The efficacy of prednisolone therapy following Kasai portoenterostomy (PE) in improving early post- operative outcomes among Biliary atresia patients: A pilot randomized controlled study

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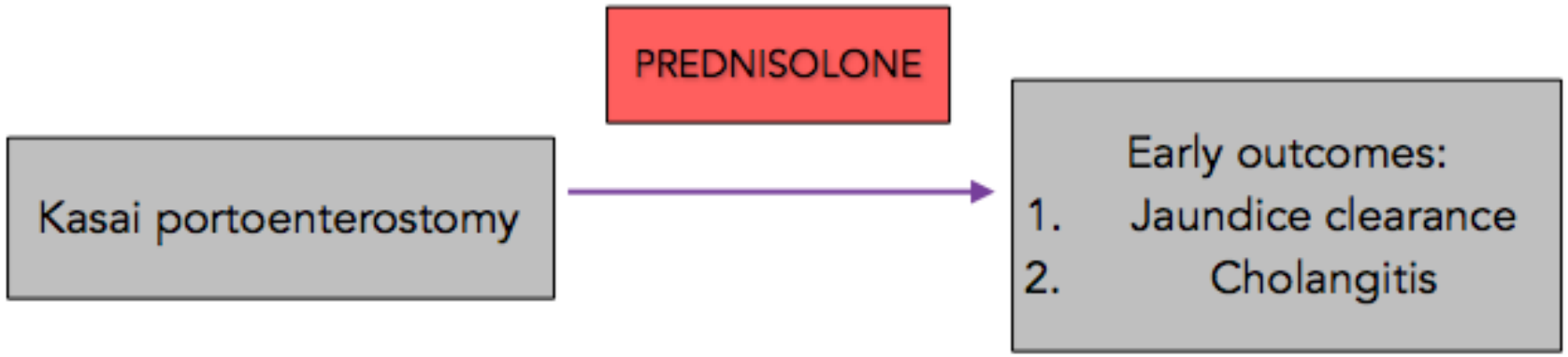
Study background

- Role of prednisolone in Biliary atresia have been reported back in 1985
- results are mixed; and most of positive results were from retrospective studies
- no prospective data in the region of Southeast Asia on the efficacy of steroids in improving outcomes after surgery

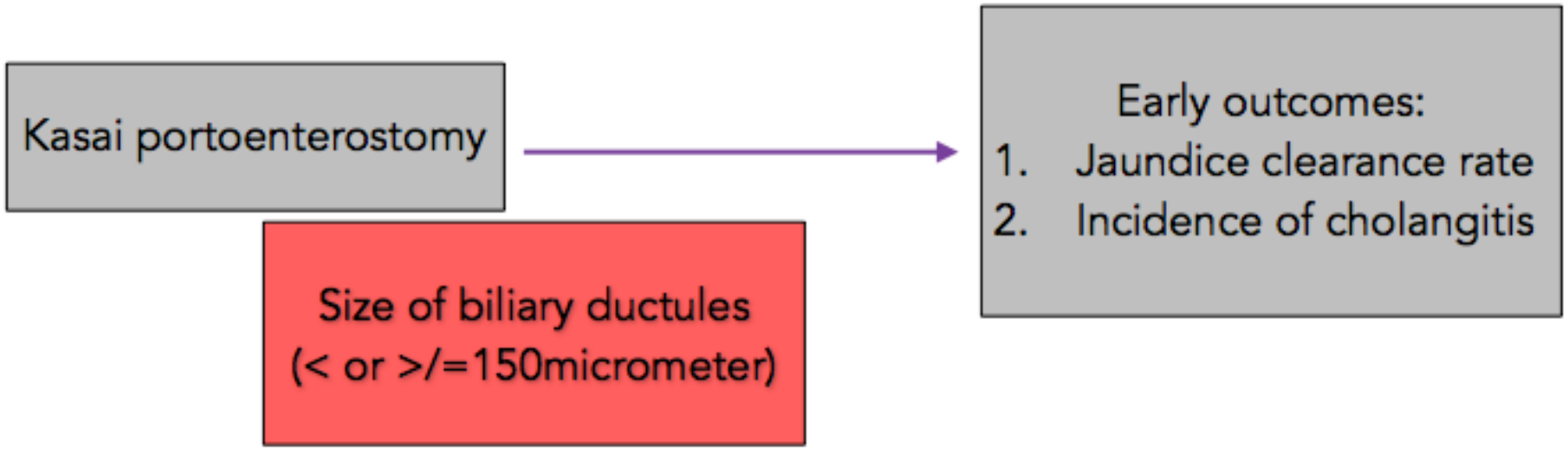
Study primary objective

- To investigate the efficacy of prednisolone after Kasai PE in improving early post operative outcomes (within 6 months post op).



