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Clinical Outcomes of Integrated Treatment strategies in Progressive Familial Intrahepatic Cholestasis: Single Center Experience

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ABSTRACT

Objective: To evaluate the effectiveness of integrated treatment modalities based on outcomes and survival.
Study Design: Progressive Longitudinal.
Place and Duration of Study: Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences (PAQSJIMS), Gambat, Pakistan, from Jan 2019 to Dec 2023.
Methodology: This study enrolled 43 patients with Progressive Familial Intrahepatic Cholestasis (PFIC), who were categorized into three treatment groups: medical management (n=22), Partial Internal Biliary Diversion (PIBD) (n=9), and Living Donor Liver Transplantation (LDLT) (n=12). Outcomes were assessed using pruritis scores, survival rates, and morbidity using Calvin-Dindo classification.
Results: In the medical management group, mean follow-up was 39.14±20.49 months, with a 90.90% survival rate and significant pruritis improvement (2.09±1.01, p=0.006) while the PIBD group had a mean follow-up of 49.89±21.07 months, a 100% survival rate, and significant pruritis reduction (0.78±0.83, p=0.021) but the LDLT group had a mean follow-up of 24.42±12.42 months, a 91.66% survival rate, and major morbidity (III-b). Overall survival across groups was 68.61±2.44 months.
Conclusion: Medical management and PIBD could be considered as initial treatments for well-compensated PFIC patients, while liver transplant is recommended only for cases with treatment failure.

Keywords: Biliary tract surgical procedures, Cholestasis, Liver transplantation, Progressive familial intrahepatic cholestasis, Pruritus.

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INTRODUCTION

Progressive Familial Intrahepatic Cholestasis (PFIC) presents with jaundice, pruritus, and failure to thrive, ultimately leading to end-stage liver disease in early childhood, with an incidence of 1 in every 50 to 100, 000 people in the world.[1] Bile is responsible for the digestion of food,[2] with different transporters, which help bile flow, called ATP-binding cassette transporters (ABC transporters).[3] Autosomal mutation causes bile flow interruption, resulting in PFIC, with complications leading to liver tumors, an important indication for liver transplant.[4] With advancement in gene studies, three subtypes have been introduced based on next generation and whole exome gene sequencing: Type IV (TJP2), Type V (NR1H4) and Type VI (MYO5B).[5] PFIC usually presents in infants and early childhood with jaundice, pruritis and hepatomegaly, along with extra hepatic manifestations like diarrhea, pancreatitis, sensory neural deafness and failure to thrive with a severe variant of the disease showing rapid progression and risk of developing hepatocellular carcinoma,[6] compared with slowly developing fibrosis of liver which can lead to liver cirrhosis as children present late.[7] The diagnosis of PFIC is with confirmatory genetic testing, however, due to cost, its usage remains limited.[8] In patients with normal liver functions, medical treatment and biliary diversion remain the treatment of choice.[9] Failure of therapies, interactable pruritis, and progression to liver cirrhosis are considered the main indications of liver transplant (LTX).**Error! Bookmark not defined.**,[10] Despite growing understanding of PFIC, significant knowledge gaps remain, particularly in developing countries like Pakistan as available epidemiological data comes from Western populations, with limited regional or ethnic-specific studies addressing the prevalence, clinical spectrum, and genetic profiles of PFIC in South Asia, thus, the aim of this study is to evaluate the effectiveness of integrated treatment modalities, based on their outcomes and survival.

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METHODOLOGY

This prospective longitudinal study was conducted at Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat, Pakistan from January 2019 to December 2023 after gaining approval of Institutional Ethics Review Board via approval letter IRB/24/15. Since this was a study involving a rare disease and the total number of eligible patients during the study period was 43, all of them were included due to the rarity of the condition. The sample size was not calculated beforehand, using a traditional power calculation, instead, it was based on non-randomized consecutive patient enrollment over the study time frame.

Inclusion Criteria: Patients of either gender, aged more than 18 years, with a working diagnosis of PFIC (on the basis of clinical history, examination, biochemical markers indicative of intrahepatic cholestasis with persistently raised bilirubin levels, liver histopathology findings consistent with PFIC), and genetic testing results, where available, were included.

