Original Article JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

Study of Adherence to Medication in Pediatric Liver Diseases ("SAMPLD" Study) in Indian Children

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Background/objectives: **Adherence to medication(s) is an essential component of holistic management in any chronic disease including in post liver transplant (LT) patients. Thus, this study aimed to assess adherence to medications in Indian pediatric liver disease patients (including post LT recipients) and to identify variables affecting its occurrence.** ***Methods:*** **A cross-sectional study was conducted among pediatric (<18 years of age) subjects with Wilson disease (WD) and autoimmune liver disease (AILD) along with post LT recipients from May 2021 to October 2021. Structured tools using prevalidated questionnaires (*Medication adherence measure* and the *Child & Adolescent Adherence to Medication Questionnaire*) were used to collect data related to nonadherence prevalence (based on missed and late doses) and factors influencing the adherence.** ***Results:*** **A total of 152 children were included in the study (WD 39.5%, AILD 32.9%, and post LT 27.6%). Prevalence of missed and late dose nonadherence (at a cut-off of ≥20%) was 12.5% and 16.4%, respectively. Older age (odd's ratio/O.R 1.185), stay in a rural area (O.R 5.08), and barriers like *bad taste of medication* (O.R 4.728) and *hard to remember the medication* (O.R 7.180) were independently associated with nonadherence ($P < 0.05$).** ***Conclusions:*** **Overall, nonadherence was seen in 12–16%, i.e., around one-sixth of the patients, with least nonadherence seen in post LT recipients (0–2.4%). Older age of the patient, rural place of stay and personal barriers like hard to remember/forgetfulness and bad medication taste were identified as factors independently leading to nonadherence. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Adherence is defined as "the extent to which a person's behavior–taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."[1] Adherence to medications is a critical aspect in the overall management and outcomes of any chronic disease[2,3]. Poor adherence attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems.[1–3] Medication nonadherence is a common problem across all pediatric chronic disease etiological groups with rates varying from 22 to 88% across chronic illnesses and from 3 to 78% amongst organ transplant population.[4–11] This has been further negatively impacted by the recent corona virus disease 2019 (COVID-19) pandemic.[12–15]

The assessment of medication adherence thus becomes an important parameter to assess during follow up of all patients. Due to a lack of similar data from the Indian population in pediatric liver diseases and post liver transplant (LT) subjects, this study thus attempted to assess adherence to medications and to identify variables affecting it in pediatric liver disease patients including post LT recipients. The knowledge about the nonadherence rates and the factors influencing the adherence in the local population would likely help to design the remedial interventions.

MATERIAL AND METHODS

This cross-sectional study was conducted over a period of 6 months (May to October 2021) and included patients below 18 years of age attending the Pediatric Hepatology Department at a tertiary care institute after obtaining ethical committee approval [IEC/2021/86/MA05]. Inclusion criteria included (1) patients below 18 years of age with primary diagnosis (as per standard criteria) being Wilson disease (WD),[16] autoimmune liver disease (AILD),[17] and post LT recipients (more than 3 months after transplant), (2) taking 2 or more drugs (as defined later), and (3) taking medications for at least 3-month duration.

Sample Size Estimation

Based on estimated baseline population size (under follow-up at the institute currently as per etiology and

Keywords: non adherence to medications, pediatric liver diseases, post liver transplant recipients, medication adherence measure, child & adolescent adherence to medication questionnaire
Received: 9.7.2022; *Accepted:* 11.10.2022; *Available online:* xxx
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Abbreviations: AILD: Autoimmune liver disease; CAAMQ: The Child & Adolescent Adherence to Medication Questionnaire; LT: liver transplant; WD: Wilson disease
https://doi.org/10.1016/j.jceh.2022.10.006

Please cite this article as: Suchismita et al., Study of Adherence to Medication in Pediatric Liver Diseases ("SAMPLD" Study) in Indian Children, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.10.006

expected hospital visits during the study period, i.e., around 250 subjects), average prevalence of medication nonadherence in previous pediatric studies in world literature (i.e. 40 ± 5%) and confidence limits as % of 100 (absolute +/− %) (*d) as 5%*, we calculated the sample size of around 150.