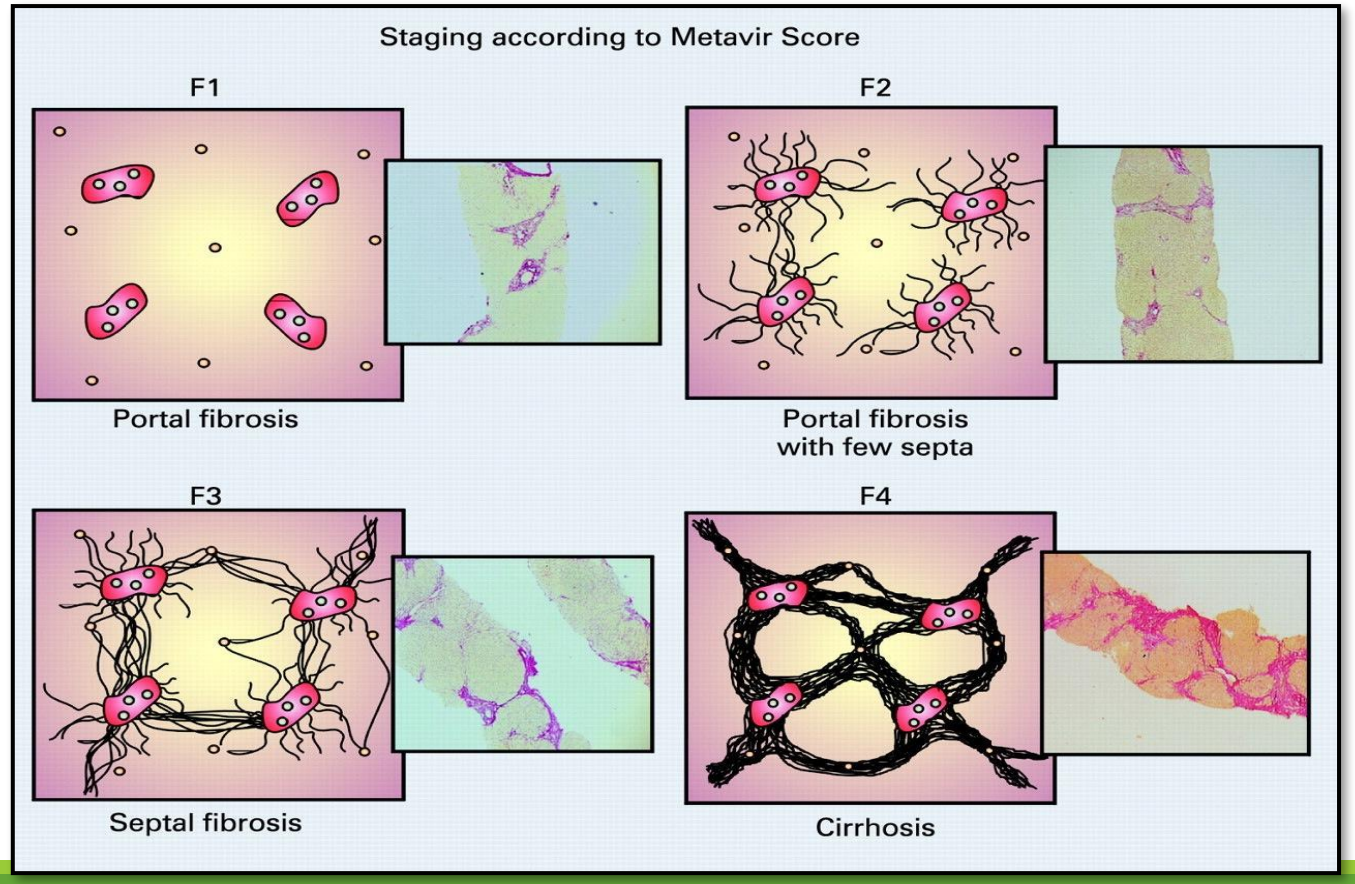
Secondary objectives

- To investigate association between size of biliary microductules and early post operative outcomes



Secondary objectives

- To investigate association between stage of liver fibrosis at the time of Kasai PE with early post operative outcomes.



