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Medication safety in patients with hepatic impairment: A survey of community pharmacists' knowledge level and their practice in caring for these patients

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Aims: To study community pharmacists' level of knowledge on medication safety in patients with hepatic impairment and their practice in caring for these patients.

Methods: Pharmacists from Dutch community pharmacies (n = 1545) were invited to participate in an online survey. The survey consisted of 27 questions covering 2 main topics: knowledge and current practice. The level of knowledge was measured by a 6-item knowledge test. Multiple linear regression was used to identify predictors of correctly answered responses.

Results: In total, 338 pharmacists (22%) completed the questionnaire. The mean knowledge score was 2.8 (standard deviation 1.6). Only 30.3% of respondents were able to appropriately advise on use of analgesics in severe cirrhosis. Postgraduate education on hepatic impairment, knowledge of recently developed practical guidance, and fewer years of practice were associated with a higher level of knowledge. In total, 70.4% indicated to evaluate medication safety in a patient with hepatic impairment at least once weekly. In the past 6 months, 83.3% of respondents consulted a prescriber about a patient with hepatic impairment. Frequently encountered barriers in practice were insufficient knowledge on the topic and a lack of essential patient information (i.e. diagnosis and severity of the impairment).

Conclusion: Community pharmacists regularly evaluate the safety of medication in patients with hepatic impairment, yet their level of knowledge was insufficient and additional education is needed. Pharmacists experienced several difficulties in providing pharmaceutical care. If these issues are resolved, pharmacists can play a more active role in ensuring medication safety in their patients with hepatic impairment.

KEYWORDS

education, hepatology, medication safety, pharmacy

Rianne A. Weersink and Marianna Abadier should be considered joint first author.

Principal investigator: The authors confirm that the Principal Investigator for this paper is Marianna Abadier.

1 | INTRODUCTION

Patients with hepatic impairment are prone to develop adverse drug reactions due to changes in the pharmacokinetics and pharmacodynamics of medicines.[1,2] Research showed that nearly 30% of patients with liver cirrhosis, the advanced stage of all chronic liver diseases, experience adverse drug reactions.[3] A Dutch study showed that almost 2/3 of patients with liver cirrhosis used potentially unsafe drugs.[4] In addition, a recent study among 57 patients with cirrhosis identified a median of 6 medication-related problems per patient.[5] Almost 60% of these problems could be resolved during a pharmacist-led medication review. This suggests that pharmacists, as medication experts, could play a key role in preventing and resolving medication-related problems in this vulnerable patient group.

A barrier for pharmacists to fulfil this role was the lack of concrete prescribing recommendations for patients with hepatic impairment and deficiencies in the information for these patients in the product labels.[6-9] However, in 2018, practical guidance for safe drug use in this specific patient group was published.[10,11] In the Netherlands, the website containing all guidance (www.drugsinlivercirrhosis.org) has been available since 2017. Furthermore, the guidance was integrated in all relevant clinical decision support systems (CDSS) used in Dutch community pharmacies. Implementing changes in practice may take time and pharmacists might encounter difficulties in practice.[12] For example, a substantial part of the recommendations depends on the severity of hepatic impairment, being expressed using the Child–Turcotte–Pugh classification.[10,13] Therefore, it is important that this severity class is registered in the medical and pharmaceutical record of a patient and exchanged between relevant healthcare providers. In addition, pharmacists need to be familiar with the recommendations and have sufficient knowledge about the topic to be able to interpret and apply the information in their practice.

Previous work focussed on knowledge and practices of physicians in prescribing analgesics for patients with chronic liver disease.[14-16] Little is known about the knowledge of community pharmacists on safe medication use in patients with hepatic impairment. A few studies have described the care provided by pharmacists for a subgroup of patients: those with viral hepatitis C,[17-19] but those studies focussed on clinical pharmacists or described care in only 1 clinic. Therefore, this study aimed to determine the level of knowledge of community pharmacists on medication safety in patients with hepatic impairment and their practice in caring for this patient group.