Exclusion Criteria: Patients were excluded in case of incomplete medical records, loss to follow-up, follow-up of less than 12 months, patients with extrahepatic manifestations of PFIC, having other liver diseases, structural abnormalities of biliary tract, prior hepatobiliary surgeries, and having cholestasis due to sepsis or other systemic disease.

Based on treatment received, patients were categorized into three groups: Group A (Medical Treatment) included patients without end-stage liver disease (ESLD), who received therapies including ursodeoxycholic acid, rifampicin, or ileal bile acid transport inhibitors, patients with persistent refractory pruritus but improved liver function were shifted to other treatment groups, Group B (Partial Internal Biliary Diversion: PIBD) included patients who failed medical treatment and poor quality of life but had no liver decompensation as they underwent surgical diversion procedures like cholecysto-jejuno-colic or cholecysto-ileo-colic diversion, Group C (Living Donor Liver Transplantation: LDLT) included patients with liver decompensation or poor quality of life due to disease progression or prior treatment failure. Treatment outcomes were evaluated based on clinical improvement which included improved quality of life in terms of severity of pruritus (assessed using the Itchy Quant Scale),[11] where scoring was done before and after the treatment by showing the scale to the patients or primary care givers and response on a scale of 0 to 10 was recorded, as shown in Figure-1. Biochemical markers including serum total bilirubin (mg/dL), liver enzymes (ALT, AST, ALP, GGT), serum albumin (g/dL) and International Normalized Ratio (INR) for coagulation function were measured while surgical and post-transplant outcomes were measured in terms of complication and survival rates. Data was annalysed using Statistical Package for Social Sciences (SPSS) version 25.0. Normality of data was checked by using Kolmogrov-Smrinov test and Shapiro-Wilk test. Descriptive statistics (Mean±SD were used for continuous variables like, follow-up, pruritis, and laboratory values, while categorical variables were presented as frequencies and percentages like types of PFIC, morbidity and mortality. Treatment outcomes across groups were compared using chi-square tests for categorical variables and One-way ANOVA test was used for normally distributed variables including age, weight, ALT, AST, ALP and STB while Kruskall-Walis test was applied for data not normally distributed, including pruritis, INR, Albumin and GGT where statistical significance was set at p-value≤0.05 while overall estimated survival was measured by Kaplan-Meier analysis.

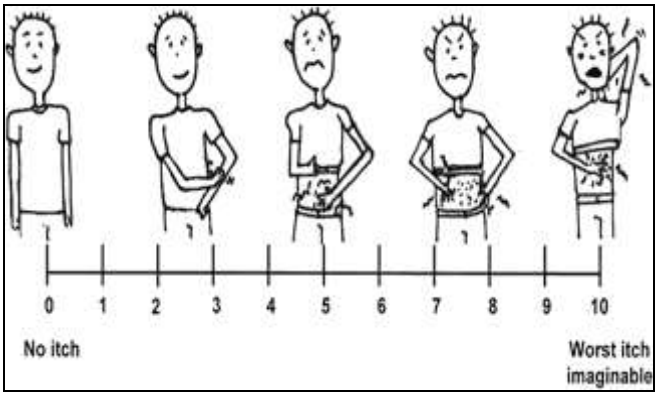

Figure-1: Itchy Quant Scale, Showing Severity of Itching on a Scale of 0 to 10 Grade

RESULTS

A total of 43 patients were enrolled in the study, of which 26(60.50 %) were male and 17(39.50 %) were female with mean age in overall study population being 5.95+4.22 years but in different treatment groups, this was variable and statistically significant (p=0.037). Consanguinity of parents was found in 20(46.5%) patients and among different treatment groups, it was found to be statistically significant

(p=0.041). There were 15(34.9%) cases with known family history of PFIC, while those patients having consanguinity as well as positive family history were only 8(18.60%), which was not statistically significant (p=0.512). Mean weight among participants was 14.33+7.42 kg which was statistically significant (p=o.018) among groups. In the study, four PFIC variants were found with Type I reported in 15(34.9 %) patients, making it the most frequent.