Aseelah T, Bieche I, Sabbagh A, Bedossa P et al. Gene expression and hepatitis C virus infection. Gut 2009; 58: 849-858

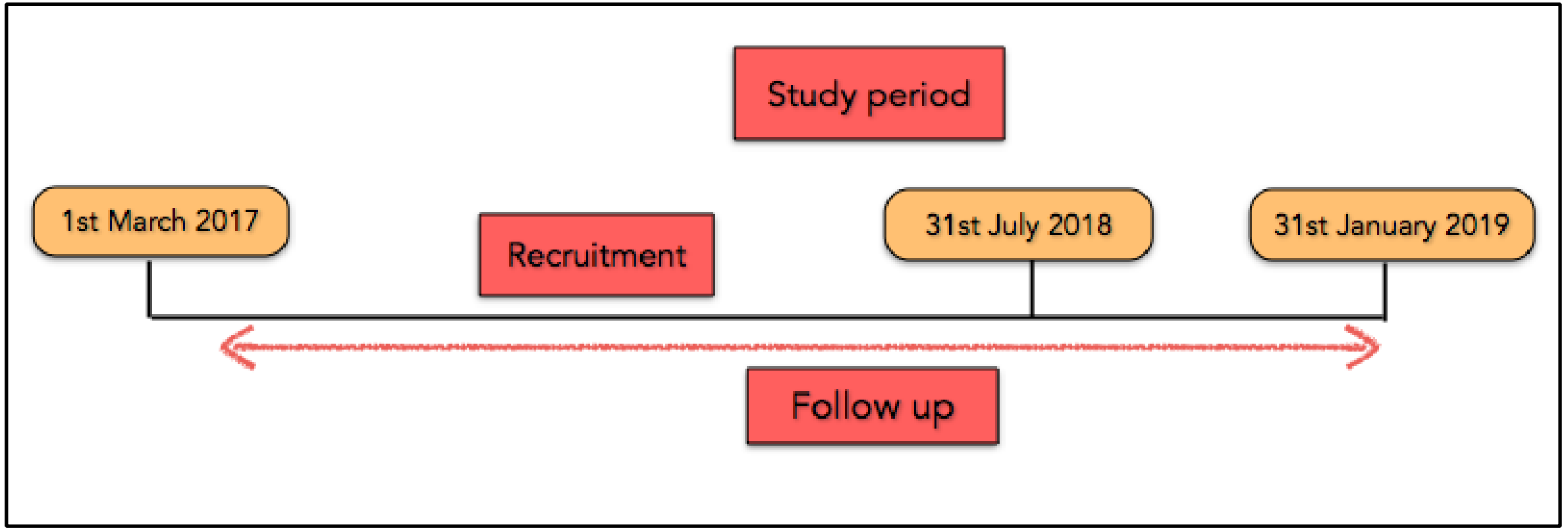
Secondary objectives

- Correlation between early cholangitis (within 3 months following Kasai PE) and jaundice clearance at 6 months post Kasai PE

Methodology

- Pilot randomized controlled study
- 2 centres involved:
  - Institute Paediatrics, KL & Sultanah Bahiyah Hospital (referral hospital for northern part of Peninsular Malaysia)
- Study period: 1/3/2017 – 31/1/2019
- Follow up for at least 6 months following Kasai PE
- Ethical approval: National (Malaysian) Medical Research Registry (NMRR)- NMRR 17-702-34473

Study period: 1/3/2017 – 31/1/2019



Jaundice clearance

Definition: Achievement of total bilirubin less than or equal to 20 micromol/L at 6 months following Kasai portoenterostomy

