

Adherence to medical regimen after pediatric liver transplantation: a systematic review and meta-analysis

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Purpose: Adherence to the medical regimen after pediatric liver transplantation is crucial for good clinical outcomes. However, the existing literature provides inconsistent evidence regarding the prevalence of and risk factors for nonadherence to the medical regimen after pediatric liver transplantation. This study aimed to investigate such nonadherence after pediatric liver transplantation and risk factors associated with this nonadherence using findings of reported studies.

Methods: The electronic databases of Excerpta Medica, Ovid Technologies, PubMed and WanFang Data were searched using the keywords “adherence”, “liver transplant” and “paediatric”. Additionally, relevant references cited in related studies were used to obtain original articles. Using 22 original articles, data regarding nonadherence to the medical regimen after pediatric liver transplantation were quantitatively combined, and risk factors associated with nonadherence were qualitatively identified. Average rates of nonadherence in four areas of medical regimens were calculated. The heterogeneity of the included original articles was also analyzed. When $I^2 > 50$ and $P < 0.05$, a random effects model was used; otherwise, a fixed effects model was used. Moreover, Egger’s and Begg’s tests were used to evaluate publication bias, if any, and original articles with $P > 0.05$ were considered to have no publication bias.

Results: The clinical attendance nonadherence rate was 45% (95% confidence interval [CI]: 39–51), global nonadherence rate was 17% (95% CI: 13–21) and immunosuppression nonadherence rates were 39% (95% CI: 26–52) and 34% (95% CI: 30–39) for cyclosporine and tacrolimus, respectively. Risk factors included older age of the pediatric patient, low family cohesion, poor social functioning, poor mental health and single-parent family.

Conclusions: The nonadherence rate in pediatric liver transplantation is high. Therefore, intervention on the basis of risk factors, such as mental health and family function, may be necessary. Moreover, a standard technique for assessing nonadherence to the medical regimen after pediatric liver transplantation, comprising as many dimensions as possible, is required in order to be more objective and comprehensive when assessing nonadherence.

Keywords: compliance, transplant, pediatrics, hepar, hepatic

Introduction

Pediatric liver transplantation is a crucial dimension of clinical liver transplantation. After nearly half a century of development since the first pediatric liver transplantation in 1963,¹ the survival rate has greatly improved. Approximately 30 years ago, pediatric liver transplantation became the standard treatment for infants, children and adolescents suffering from life-threatening, end-stage liver diseases.² Currently, it is one of the most successful solid-organ transplantations with a 5-year survival rate of $>70\%$ globally. In developed countries, such as the United States and Japan, the proportion of pediatric liver

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transplantation is >10% of the total liver transplantation cases, and the 5-year survival rate is approximately 80%, with the living-donor survival rate being even higher.^{2,3} In China, from 1996 to end of 2013, the liver transplantation for children under the age of 18 years registered in the Chinese Liver Transplant Registry (CLTR) is 935 cases, accounting for 3.6% of the total liver transplants in mainland China. Clinical guidelines for pediatric liver transplantation in China (2015)⁴ also gives detailed clinical guidelines for the diagnosis and treatment for different age-groups, different degree of disease and aspects, etc. Adherence to the medical regimen after liver transplantation is considered critical for avoiding late organ-rejection episodes, graft loss and death, and for decreasing medical costs.⁵ The nonadherence rate to the medical regimen after single-center pediatric liver transplantation is as high as 50%–70%.⁶ Alternatively, research on risk factors associated with such nonadherence after pediatric liver transplantation is limited.

In this study, we performed a meta-analysis on the nonadherence to the medical regimen after pediatric liver transplantation to retrieve original articles published in any language. The nonadherence rate in four areas of the medical regimen was assessed. Moreover, findings of original articles regarding risk factors associated with nonadherence to the medical regimen after pediatric liver transplantation were investigated.

Materials and methods

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.⁷

Original article search

The electronic Excerpta Medica database (EMBASE) Ovid Technologies, PubMed and WanFang Data were searched using the keywords “adherence”, “liver transplant” and “paediatric”. Moreover, relevant references cited in related studies were used to obtain original articles. Two of the authors separately performed original article search; a third-party expert was consulted in case of disagreement. An attempt was made to retrieve as many original articles as possible, with no limit on the publication language.