What is already known about this subject

- Patients with hepatic impairment have an increased risk of medication-related problems due to alterations in pharmacokinetics and pharmacodynamics of medicines.
- Pharmacists could play a key role in preventing and resolving medication-related problems in this vulnerable patient group.

What this study adds

- Community pharmacists frequently evaluated the safety of a medicine in patients with hepatic impairment.
- The level of knowledge of pharmacists on medication safety in patients with hepatic impairment was limited and more education on the topic is needed and wanted.
- Community pharmacists experienced limited access to relevant patient data (e.g. diagnosis and severity of hepatic impairment) which may adversely affect their practice.

2 | METHODS

2.1 | Study setting

In the Netherlands, patients are usually registered with 1 general practitioner (GP) and 1 community pharmacy.[20] The GP keeps a medical record per patient and the pharmacist a pharmaceutical record. In general, these are electronic records which operate a CDSS. Clinical risk management of medication use is an important activity of Dutch community pharmacists.[21] In case the CDSS generates a medication safety alert (e.g. contraindications, drug–drug interactions), the pharmacist assesses the clinical relevance of the alert and if applicable, takes action (e.g. inform the patients, adjust the dose or switch drugs in cooperation with the GP).

2.2 | Study population

We conducted a cross-sectional survey among pharmacists from the Utrecht Pharmacy Practice network for Education and Research (UPPER) network. The UPPER network consists of 1545 community pharmacies, representing 75% of all community pharmacies in the Netherlands at the time the survey was performed.[22] An invitation for the pharmacist to participate in the electronic survey was sent in March 2018, one and a half years after the implementation of the first safety and dosing advices in cirrhosis.[10] A reminder was sent 2 weeks later and the questionnaire was closed 2 weeks thereafter. As an incentive, all respondents were given the option to receive additional information about "pharmaceutical care in patients with hepatic impairment" by providing their email address at the end. The survey was conducted with Survey Monkey software. It was approved by the UPPER Institutional Review Board of Utrecht University (number: UPF1801).

2.3 | Survey

The survey consisted of 27 questions covering 2 main topics: knowledge and current practice and can be found in the Supplementary

Data. The questionnaire was developed by the authors with expertise in hepatic impairment and pharmacy practice, and piloted among 13 pharmacists. We refined the questionnaire based on the pilot: we adjusted the formulation of some answers and changed the order of the questions slightly.

The topic knowledge was divided into self-perceived knowledge of pharmacists, questions on educational needs and a brief knowledge test. Self-perceived knowledge was tested by 4 statements where pharmacists recorded their agreement on a 5-point Likert scale. To investigate educational needs, we asked the pharmacists about the training they received on medication safety in patients with hepatic impairment and if they wished to receive additional education. The knowledge test consisted of 6 multiple-choice questions and the participants were instructed to complete those without using reference works.

The topic of current practice was covered with questions on how often the pharmacists encountered a medication safety alert from their CDSS about a patient with hepatic impairment, the familiarity of pharmacists with the new recommendations and website,[10] and questions about contact with other healthcare professionals. To include potential topics that were not covered by the survey, we added 3 open-ended questions about current practice and difficulties experienced in providing pharmaceutical care to patients with hepatic impairment at the end of the questionnaire.

2.4 | Data analysis

We used both descriptive and inferential statistics to analyse the data. Due to missing values, the number of respondents per question varied and, where appropriate, the absolute number of respondents per questions was listed. In total, <5% of items were missing. Due to the low rate scoring of some of the multiple-choice questions, we merged responses from selected questions into fewer categories. The statements on knowledge were recoded from a 5-point Likert scale into a 3-level scale: *strongly disagree/disagree*, *neutral*, *agree/strongly agree*. The answers on the frequency of a medication safety alert were recoded into *often* (daily/weekly) and *rarely* (monthly/less than once a month). The answers *countryside* and *village* from the variable *location of pharmacy* were combined into *village or countryside*. Answers to the question about the community pharmacy registration were merged into *registered as community pharmacist* and *not (yet) registered as community pharmacist*.