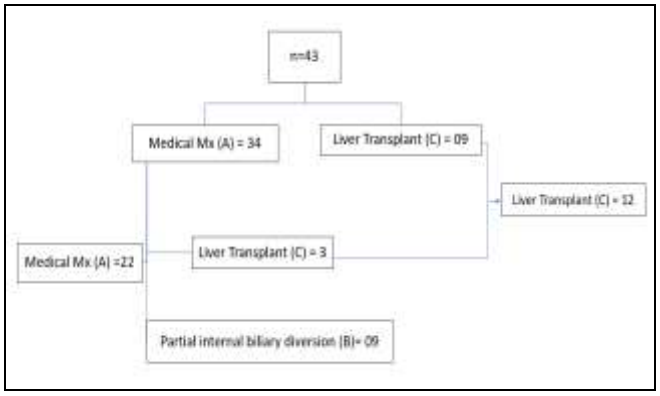

Figure-II: Patient Flow Diagram Showing Distribution into Different Groups, (n=43)

Initially 34(79.06%) patients were enrolled for medical management but 12(27.90%) patients dropped from this group while 1(2.32%) patient, who developed hepatocellular carcinoma (HCC) was enlisted for LDLT, and 11(25.58%) patients were refractory to medical treatment, among these, 7(16.27 %) had interactable pruritis with optimal hepatic functions, due to which they were enrolled in PIBD group but 4(9.30%) patients had interactable pruritis as well as deranged liver functions, so they were shifted to LDLT group of which 2(4.65 %) patients underwent LDLT, while 2(4.65%) patients, due to non-availability of living liver donor, opted for PIBD. During the study, 9(20.93%) patients were directly enrolled for LDLT, thus, the total number of patients in Group A was 22(51.16%), in Group B was 9(20.93%) and in Group C was 12(27.90%). Detailed demographic comparisons of all groups are shown in Table-I.

In Group-A(22,51.16%), 18 patients responded well with significant pruritus improvement (6.64±1.59 to 2.09±1.01), though 2(9.10%) died from decompensated liver failure and 4 remained on therapy due to lack of liver donors. In Group-B, 9(20.93%) patients showed excellent pruritus reduction (6.89±1.45 to 0.78±0.83), with all patients

Table-I: Comparison of Baseline Parameters Among Treatment Groups, (n=43)

Parameters	Group-A Medical management (n=22)	Group-B PIBD (n=9)	Group-C LDLT (n=12)	p-value
Age (years)	4.59 ± 3.60	6.22 ± 4.99	8.25 ± 3.93	0.037
Weight (kg)	11.75 ± 6.74	14.88 ± 7.00	18.66 ± 7.32	0.018
AST (U/L)	64.68 ± 35.09	49.44 ± 14.99	97.83 ± 23.75	0.312
ALT (U/L)	75.18 ± 48.38	54.66 ± 13.36	126.50 ± 81.73	0.064
ALP (U/L)	285.86 ± 197.52	392.55 ± 220.51	325.92 ± 375.07	0.521
Total Serum Bilirubin (mg/dL)	4.78 ± 4.55	2.65 ± 2.90	3.91 ± 4.79	0.455
Gender				0.231
Male	14 (63.6%)	4 (44.4%)	4 (33.3%)	
Female	8 (36.4%)	5 (55.6%)	5 (41.7%)	
Consanguinity				0.041
Yes	13 (59.1%)	4 (44.4%)	3 (25.0%)	
No	9 (40.9%)	5 (55.6%)	9 (75.0%)	
Family History				0.384
Positive	9 (40.9%)	3 (33.3%)	3 (25.0%)	
Negative	13 (59.1%)	6 (66.7%)	9 (75.0%)	
PFIC Type				0.452
Type I	7 (31.8%)	4 (44.4%)	4 (33.3%)	
Type II	1 (4.5%)	1 (11.1%)	2 (16.7%)	
Type III	12 (54.5%)	4 (44.4%)	6 (50.0%)	
Type IV	2 (9.1%)	0 (0.0%)	0 (0.0%)	

ALT: Alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase

Table-II: Comparison of Biochemical and Clinical Parameters Using Median and Interquartile Range (IQR) Across Treatment Groups, (n=43)