Inclusion and exclusion criteria

Inclusion criteria including: 1) pediatrics liver transplant relevant researchers or patient with age 1–17 years old;⁸ 2) original articles included datum of nonadherence rate; 3) articles provided risk factors of nonadherence of liver post-transplantation.

Exclusion criteria were: 1) patients not children or adolescent; 2) duplicated reports or research or cohort

with the same patients; 3) reviews or systematic reviews; 4) case report.

Nonadherence outcomes

We examined three aspects of nonadherence outcomes: 1) immunosuppression medication nonadherence; 2) nonadherence to clinical attendance (patients do not follow doctor’s orders to regular clinic appointment and test, reflected from clinical record); 3) “global” nonadherence outcome (original author did not provide a specific nonadherence assessment aspect like immunosuppression or clinical attendance but could reflect nonadherence in multiple, global areas).

Adverse outcomes

Main adverse outcomes were: 1) rejection; 2) re-transplantation; 3) death.

Information extraction

We extracted the information of first author, publish year, country, sample age, assessment of nonadherence, sample size, no of nonadherence, duration of observation and study design. If the age-group reported in the original literature was children or adolescents, then we recorded the age-group as the information provided in the original literature. If the original literature did not provide the aforementioned information, we recorded pediatric patients aged 12–17 as adolescent, others as children.^{8,9}

From each original article, information regarding the association of each medical regimen nonadherence outcome with a series of potential risk factors was assessed. The maximum possible number of risk factors hypothesized in the original articles was assessed; these risk factors included i) sociodemographic factors (gender, race/ethnicity, age, family income, parents education status and health insurance) and ii) social psychological factors (single parent or not, mental health of children, family cohesion and social function of children). However, since only a small number of studies examined most of these variables, we could not include these variables in our quantitative analysis.

Article quality assessment

We used Newcastle-Ottawa scale (NOS)¹⁰ scale to proceed the quality assessment of retrieved original articles. When NOS scores were lower than five they were regarded as low quality articles and were deleted from our analysis.

Statistical analysis

Nonadherence rates were combined based on the subgroups. When the sample size from any original article was <100, a specific transform formula¹¹ was used to estimate the nonadherence rate and the standard error (SE):

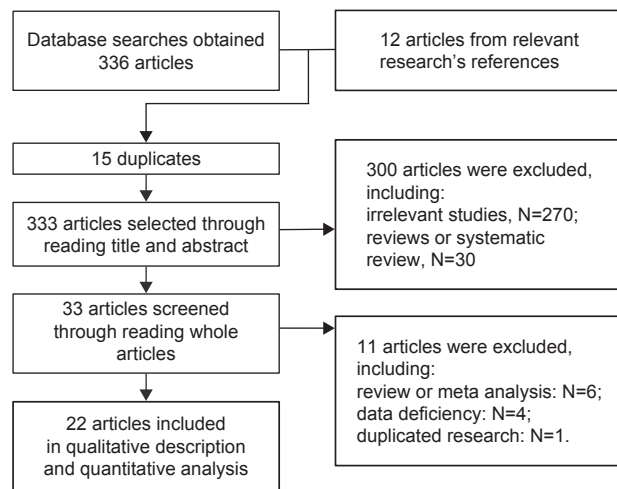


Figure 1 Meta-analysis article screening flowchart.

where number of nonadherence (*n*) is the numerator and number of patients (*N*) is the denominator.