Questionnaires [for details, see Supplementary Material/SM-1]

- Prevalidated questionnaires were administered by the principal investigators (first author/AS and second author/AA) during physical consultation.
  - Overall, the questionnaire consisted of three parts: part 1 involved basic questions about demographic and clinical details, part 2 involved the medication module of the "Medication adherence measure" (MAM),[9] and part 3 included the "The Child and Adolescent Adherence to Medication Questionnaire" (CAAMQ).[6] In addition, part 2 included three questions specifically addressed to assess the effect of COVID-19 pandemic on the medication adherence.
- For children <12 years of age, only parents were requested to fill up the questionnaire and for children ≥12 years of age, both the child and one of the parent were requested to fill up the questionnaire (in the same visit but in different physical settings).

Statistical Analysis

For baseline descriptive analysis, normally distributed continuous study variables were expressed as mean (± standard deviation or SD), and the study variables with skewed distribution were expressed as median (interquartile range or IQR). Individual medications and overall adherence rates were calculated as per mentioned formula (see SM-1). Medication nonadherence (both missed and late) was defined as a patient taking less than 80% of the prescribed medication.[2,19,20] Two-tailed Spearman rank correlations were used to examine whether the total number of barriers reported and ability to recall medications associated with higher rates of nonadherence. Agreement analysis (using Kappa value and intraclass correlation coefficient [ICC]) was done for assessing differences between responses given by children ≥12 years age versus their parents.

For comparing risk factors for medical nonadherence, the mean differences between the groups were tested by using nonparametric tests (Mann–Whitney U test for upto two groups and Kruskal–Wallis H test for >two groups) because of the skewed distribution of adherence rates, while the chi square (or Fisher's exact) test was for categorical variables. Binary logistic regression analysis was then attempted for assessing independent risk factors. Significance was defined as two-tailed *P* value of less than 0.05. For part 3 of the questionnaire, a one-sample t-test between proportions was performed to assess the preference over one option or the other. Data were analyzed by using the Statistical Package for the Social Sciences version 22 (IBM corp Ltd.; Armonk NY, USA).

RESULTS

Demographic and Clinical Profile [Table 1]

A total of 152 patients were included in the study. Of these, 60 (39.5%) patients were in the WD group (predominantly hepatic form), 50 (32.9%) were in the AILD group, and 42 (27.6%) were in the post LT group. Mean age of the patients was 11.6 ± 4.5 years with 81 patients aged ≥12 years. Almost three-fourths (73.8%) of the post LT patients had duration of medication intake were between 1 and 5 years after LT. There was a male preponderance (91 males: 61 females) which was seen across all etiological groups except AILD [male (%) - WD: 70%, AILD: 38% and post LT: 71.4%] (SM-2). Majority (72.2%) of the families stayed in the urban areas with almost equal proportions having joint (50.3%) versus nuclear (49.7%) family setup. One-fourth (25%) of the families were dependent on external support for managing the finances related to the medical bills.

The most common system used to organize or keep the medications at home was the common plastic bag or box (73.9%), while the pill box (daily or weekly) was used by only 3.3% of the families ($P > 0.05$). Majority of the families considered the morning hours (48%) as the most difficult time of the day for medication intake followed by dinner hours (18%) ($P > 0.05$). For <12-year-old patient, parents primarily (78.9%) took the responsibility for giving the medications, while in those ≥12 years age, it was the patients (42%) who were the primary person responsible for taking medications (see SM-3). Patient reported side-effects are mentioned in SM-4.