Parameters	Group-A Medical management (n=22)	Group-B PIBD (n=9)	Group-C LDLT (n=12)	p-value
Pruritus Score	Median (IQR)	Median (IQR)	Median (IQR)	
Pre-treatment	6.64 (5.0–8.0)	6.89 (6.0–8.0)	–	0.002
Post-treatment	2.09 (1.0–3.0)	0.78 (0.0–1.0)	–	
INR	1.50 (1.2–1.8)	1.16 (1.0–1.3)	1.25 (1.0–1.4)	0.211
Albumin (g/dL)	3.75 (3.2–4.2)	3.56 (3.0–4.0)	3.03 (2.6–3.4)	0.065
GGT (U/L)	116.36 (60–180)	77.00 (30–140)	102.00 (40–160)	0.543

INR: International normalization ratio, GGT: Gamma glutamyl transferase

responding well despite minor complications in 33.33%; but 4 patients with Type III PFIC were advised LDLT. Group-C (12,27.90%) experienced major morbidity (Clavien-Dindo IIIb) including strictures, bile leak, and rejection, with 1 mortality (8.33%) from sepsis, though biochemical parameters improved across all groups, as shown in Table-II. Additionally, overall quality of life in terms of pruritis was significantly improved among Group-A and Group-B (p=0.002).

According to Calvin-Dindo classification, most mortality fell into IIIb category but the mean follow-up in study was 37.28+20.45 months with no long-term follow-up done. Thus, with 3 mortalities, an overall survival rate of 93.02% was noted with no mortality reported in Group-B (survival rate =100%), 2 mortalities in Group-A (survival rate=90.66%) and 1 patient expired in Group-C (survival rate = 90.90%). The overall estimated survival measured by Kaplan-Meier was 68.61+2.44 months, with 95% confidence interval as shown in Figure-III.

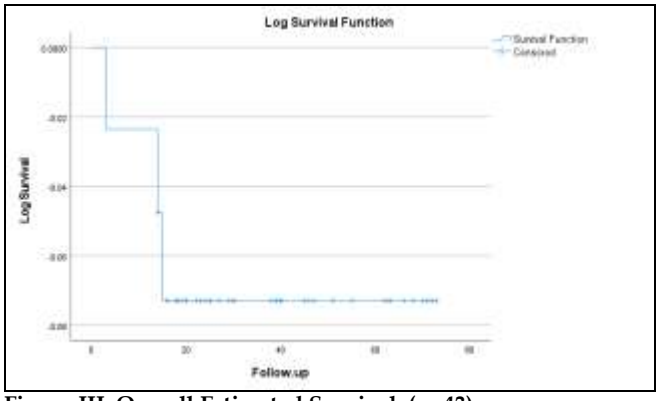

Figure-III: Overall Estimated Survival, (n=43)

DISCUSSION

PFIC is a rare genetic disorder with Type 1 and 2 being the most common types.[8,12,13] Consanguinity was found in only in 46.5% parents, unlike another study which reported consanguinity between parents at 85.3% (n = 29).**Error! Bookmark not defined.** In medical management group, there was improvement in quality of life in terms of pruritis which was statistically significant with similar results reported in another where pruritis improved in two third cases,**Error! Bookmark not defined.** however, there were chances of treatment failure as reported by another author.[14] In PIBD group only 1 major complication was reported which was intestinal obstruction with no mortality, unlike another study where 2 mortalities were reported.[15] In our study, only 1 patient developed HCC, who underwent transplant similar to another study.[16] Post-transplant mortality was 1(8.33 %) in our study with similar results reported in another study with the mortality rate of 7 % but larger sample size.[17] In our study population, Type III PFIC was the predominant type as compared to type I and II found in literature.[18]

LIMITATIONS OF STUDY

This study has several limitations. The small sample size per treatment group, inherent to the rarity of PFIC, limits statistical power and precision in outcome comparisons. The study design at a single center restricts generalizability to diverse populations or healthcare settings. Variable follow-up durations across groups may confound survival and pruritus assessments. Allocation to treatment groups was not randomized, introducing potential selection bias, and the study did not standardize medical management protocols or report long-term quality-of-life metrics beyond pruritus and Clavien-Dindo morbidity.

CONCLUSION

All patients with intact liver functions should receive medical management or PIBD as initial treatment while patients on medical management with intractable itching must be shifted to PIBD with liver transplantation reserved as a last resort for the management of PFIC, to emphasizes the importance of exploring alternative therapeutic options before considering transplant.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HBA & SHA: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

HAB & MUAR: Data acquisition, data analysis, approval of the final version to be published.

SWH & MU: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be 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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