which effectively constitutes a non-anatomical reduction of Segment 3 altering volume and thickness and allowing primary closure.

Experience is paramount and needs to be considered in, for these techniques to be seen as an established modality of treatment.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-792/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-792/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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