The overall median duration of medication intake was 36 months (IQR 22–48 months) which was similar across all groups (WD: 41 months/AILD: 35 months/post LT: 35.5 months) ($P > 0.05$). The overall median monthly cost of the medications was 1557.5 INR (or ₹) (IQR 1128.3 to 2853.8) which was lower for the AILD group (680 INR, IQR 400 to 2502.5) compared to the other two groups (WD: INR 1500, IQR 1307.5 to 2000 and post LT: INR 3111.5, IQR 1800 to 4260) ($\chi 2$ (2) = 32.3, $P < 0.001$; AILD vs. WD: P 0.004, AILD vs. post LT: $P < 0.001$, and WD vs. post LT: $P < 0.001$) (SM-5).

Agreement Analysis

On agreement analysis, high levels of agreement between the responses given by the subjects in ≥12 year age-group and their parents. The ICC between patient and parents' responses indicated >70% agreement with respect to the response to number of barriers to medication intake (ICC values 0.799 [95% C.I 0.686 to 0.872]) and the drug recall percentage (ICC values 0.730 [95% C.I 0.577 to 0.828]) suggestive of good and moderate reliability respectively (see the Bland–Altman plots in Figure 1) (See Figure 2 also).

Similarly, with respect to drug adherence as per missed and late doses, there was good agreement in their responses

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Table 1 Basic Demographic and Clinical Profile of Patients.

Demographic variables	Frequency (f)	Percentage (%)
Age at enrollment		
• <12 Years	71	46.7
• ≥12 Years	81	53.3
Gender		
• Male	91	59.9
• Female	61	40.1
Family type		
• Nuclear	74	49.7
• Joint	77	50.3
Place of stay		
• Rural	42	27.8
• Urban	109	72.2
Educational qualification of the patients		
• Not yet enrolled in school	14	9.2
• Primary educational level	47	30.9
• Secondary educational level	38	25
• Senior secondary education level	45	29.6
• Dropped out of school	08	5.3
Educational qualification of father		
• No formal education	7	4.6
• Primary educational level	5	3.3
• Secondary or Higher secondary level	67	44.4
• Graduate or above	72	47.7
Educational qualification of the mother		
• No formal education	15	9.9
• Primary educational level	13	7.9
• Secondary or Higher secondary level	64	42.4
• Graduate or above	60	39.8
Occupation of father		
• Employed	152	100
• Unemployed	0	0
Occupation of mother		
• Employed	23	15.2
• Homemaker	123	84.8
Family support		
• Living with both parents	141	92.8
• With either of parents	10	6.6
• Other (Family members etc)	01	0.7
Family income (per month)		
• Rs <10,000	09	5.9
• Rs 10,001–20,000	35	23
• Rs 20,001–50,000	54	35.5
• Rs > 50,000	31	20.4
• Below Poverty Line/Economically Weaker Section (EWS)	23	15.1
Financial support for monthly drug bill		
• Self	114	75.0
• Family or relatives	17	11.2
• NGO	02	1.3
• Government support	19	12.5

(*Continued on next page*)

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Table 1 (*Continued*)

Demographic variables	Frequency (f)	Percentage (%)
Distance from the institute		
• Within Delhi NCR region	62	40.8
• Outside Delhi NCR region	90	59.2
Post liver transplant group		
Duration post-transplant		
• 3 months to < 1 year	4	09.5
• 1 to < 5 years	31	73.8
• ≥ 5 Years	7	16.7
Donor type		
• Living donor liver transplant	41	97.6
• Deceased donor liver transplant	1	2.4
Relation with donor		
• Father	12	29.3
• Mother	24	56.1
• Siblings	3	7.3
• Relatives	3	7.3
History of rejection		
• Yes	13	31.7
• No	29	68.3

NGO: Non-Governmental Organization; NCR: National Capital Region (NCR) of India.

(for missed doses ≥20%, Cohen's kappa value was 0.827 [95% C.I 0.659 to 0.995] suggestive of near perfect agreement, and for late doses ≥20%, Cohen's kappa value was 0.765 [95% C.I was 0.585–0.945] suggestive of substantial agreement).