After the meta-analysis, the summarized estimate and 95% confidence interval (CI) boundaries were extrapolated back to proportions using the following formula:

$$\text{AnyProportion} = [\sin(\text{AnyTransformedP}/2)]^2.$$

When the original sample size was ≥ 100 and the provided proportions were not close to 0 or 1, the provided proportions were used with the following formula:

$$\text{SE} = \text{sqrt}[P \times (1 - P)/N].$$

Moreover, the heterogeneity of the original articles was analyzed. When $I^2 > 50$ and $P < 0.05$, a random effects model was used to combine the data; otherwise, a fixed effects model was used.¹² Egger's and Begg's tests were used to evaluate publication bias, if any; $P > 0.05$ was considered to indicate no publication bias in the original articles.

$$\begin{aligned} \text{TransformedP} &= \text{asin} \{ \text{sqrt}[n/(N + 1)] \} + \\ &\quad \text{asin} \{ \text{sqrt}[(n + 1)/(N + 1)] \}; \\ \text{SetransformedP} &= \text{sqrt}[1/(N + 1)] \end{aligned}$$

Table 1 Characteristic of original studies

First author	Year	Country	Sample age	Assessment of nonadherence	Patients (n)		Duration of observation (years)	Study design	NOS scores
Kennard ¹³	1991	USA	Children	Clinical record	35	11	0.5	Cohort	5
Debolt ¹⁴	1995	USA	Children and adolescent	Cyclosporine	39	0	4	Cohort	5
Sellers ¹⁵	1997	USA	Children and adolescent	Global	57	11	3.7	Cohort	6
Sudan ¹⁶	1997	USA	Children and adolescent	Global	23	4	1	Cohort	7
Molmenti ¹⁷	1999	USA	Children and adolescent	Cyclosporine	28	11	9	Cohort	7
Lurie ¹⁸	2000	USA	Children and adolescent	Global	19	3	9	Cohort	7
Avitzur ¹	2004	Canada	Children and adolescent	Global	32	2	1.5	Cohort	7
			Children and adolescent	Cyclosporine	32	8	1.5	Cohort	7
Berquist ¹⁹	2006	USA	Adolescent	Clinical record	97	37	10	Cohort	7
			Adolescent	Cyclosporine	27	14	10	Cohort	6
			Adolescent	Tacrolimus	62	23	10	Cohort	7
Annunziato ²⁰	2007	USA	Adolescent	Global	14	4	3	Cohort	7
Bueno ²¹	2007	Spain	Children	Global	50	5	3.3	Cohort	8
Fredericks ²²	2007	USA	Children	Clinical record	38	19	10	Cohort	7
Berquist ²³	2008	USA	Adolescent	Clinical record	111	50	5	Cohort	6
			Adolescent	Cyclosporine	38	21	5	Cohort	7
			Adolescent	Tacrolimus	73	29	5	Cohort	6
Fredericks ²⁴	2008	USA	Adolescent	Tacrolimus	25	8	2	Cohort	7
Shemesh ²⁵	2008	USA	Children and adolescent	Tacrolimus	23	6	1	Cohort	7
Stuber ²⁶	2008	USA	Children and adolescent	Tacrolimus	68	26	2	Cohort	7
Venkat ²⁷	2008	USA	Children	Tacrolimus	101	32	5.3	Cohort	8
Miloh ²⁸	2009	USA	Children and adolescent	Clinical record	41	17	2	Cohort	7
Fredericks ²⁹	2010	USA	Children and adolescent	Clinical record	71	40	9.41	Cohort	6
			Children and adolescent	Cyclosporine	71	19	9.41	Cohort	7
			Children and adolescent	Tacrolimus	71	22	9.41	Cohort	5
Bilhartz ³⁰	2015	USA	Adolescent	Tacrolimus	48	16	12	Cohort	7
Fredericks ³¹	2015	USA	Children and adolescent	Clinical record	45	24	1	Cohort	7
Bahador ³²	2015	Iran	Children	Global	112	21	5	Cohort	7
Shemesh ³³	2018	USA	Children and adolescent	Global	222	41	10	Cohort	7

Abbreviation: NOS, Newcastle-Ottawa scale.