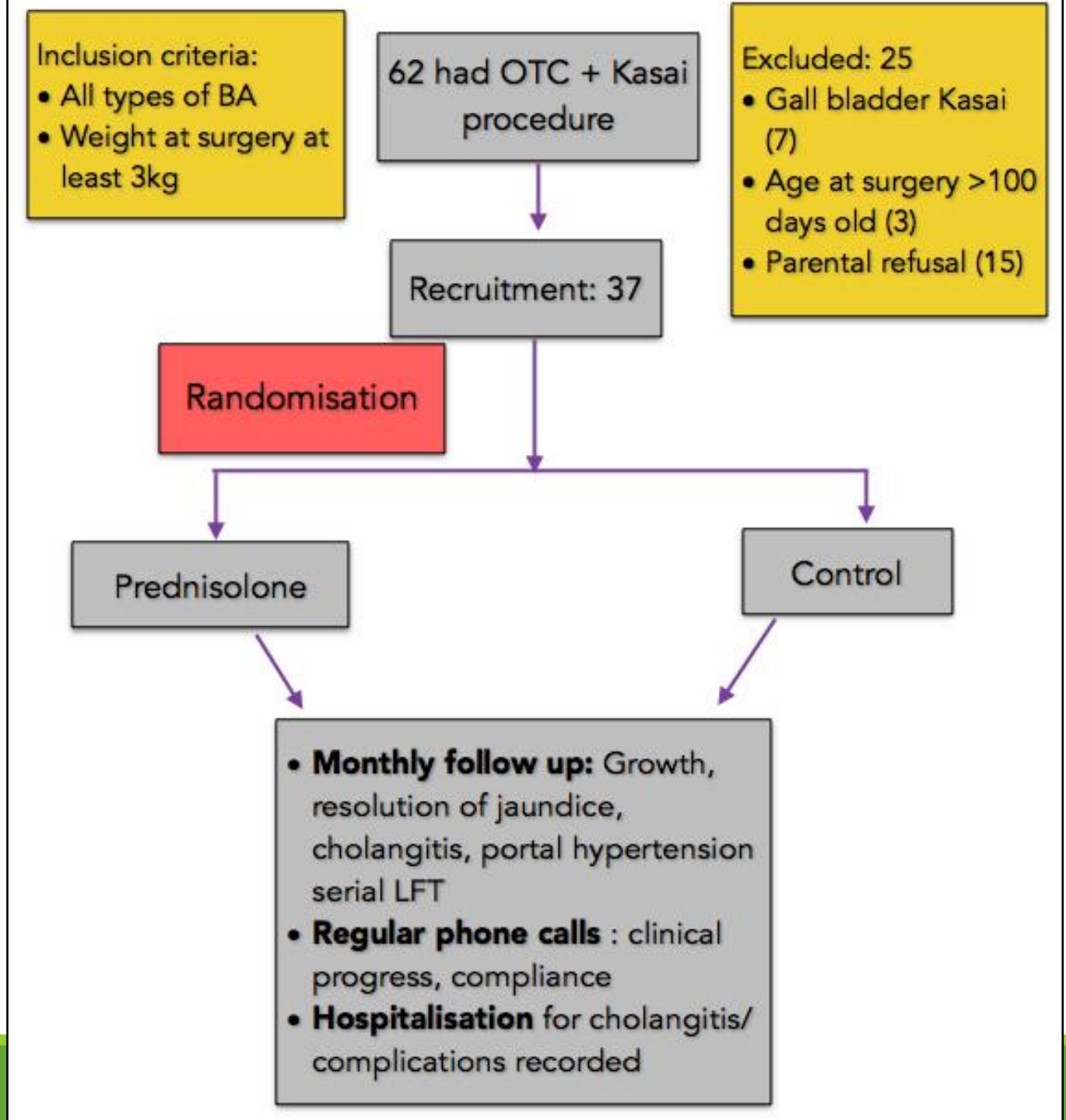
Davenport M, Stringer MD, Tizzard SA et al. Randomised, Double- blind, Placebo- controlled Trial of Corticosteroids after Kasai portoenterostomy for Biliary atresia. Hepatology 2007, 46: 1821-1827

Cholangitis

- Definition: Fever (temperature:38 degrees/ more) without any other identifiable source of infection, assoc with 1/ > of following criteria:
- Jaundice or acholic stool, sudden elevation of bilirubin or liver enzymes, or isolation of bacteria on blood culture

1. Shin JH, Chang EY, Chang HK et al. Home intravenous antibiotic treatment for intractable cholangitis in patients with biliary atresia following Kasai portoenterostomies. Journal of Korean Surgical Society 2011, 80: 355-361.
2. LW Ernest Van Heurn, Htut Saing, Paul KH Tam. Cholangitis after hepatic portoenterostomy for Biliary atresia: A multivariate analysis of risk factors.
Journal of Pediatrics 2003, 142: 566-71