The outcome of the knowledge test was the number of *correctly answered questions*, with a maximum of 6. Univariate analyses were performed for all potential explanatory variables. The variables age and years of practice were highly correlated and therefore only 1 variable (i.e. years of practice) was included in the analysis. After univariate analyses, variables with *P*-values <.25 were included in multiple linear regression analysis. Cases with missing data were deleted pairwise. A *P*-value <.05 was considered statistically significant. The analyses were performed with SPSS, version 25.

3 | RESULTS

In total, 338 pharmacists (22%) completed the survey of the 1545 pharmacies the invitation was sent to. The characteristics of the respondents are presented in Table 1. Respondents were predominantly female pharmacists, working in a community pharmacy in an urban area.

3.1 | Knowledge

Respondents were asked about their self-perceived knowledge on medication safety in hepatic impairment (Figure 1). A minority of pharmacists (20.4%) perceived their knowledge about the influence of hepatic impairment on medication as sufficient, and 29.0% indicated that they were able to interpret hepatic laboratory values. In total, 69.6% (*n* = 218) of respondents received prior education on medication safety in hepatic impairment. Almost half (44.1%; *n* = 138) of pharmacists received training while in pharmacy school, and 18.2% (*n* = 57) during their 2-year registration period as community pharmacist. A total of 42.8% (*n* = 134) received education during a postgraduate course or a pharmacotherapy meeting. Almost all respondents (90.7%; *n* = 284) expressed a wish for additional education on this topic.

The mean score of the respondents on the knowledge test was 2.8 (standard deviation 1.6) correct answers out of 6 questions (mode 2.0). Fifteen respondents (4.7%) were able to answer all 6 questions correctly, and 6.3% answered all incorrectly (*n* = 20). As can be seen in

TABLE 1 Characteristics of the respondents

	n (%)
Sex[a]	
Female	207 (66.6)
Male	104 (33.4)
Age (y)[a], mean ± SD	42 ± 11
Registered as community pharmacist[b]	
Yes	274 (89.8)
No or not yet	31 (10.2)
Years of practice[b], median (IQR)	15 (7–25)
≤10	112 (36.7)
11–20	98 (32.1)
21–30	67 (22.0)
≥31	28 (9.2)
Practice setting[a]	
Community pharmacy	295 (94.9)
Outpatient pharmacy	16 (5.1)
Location of pharmacy[b]	
Urban area	190 (62.3)
Village or countryside	115 (37.7)

SD, standard deviation; IQR, interquartile range.
[a]number of respondents is 311;
[b]number of respondents is 305

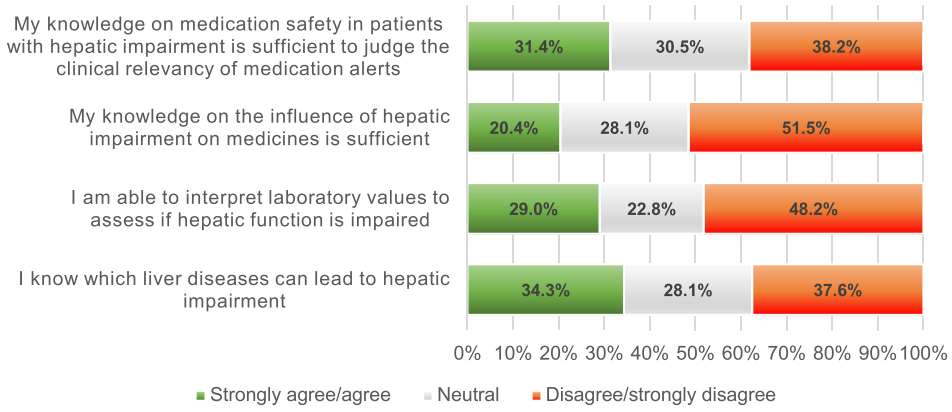

FIGURE 1 Self-perceived knowledge on medication safety in hepatic impairment among pharmacists (n = 338)