MEDICATION NONADHERENCE

The majority (93.2%) of subjects were using only two of the medications as per the etiology (as mentioned earlier). Defining nonadherence as a missed dose percentage more than 20%, the nonadherence rate was 12.5% in our cohort. Using same cutoff, nonadherence to timing of drug was seen in 16.4%. Using a cutoff of ≥10%, these proportions increased to 17.8% and 32.2%, respectively.

On comparing etiology-wise nonadherence, there was significant difference for both missed and late doses suggesting adherence varying as per the etiology with lower rates of nonadherence in the posttransplant group compared to others (see Figure 3). For missed doses, WD group had higher nonadherence compared to post LT group (overall $\chi 2$ (2) = 6.2, P < 0.047; for WD vs. post LT: $\chi 2$ (1) = 5.8, P 0.016, mean ranks 56.8 vs. 43.9; AILD vs. WD: P 0.108, and AILD vs. post LT: P 0.586).

For late doses, AILD group took more late doses compared to both WD and post LT group (overall $\chi 2$ (2) = 10.5, P 0.005; for AILD vs. WD: $\chi 2$ (1) = 6.5, P 0.011, mean ranks 63.8 vs. 48.6; for AILD vs. post LT: $\chi 2$ (1) = 9.2, P 0.002, mean ranks 54.1 vs. 37.5; and WD vs. post LT P 0.736).

Barriers to Drug Adherence

On analysis of the barriers related to nonadherence, 41.9% of subjects had more than one barrier. Most common barriers were *do not want to take medication/ refusal* (28.8%), *hate the taste of medication* (24.8%), and *ran out of medications* (15.7%). Bad taste as a barrier was more commonly reported in <12 years old while refusal to take medications was more commonly seen in ≥12 years age (Figure 2).

Factors Affecting Medication Adherence

Average missed dose percentage directly correlated with the total number of barriers (r = 0.31, P < 0.001, weak to moderate relationship) and inversely correlated with the ability to recall the medications (r = −0.28, P 0.001; weak to moderate relationship). Similarly, average late dose percentage directly correlated with the total number of barriers (r = 0.17, P 0.037; weak relationship).

For missed dose nonadherence (≥20%), on multivariate analysis, rural place of stay (odd's ratio/O.R 5.08), older current age (O.R 1.185), and barriers like *bad taste of medication* (O.R 4.728) and *hard to remember the medication* (O.R 7.180) were independently associated with nonadherence (P < 0.05) with no relation to duration of medication intake, primary responsibility over medication, difficult time of day, or system used to organize medication (Table 2). For late dose nonadherence (≥20%), only *bad taste of medication* (z −2.2, mean ranks 89.9 vs. 72, P 0.025) was significantly associated with nonadherence.

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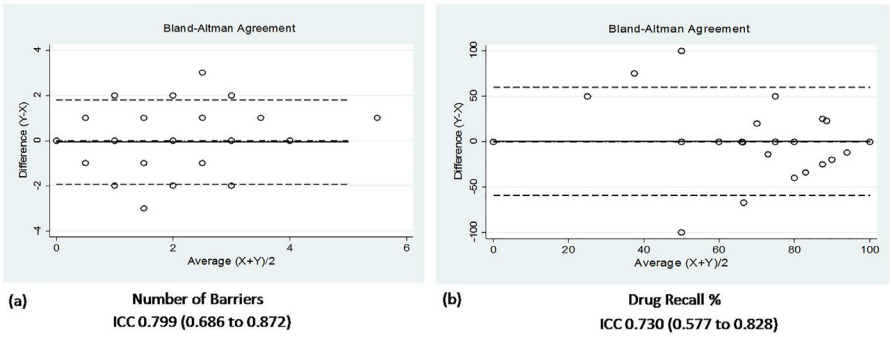

Figure 1 The Bland–Altman plots for the agreement (reliability) analysis between responses given by the subjects in ≥12 year age-group and their parents using the intraclass correlation coefficient (ICC): with respect to the response to number of barriers to medication intake (a) and the drug recall percentage (b).