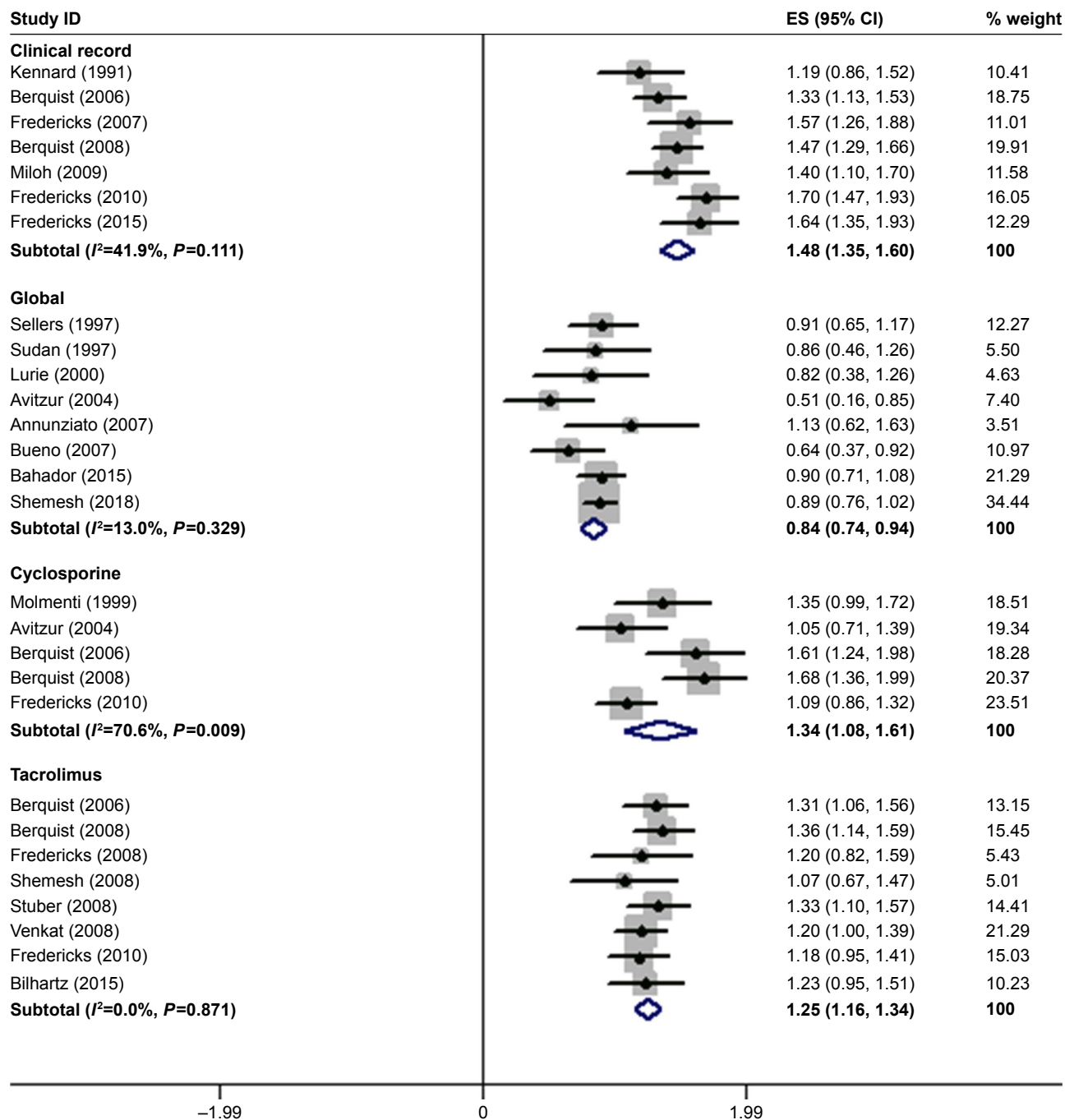


Figure 2 Summary of meta-analysis regarding to different subgroups.

Note: Weights are from random effects analysis.

Abbreviation: ES, estimated statistics (transformed proportion).

Table 2 Summary of nonadherence rate

Nonadherence	Transformed proportion	Transformed 95% CI		Estimated nonadherence rate (%)	95% CI	
		Lower	Higher		Lower (%)	Higher (%)
Clinical	1.48	1.35	1.60	45	39	51
Global	0.84	0.74	0.94	17	13	21
Cyclosporine	1.34	1.08	1.61	39	26	52
Tacrolimus	1.25	1.16	1.34	34	30	39

Abbreviation: CI, confidence interval.