TABLE 2 An overview of the knowledge test containing the questions, the correct and incorrect answers (n = 317)

QUESTION	n (%)
Which laboratory parameters are used to assess liver function?	
Correct: Albumin, bilirubin and INR	**71 (22.4)**
Incorrect	**246 (77.6)**
Gamma-GT and alkaline phosphatase	17 (5.4)
ASAT and ALAT	210 (66.2)
Lactate dehydrogenase and ammonia	1 (0.3)
I do not know	18 (5.7)
Which classification is used to estimate the severity of hepatic impairment?	
Correct: Child–Pugh	**203 (64.0)**
Incorrect	**114 (36.0)**
ASAT/ALAT ratio	31 (9.8)
Hy's law	0 (0)
None of the above answers	7 (2.2)
I do not know	76 (24.0)
In which of the following diseases is the impairment of hepatic function clinically relevant for medication use?	
Correct: Liver cirrhosis	**196 (61.8)**
Incorrect	**121 (38.2)**
Viral hepatitis	1 (0.3)
Steatosis hepatis (fatty liver)	2 (0.6)
All 3 answers mentioned	80 (25.2)
None of the above answers	2 (0.6)
I do not know	36 (11.4)
What do you do if a GP adds the contraindication "hepatic impairment" in the medical record of a patient because of a liver cyst?	
Correct: The contraindication is irrelevant, I remove it in consultation with the GP	**165 (52.1)**
Incorrect	**152 (47.9)**
The contraindication is relevant, I do not do anything	19 (6.0)
I do not know what to do	133 (42.0)
A physician asks your advice on pain relief in a patient with arthrosis and severe liver cirrhosis. Which analgesic would you certainly not recommend?	
Correct: Diclofenac	**96 (30.3)**
Incorrect	**221 (69.7)**
Acetaminophen (paracetamol)	140 (44.2)
Tramadol	12 (3.8)
Morphine	19 (6.0)
I do not know	50 (15.8)
Which pharmacokinetic process (es) are affected by hepatic impairment?	
Correct: All of the pharmacokinetic processes	**158 (49.8)**
Incorrect	**159 (50.2)**
Absorption	0 (0)
Distribution	0 (0)
Metabolism	125 (39.4)
Excretion	19 (6.0)
No influence on pharmacokinetics	0 (0)
I do not know	15 (4.7)

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GP, general practitioner; GT, glutamyltransferase; INR, international normalized ratio

Table 2, 77.6% of pharmacists did not know which laboratory parameters are used to assess hepatic function, and 69.7% were not able to give a proper analgesic advice in a patient with severe cirrhosis. By contrast, 64.0% of the pharmacists were familiar with the Child–Pugh classification, and 61.8% knew that medication adjustments are only needed in patients with cirrhosis and not (yet) in patients with viral hepatitis or steatosis.

In multiple linear regression analysis, 3 variables were associated with the total knowledge score (Table 3). Higher knowledge scores were associated with postgraduate education or a pharmacotherapy meeting on hepatic impairment (P < .001) and familiarity with the new recommendations or website (P < .001). A higher total knowledge score was also negatively correlated to years of practice (P < .001).

TABLE 3 Multiple linear regression analysis of variables associated with total knowledge score. Variables predicting knowledge levels of pharmacists in a multiple linear regression model (n = 305)

Predictors	Coefficient (β)	SE	95% CI		*P*-value
[intercept]	2.019	0.192			
Years of practice[a]	−0.029	0.008	−0.045	−0.014	<.001
Postgraduate education course or pharmacotherapy meeting	0.720	0.161	0.403	1.037	<.001
Familiar with new recommendations or website	1.372	0.171	1.035	1.709	<.001

Adjusted R^2 = 0.27. SE, standard error; 95% CI, 95% confidence intervals of the coefficients.
[a]years of practice was included as continuous variable in the analysis.