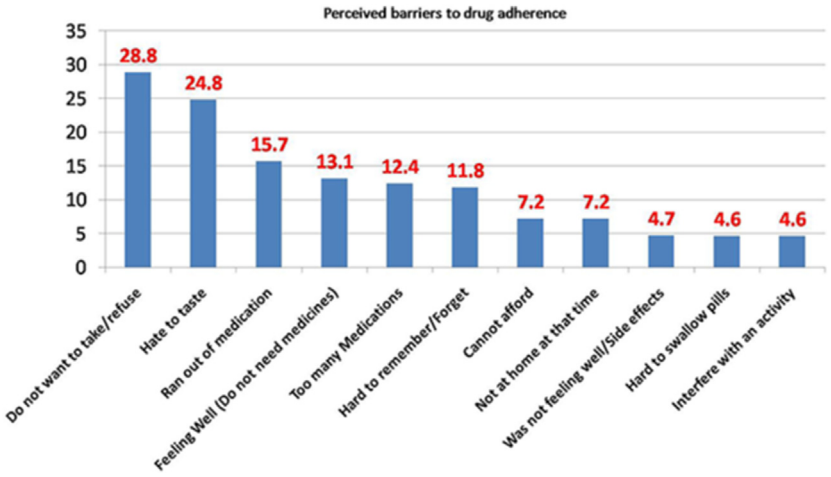

Figure 2 Perceived barriers to drug adherence.

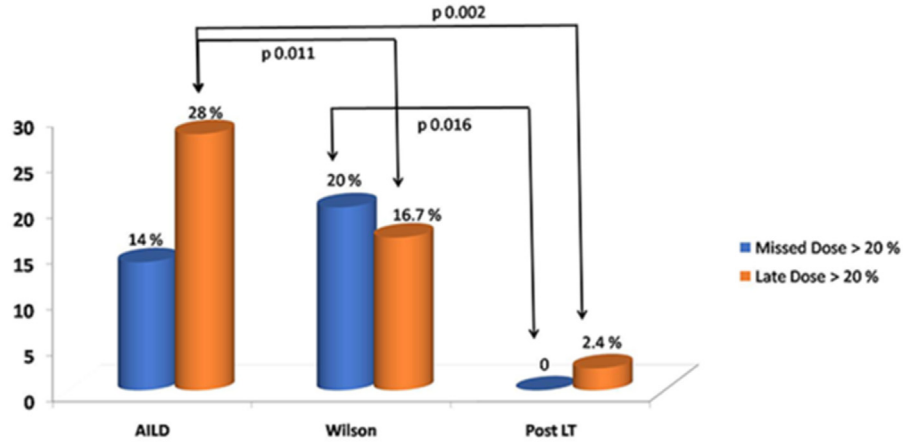

Figure 3 Etiology-wise medication nonadherence •Abbreviations: AILD: autoimmune liver disease, LT: liver transplantation.

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Table 2 Factors Affecting Medication Adherence.

Univariate analysis			
Parameters	**Nonadherent vs. Adherent**	**Effect Size[a]**	***P* value****
Place of stay (%)	Rural (23.8%) vs. Urban (8.2%)	0.29, (0.11–0.78)	0.014
Hard to remember (%)	33.3 vs. 9.7	4.6, (1.5–14.5)	0.012
Bad Taste (%)	26.3 vs. 7.9	4.2, (1.5–11.2)	0.008
Side effects (%)	42.3 vs. 11	6, (1.2–29.5)	0.042
Current Age (years)	14.1 ± 2.4 vs. 11.3 ± 4.6	−2.6, 100.6 vs. 73.1	0.011
Age at diagnosis (years)	10.7 ± 2.1 vs. 8.5 ± 3.9	−2.7, 94.8 vs. 67.3	0.006
Multivariate analysis			
Parameters	***β coefficient***	**Adjusted OR (95% C.I)**	***P* value**
Place of stay (%)	1.627	5.08 (1.578–16.397)	0.006
Hard to remember (%)	1.971	7.180 (1.824–28.259	0.005
Bad taste (%)	1.554	4.728 (1.543–14.493)	0.007
Current age in (Years)	0.170	1.185 (1.015–1.385)	0.032

[a]z value, mean ranks for comparison of means, OR/95% CI for comparison of proportions, ** *P*-value < 0.05 as significant.