Results

The EMBASE search and citations of relevant references resulted in 336 and 12 original articles, respectively, of which 15 were excluded as they were duplicates. The final screening of the 333 original articles provided 22 original articles,^{1,13–33} which were categorized into two groups for qualitative and quantitative analyses. Figure 1 shows the flowchart of this selection process. The follow-up period was 6 months to 10 years (Table 1). The clinical attendance nonadherence rate was 45% (95% CI: 39–51), global regimen nonadherence rate was 17% (95% CI: 13–21) and immunosuppression nonadherence rates were 39% (95% CI: 26–52) and 34% (95% CI: 30–39) for cyclosporine and tacrolimus (two common immunosuppressors), respectively. Figure 2 provides details regarding the combination result. The way of assessment of nonadherence in methods is various and no standard, thus we did not regroup data into different assessment methods considering the limits of information from original articles. The transform formula was used to proceed with the meta-analysis and to obtain the final combined clinical attendance, global and immunosuppression nonadherence rates (Table 2) and the transformed results will be regarded as our final results. No publication bias was noted among the different subgroups and the overall model (Table 3).

Analysis of all the risk factors associated with nonadherence to medical regimens in pediatric liver transplantation reported in original articles (Table 4) revealed the following five risk factors for poor adherence: older age of the pediatric patient, low family cohesion, poor social functioning, poor mental health, and single-parent family. Evidence from the original articles also suggested that pediatric patients not adhering to the medical regimen are at a higher risk of post-liver transplantation rejection, graft loss and death than those with better adherence to the medical regimen.

Discussion

Nonadherence to the postoperative medical regimen remains a major cause of morbidity and mortality in different clinical settings.¹⁸ Many studies have reported on the nonadherence of medical regimens after liver transplantation in adults but not too many studies have been reported regarding the same in children and adolescents.²⁵ This study is based on a systematic review and meta-analysis of the nonadherence rate

in pediatric patients, and it is an investigation and summary of the risk factors associated with nonadherence to provide constructive suggestions for future clinical practice.

Many studies have used immunosuppression levels to define nonadherence to medical regimen after pediatric liver transplantation, with cyclosporine and tacrolimus being the two common immunosuppressors. By combining the provided nonadherence rates associated with cyclosporine and tacrolimus, we found that the immunosuppressor nonadherence rate is around 30%, which is consistent with adult post-liver transplantation immunosuppressors nonadherence and it is a high rate of nonadherence.³⁴ The clinical attendance nonadherence rate was found to be much higher than immunosuppression nonadherence rates. The global nonadherence rate was the lowest of the three but still high. Dew et al⁵ investigated the outcomes of nonadherence to medical regimen in pediatric solid-organ transplantation, including liver transplantation, and their results were consistent with our major findings. Children and adolescents are undergoing psychological and physiological development and because of this they have limited capability of withstanding long-term medication and clinical treatment, and that could be one of the reasons why pediatric post-liver transplantation nonadherence is relatively high. Another possible reason is that the criteria for compliance are not perfect, which could overestimate or underestimate the rate of nonadherence.^{34,35}

For better investigation of the reasons for nonadherence of pediatric post-liver transplantation, we recorded several main risk factors from original articles' information. In this study, risk factors identified for such nonadherence in pediatric liver transplantation were older age of the pediatric patient, low family cohesion, poor social functioning, poor mental health and single-parent family. Despite the above risk factors that we found, Dew et al⁵ also reported that high parental distress and patients' high distress and low family income were significantly correlated with poorer adherence to medical regimens. During the adolescence period, adolescents begin to have their own independent thought and behavior, but their psychological development is not yet sound and may not produce wholesome health awareness and health beliefs. That may cause older pediatric patients to have a higher nonadherence rate. Studies found that adult patients with low health beliefs, poor mental health, long-term treatment period, poor

Table 3 Summary of publication bias (P)