3.2 | Current practice

Seventy percent of pharmacists indicated to encounter at least once a week a medication safety alert from their CDSS concerning a patient with hepatic impairment (Table 4). A proportion of 53.4% were familiar with the new alerts in their CDSS. A total of 55.4% were aware of the website with advice about medication safety in cirrhosis.

Among healthcare professionals, the GP was most often consulted with a question about a prescription in a patient with hepatic impairment. A total of 71.3% of respondents contacted a prescriber in the past 6 months to retrieve the severity of a patient's hepatic impairment. More than half of these respondents experienced difficulties during that contact. In an open question, pharmacists explained these difficulties. A frequently mentioned remark was the lack of relevant patient information (e.g. severity of hepatic impairment or diagnosis of cirrhosis): *"General practitioners become irritated when I ask for a patient's renal function, let alone when I also ask which patients have cirrhosis."* (Female, age 63 years). Respondents also indicated that there was a lack of knowledge on this topic: *"My general practitioners have no idea what hepatic impairment exactly means. The contraindication hepatic impairment is registered while the patient 'only' had an increase in ALAT and/or ASAT."* (Female, age 36 years).

Another open-ended question asked about the role of pharmacists in caring for patients with hepatic impairment. Overall, there was a sense of willingness amongst respondents to take responsibility in ensuring optimal medication use in patients with hepatic impairment: "*Our role is to provide information about the use of medication when a patient has hepatic impairment and the possible consequences.*" (Female, age 57 years).

TABLE 4 Current practice among pharmacists in caring for patients with hepatic impairment

	n (%)	
	Often (daily/ weekly)	Rarely (monthly or less)
How often do you encounter a *hepatic impairment* medication safety alert in your CDSS?	238 (70.4)	100 (29.3)
	Yes	**No**
Familiarity with new CDSS alerts or website	**218 (69.6)**	**95 (30.4)**
Are you familiar with the new CDSS alerts?	167 (53.4)	146 (46.6)
Are you familiar with the website?	173 (55.4)	139 (44.6)
In the past 6 months, have you consulted 1 of the following prescribers with a question about medication safety in a patient with hepatic impairment?	**279 (83.3)**	**56 (16.7)**
General practitioner	262 (78.2)	73 (21.8)
Gastroenterologist	86 (25.7)	249 (74.3)
Other prescriber	54 (16.1)	281 (83.9)
In the past 6 months, have you consulted a prescriber about a patient's severity of hepatic impairment?	**239 (71.3)**	**96 (28.7)**
If yes, did you encounter difficulties during that contact?	135 (56.7)	103 (43.3)

Number of respondents varied per question from 312–338 and n = 238 for the last question. CDSS, clinical decision support system.

4 | DISCUSSION

This study is unique in assessing community pharmacists' level of knowledge on medication safety in patients with hepatic impairment and their practice in caring for these patients. We demonstrated that 70% of the respondents evaluated the safety of a medicine in a patient with hepatic impairment at least once a week and <80% consulted a prescriber in the past 6 months with a medication safety question. However, the pharmacists' knowledge level—subjective and objective—was insufficient and they expressed a wish for additional education. Furthermore, pharmacists experienced difficulties in caring for these patients due to problems in the contact with prescribers and limited access to essential patient data, like the severity of hepatic impairment.

Pharmacists had limited knowledge on different topics of pharmaceutical care in hepatic impairment. Strikingly, only about 1/5 of respondents knew which laboratory parameters are used to evaluate

hepatic function. In addition, a large proportion of pharmacists was not able to give correct advice on analgesic use in severe cirrhosis. Knowledge of pharmacists on this topic does not seem to have been assessed previously, yet a few studies evaluated physicians' practices in prescribing analgesics in patients with cirrhosis.[14-16] These studies found similar results: an overall limited knowledge on the topic. Possible explanations for this finding are that medication safety in hepatic impairment is a rather complex topic. Gastroenterologists, specialized in caring for these patients, also knew more often which analgesic was safe to prescribe compared to nongastroenterologists.[14] In addition, the former lack of practical guidance possibly contributed to the low knowledge level. This lack of guidance probably also limited the quantity and quality of education on the topic: less than half of the respondents in our survey had some training in hepatic impairment during their pharmacy degree. These results mark the need for additional or higher quality education about medication safety in hepatic impairment. The respondents in our study who took a postgraduate course also had a higher score on the knowledge test, possibly indicating the effect of additional education. However, we do not know how recently the respondents took this course and how often they took a postgraduate course on this topic.