The Child and Adolescent Adherence to Medication Questionnaire (CAAMQ) (Part 3): Prednisolone was cited as the most disliked medication (36%) followed by zinc (28%) (see SM-7). Almost three-fourths (72.5% and 73.2% respectively) of the respondents confirmed that it did *bother them to take their medications daily*, and that they did "feel upset about taking medicines" ($P < 0.05$). But majority (83.7%) of them mentioned that their medications *did not interfere with their daily activities* ($P < 0.05$). One-third (31.4% and 30.1% respectively) of them felt that an alarm system or a pill box would help them to remember taking their daily medications in a better way ($P < 0.05$). Also, almost half (47.7%) agreed that a better tasting medicine would help them remember to take their medicine. Please see SM-6 for further details.

Effect of COVID-19 Pandemic

Majority (90%) of the participants did not discontinue their medication during the pandemic. The most common reasons behind discontinuation (if any) were *unavailability of medication during lockdown* (35.7%), *financial issues* (21.4%) and *actually suffered from Covid-19 infection/fear of immunosuppressive effect of medications* (14.3%). Almost one-third (28.9%) of the subjects did not turn up for their routine outpatient department consultation (see SM-7).

DISCUSSION

The current study is the largest study from the Indian subcontinent (and the first report from India) on the status of medication adherence in liver diseases (including post LT cases) in pediatric population. Its strengths further include a comparatively larger sample size, use of previously validated pediatric adherence measures, and also inclusion of both the parents and patients (in ≥12 years age group) in the study.

It is a well known fact that adherence to medications is a critical aspect in achieving optimum outcomes in any chronic disease.[2,3] This becomes especially important in the pediatric age group since they may have to take medications either lifelong or for decades altogether. Similarly, in post-transplant patients, graft survival is dependent on lifelong immunosuppression. As discussed previously, nonadherence is a common problem across the entire disease spectrum with rates varying from 22 to 88% [4–11; also see SM-9]. In the current study, we found lower (12–16%) rates of nonadherence as compared to other studies (as shown in SM-8). But these adherence rates were comparable with other studies where cutoffs of ≥10% or ≥20% have been used for missed or late doses (for missed doses: 12.5–17.8% in current study, 21.8–38.2%[9] and 4.2%[18]; for late doses: 16.4–32.2% in current study, 10.9–23.6%[9] and 11.4%[18]; for missed or late doses >10%: 18.2–33.3%[19]). In the present study, better adherence rates were seen in post-transplant patients versus the other two groups. Although no statistically validated differences were found in the barriers to adherence between these two groups, the most plausible explanation is the extra attention and repeated counseling the post-transplant patients usually receive from multiple caregivers (including the surgeons, physicians, nurses, and transplant coordinators).

Although there is no actual "gold standard" to assess adherence, self-reporting by patients (including the use of questionnaires) is still the most commonly used method in clinical practice.[2,7,18–26] Some inherent shortcomings of questionnaire based approach including conscious

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manipulation of the responses by the respondents may have affected the nonadherence rates in current study. We did try to decrease the overall error by ensuring investigator-administered (in the native language) questionnaire approach so as to address various limitations like incomplete answers, unanswered questions, wrong understanding or interpretation of questions, illegibility, and so on. Also, in those patients >12 years of age, the questionnaires were administered to the patient and parent in separate settings so as to allow nonbiased recording of their individual responses. This we also documented by doing the agreement analysis (see Figure 1) where high levels of agreement between the responses given by the subjects in ≥12 year age-group and their respective parents.