Publication bias	Global	Clinical record	Tacrolimus	Cyclosporine	Overall
Begg's	0.536	0.548	0.266	0.462	0.248
Egger's	0.55	0.989	0.423	0.348	0.419

Table 4 Outcome variables assessed in original articles

	Year	Sociodemographic characteristics						Adverse effect			Social psychological factors			
		Gender	Race	Age	Family income	Parent education	Health insurance	Rejection	Graft loss	Death	Single parent	Mental health	Parent cohesion	Social function
Kennard ¹³	1991				×		✓				✓			×
Sudan ¹⁶	1997				✓									
Sellers ¹⁵	1997		×											
Molmenti ¹⁷	1999													
Avitzur ¹	2004				✓									
Berquist ¹⁹	2006			✓			✓							
Annunziato ²⁰	2007	×		✓										
Fredericks ²²	2007			✓								✓		✓
Berquist ²³	2008	×		✓										
Fredericks ²⁴	2008			✓								✓		✓
Stuber ²⁶	2008			✓										
Venkat ²⁷	2008													
Miloh ²⁸	2009		×											
Fredericks ²⁹	2010		×	✓										✓
Bilhartz ³⁰	2015			×									✓	
Fredericks ³¹	2015			✓									✓	
Bahador ³²	2015													
Shemesh ³³	2018					✓								✓

Notes: ✓ means significance from original articles of risk factors; × means no significant reports of risk factors. Blank cells indicate no relevant record in original articles.

social support and poor socioeconomic status could cause high nonadherence rates among adult organ transplant patients.^{36,37} Differing from adults, pediatric patients' adherence highly relies on their original family. Thus recent studies have tended to investigate the mental health of pediatric patients and family function as risk factors. Fredricks³⁸ mentioned that good family function could improve the rate of adherence and quality of life. Annunziato et al⁸ found that good self-management and psychological health are protective factors for medical regimen nonadherence. Furthermore, a good health care system like good health insurance could decrease parents' financial burden, in other words, lower financial burden can improve patients' adherence in some aspects.³⁹

In this study, findings from the original articles indicated that pediatric patients who do not adhere to the medical regimen may have a higher risk of post-liver transplantation rejection, graft loss and death than those who show better adherence to the medical regimen post-liver transplantation. Intervention with respect to the risk factors may improve medical regimen adherence and decrease adverse events. Shemesh et al²⁵ reported that with intervention, the nonadherence rate declined in 2003 and the rate of adverse events reduces compared with that observed without intervention in 1999 and 2000. However, such intervention reports are limited. We suggest that future studies or clinical practice should focus more on the effects of intervention in pediatric patients and their parents during and after pediatric liver transplantation. We found that although studies have mainly focused on medical regimen nonadherence, only a small group of studies researched risk factors associated with nonadherence to medical regimen in pediatric liver transplantation. Thus, we suggest that more study can make efforts to investigate the risk factors toward pediatric nonadherence after liver transplantation.

Our study has several advantages and shortfalls. We quantitatively combined the nonadherence of pediatric patients' nonadherence after liver transplant and qualitatively described the risk factors of this scope through which we provided significant suggestions for clinical practice and research. However, the shortcomings of our study are that we did not regroup data of nonadherence assessment methods because of the limited information from original articles and we did not perform correlation analysis of risk factors and side effects to produce qualitative results of the assessment on how risk factors influence pediatric with liver transplantation. In addition, regarding the risk factors of nonadherence of pediatric post-liver transplantation patients, we can suggest important risk factors but we cannot identify them all.

Conclusion

The nonadherence rate post-liver transplantation in pediatric patients is high. Therefore, intervention based on risk factors for medical regimen nonadherence, such as mental health and family function, is necessary. In addition, a standard assessment of pediatric medical regimen nonadherence including as many dimensions as possible is required in order to be more objective and comprehensive when assessing nonadherence to medical regimen in pediatric liver transplantation.

Availability of data and material

All data used for analysis during the current study are displayed in Table 1.

Ethics approval

Ethical approval was given by the Ethics Committee of Tianjin First Center Hospital, Tianjin, China.

Disclosure

The authors report no conflicts of interest in this work.

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