Study flow chart

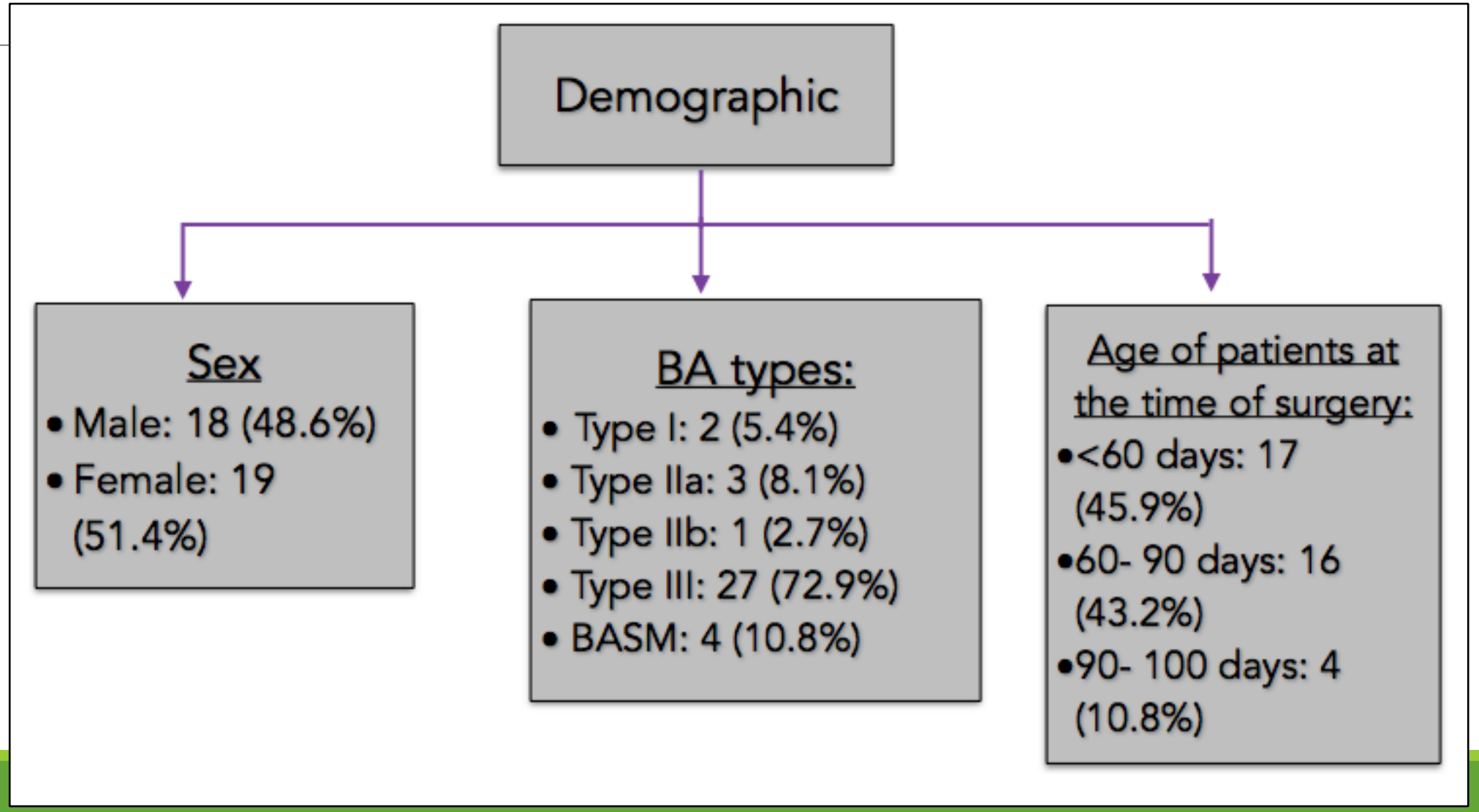


Medications given for each study arm:

PREDNISOLONE ARM	CONTROL ARM
1. Oral Prednisolone * for 3 months in tapering doses 2. Syp Trimethoprim 4mg/kg OD 3. Syp Ursodeoxycholic acid 15mg/kg OD 4. Syp Vitamin K 1mg OD 5. Syp Multivitamin 2 ml OD 6. Syp Ranitidine 2mg/kg BD	1. Syp Trimethoprim 4mg/kg OD 2. Syp Ursodeoxycholic acid 15mg/kg OD 3. Syp Vitamin K 1mg OD 4. Syp Multivitamin 2 ml OD 5. Syp Ranitidine 2mg/kg BD