The study identified older age of the patient as one of the independent factors predicting nonadherence. This pattern of nonadherence in the adolescent period has been documented in the previous literature with younger age of the patient associated with better adherence.[9,26–29] This was also reflected in the pattern of responsibility over medication intake where as the age of the patient increased, they more likely became responsible for medication intake (SM-3) ($P > 0.05$). Similar results were found in the previous studies where adolescents took primary responsibility (12–75%) for their medication intake (42% in the current study).[9,26,30] This is compounded by the erratic and defiant behavior more commonly seen in adolescence with increasing risk of refusal to take medications due to various social and physiological factors. For this group, disease specific support/self help groups would encourage them and alleviate their fears. Realizing this shortcoming, we have initiated support groups for Wilson and autoimmune liver disease patients and post LT recipients which have been well received by the patients, especially adolescents.

Similarly, rural place of residence was identified as one of the risk factors of nonadherence. These patients may have faced issues with local medication procurement and regular follow-up visits secondary to the prevailing pandemic. This may have been compounded with the financial constraints secondary to loss of jobs in this period. Previous studies have shown conflicting results with respect to relation of residence and adherence rates.[21,31]

Barriers like *hard to remember/forgetfulness* and *bad medication taste* were identified as independent factors leading to nonadherence in current study, as also seen in previous studies.[9,20,24,26,32,33] It is imperative to address these issues at the earliest since many of them are amenable to a significant improvement if intensive counseling is done and simple changes are made to the daily routine of the patient. These may include use of daily medication reminders (including alarm system), taste maskers (for bad taste), rewards/incentives for timely adherence, and decrease in overall medication burden (number as well as frequency, e.g., once daily dosage using long acting formulations) among others.[9,26,34–40] Almost one-third of the subjects actually felt that an alarm system or a pill box would better help them to remember taking their daily medications. A practical tool to overcome the "forgetfulness" barrier would be a "disease specific customized pill box" which could be given to the patients after detailed explanation. Thus, these simple remedial measures may actually help take care of some of these common personal barriers.[41]

The recent COVID-19 pandemic has had a negative overall impact on medication adherence.[12–15] Despite the fact that the current study was conducted during the peak of the pandemic phase in the region, the nonadherence rates were surprisingly low in the study. This may be secondary to a probable selection bias because the subjects (parents and the children), who followed up for their routine physical visits/consultations even during the pandemic period, are the ones who are likely more compliant with the medications.

Apart from being a single center study, the current study was limited by use of the investigator-driven questionnaire-based methodology with its inherent shortcomings and a likely chance of selection bias as mentioned earlier. We assessed adherence only for main disease-related drugs and not for the whole prescribed regimen (e.g., nutritional supplements). It was a cross-sectional study, so we could not assess adherence over a period of time after the pandemic was actually over. We did not attempt subgroup analysis to assess etiology-specific predictive factors for nonadherence due to limited number of subjects.

To conclude, medication nonadherence is likely an underestimated problem in Indian children with liver diseases. This may adversely affect long-term disease outcomes, and thus, further larger and multicentric studies are mandated in this study population to identify potentially modifiable factors to allow effective interventions to manage nonadherence. If such factors can be identified, simple remedial measures can be instituted to decrease overall nonadherence.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

VS, BBL, RK, and SA conceptualized the research paper; AS, AA, and VS did the acquisition, analysis, and interpretation of data for the work; GK did the statistical analysis; and VS, AS, and AA prepared the first draft. All authors reviewed the manuscript, provided critical inputs, and approved the final version.

CONFLICTS OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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FUNDING

The authors did not receive support from any organization for the submitted work.

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Please cite this article as: Suchismita et al., Study of Adherence to Medication in Pediatric Liver Diseases ("SAMPLD" Study) in Indian Children, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.10.006

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APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.10.006.

Please cite this article as: Suchismita et al., Study of Adherence to Medication in Pediatric Liver Diseases ("SAMPLD" Study) in Indian Children, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.10.006