Prednisolone *:
Initiation dose: 4mg/kg OD x 2 weeks, then 2mg/kg OD x 2 weeks, then 1mg/kg OD x 2 month

Results


Demographic
Sex
• Male: 18 (48.6%)
• Female: 19 (51.4%)
BA types:
• Type I: 2 (5.4%)
• Type IIa: 3 (8.1%)
• Type IIb: 1 (2.7%)
• Type III: 27 (72.9%)
• BASM: 4 (10.8%)
Age of patients at the time of surgery:
•<60 days: 17 (45.9%)
•60- 90 days: 16 (43.2%)
•90- 100 days: 4 (10.8%)

Outcome 1: Jaundice clearance

- Overall jaundice clearance rate: 19/37 (51.4%)
- prednisolone: 13/19 (68%),
- control: 6/19 (32%)

Variable	Prednisolone		Control		X^2 statistic (df)	p value [a]
	n	**%**	**n**	**%**		
Jaundice clearance					1.30 (1)	0.254
Yes	13	68.4	6	31.6		
No	9	50	9	50		

[a] Chi-square test

Outcome 2: Cholangitis

Overall incidence: 22/ 37 (59%)

Prednisolone: 13/22 (59%)

Control: 9/22 (41%)

Variable	Prednisolone		Control		X^2 statistic (df)	p value [a]
	n	%	n	%		
Cholangitis					0.003(1)	0.956
Yes	13	59.1	9	40.9		
No	9	60.0	6	40.0		

[a] Chi-square test

Secondary objectives:

1. To investigate association between size of microductules & early post-operative outcomes
2. To investigate association between stage of liver fibrosis at Kasai PE with early post-operative outcomes
3. To investigate correlation between early cholangitis and jaundice clearance at 6 months after Kasai PE

1. No significant correlation between size of biliary microductules and outcomes.

Variable	Size of biliary microductules				X^2 statistic (df)	p-value [a]
	< 150 micrometer		>/= 150 micrometer			
	n	%	n	%		
Jaundice clearance					0.02 (1)	0.877
Yes	10	52.6	9	47.4		
No	8	50.0	8	50.0		
Cholangitis					0.69 (1)	0.407
Yes	12	57.1	9	42.9		
No	6	42.9	8	57.1		

[a] Chi-square test

2. No significant association between stage of liver fibrosis and post operative outcomes

Variable	Stage of liver fibrosis				X^2 statistic (df)	P-value[a]
	Low fibrosis stage		High fibrosis stage			
	n	%	n	%		
Jaundice clearance					0.17 (1)	0.678
Yes	12	63.2	7	36.8		
No	9	56.3	7	43.8		
Cholangitis					0.49 (1)	0.486
Yes	11	55.0	9	45.0		
No	10	66.7	5	33.3		

Chi-square test
Low fibrosis stage: Metavir 0,1, 2
High fibrosis stage: Metavir 3, 4

3. No significant association between early cholangitis (within 3 months post op) and jaundice clearance at 6 months following Kasai PE

	Jaundice clearance				p value [a]
Variable	Yes		No		
	n	%	n	%	
Cholangitis					0.613
Early	7	41.2	10	58.8	
Late	1	20.0	4	80.0	

[a] Fisher's exact test

Discussion

- Overall jaundice clearance rate in our cohort: 51% (Previous reports: 40-60%).
- Jaundice clearance better in prednisolone arm, but this was not statistically significant
  - small sample

- Patients achieved jaundice clearance
  - 12/19 - no cholangitis within 6 months
  - 13/19 - prednisolone arm

Discussion

- Overall cholangitis incidence: 59% (previous reports: 30-60%)
- higher incidence in prednisolone (not statistically significant)
- possible contributed by poor nutritional status
- Li et al (2017): Pre operative nutritional status was significantly associated with post op cholangitis

Li D, Chen X, Fu K et al. Preoperative nutritional status ad its impact on cholangitis after Kasai portoenterostomy in biliary atresia patients. Pediatric Surgery International 2017, 33: 901-906

Conclusion

Prednisolone seems to have role in jaundice clearance
Uncertain about its role in reducing cholangitis rates

Future multi-centre study with longer duration of follow up is needed.
Nutritional aspect should be assessed in future study

Questions?

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