Pharmacists with less years in practice scored higher on the knowledge test. Previous studies assessing healthcare professionals' knowledge on other topics (e.g. [pharmaco]genetics) also showed that more recent graduation was related to higher knowledge scores.[23,24] Recent graduates probably remember most from the education received during pharmacy school or their registration period and may be more willing to learn. Also notable was the association between familiarity with the new recommendations in the CDSS or the website and a higher score on the knowledge test. Participants familiar with the website or recommendations are possibly more interested in the topic and might have read background information about medication safety in patients with hepatic impairment.

When consulting prescribers about patients with hepatic impairment, more than half of the pharmacists experienced difficulties during that contact. One of the difficulties mentioned was the lack of relevant patient information, i.e. data on the diagnosis and the severity of hepatic impairment. This can partly be explained by the complex classification used to grade the severity of hepatic impairment (i.e. the Child–Pugh classification[13]). This classification consists of 5 parameters and 2 of these include clinical symptoms (i.e. degree of ascites and of hepatic encephalopathy). Pharmacists cannot determine the severity of hepatic impairment themselves and need the information from physicians. Exchange of relevant patient data between physicians and pharmacists is therefore necessary. Warholak *et al*. showed that pharmacists were able to give better pharmaceutical support when they had a more complete overview of a patient's medical record.[25] Furthermore, a review on clinical decision support noted that drug-disease interaction alerts could only work if the diagnoses and conditions of a patient, even as the degree of impairment have been accurately entered into the medical or pharmaceutical record of a patient.[26] Efforts are needed to improve exchange of these patient data.

4.1 | Limitations

The current study achieved a response rate of 22%. Because there are also general pharmacy email addresses included in the UPPER network mailing list, this percentage could be lower if >1 pharmacist per pharmacy filled out the questionnaire. The response rate is considered low for web-based questionnaires.[27,28] However, it is reasonable for the UPPER network, with a usual response rate of 10–15% in their surveys.[22,29] Nonresponse bias was possible: pharmacists with limited interest and knowledge on this topic possibly did not participate resulting in a higher average knowledge score. By contrast, participants received additional information on the topic as incentive, which could have attracted pharmacists with limited knowledge resulting in a lower mean level of knowledge. When comparing characteristics of respondents with Dutch national data from 2004, a high frequency of female pharmacists was noted in our sample.[30] A likely explanation is that in the past 15 years, the male/female ratio among community pharmacists in the Netherlands has changed, as described by the Dutch Foundation for Pharmaceutical Statistics.[31]

To test the level of knowledge of participants, we used 6 multiple-choice questions. Thus, the score on the knowledge test only gives a global impression about the pharmacists' knowledge. Nevertheless, in our opinion, the designed questions represent minimal requirements for providing proper care in these patients.

4.2 | Implications for practice and future research

The results of this study indicate a compelling need for more education on medication safety in patients with hepatic impairment. It is recommended to provide basic knowledge and create awareness for this patient group during the pharmacy and medicine undergraduate studies and provide more advanced practice-based education in a postgraduate course. In a couple of years, this study and especially the knowledge test could be repeated to evaluate improvement. In further research, one could also study the actual care provided by the pharmacists. For example, by assessing how pharmacists manage alerts in their CDSS on medication safety in patients with hepatic impairment or by examining if pharmacists ask their customers about liver disease before they recommend a nonsteroidal anti-inflammatory drug.

To improve medication safety in patients with hepatic impairment, pharmacists and prescribers can be supported by their CDSS.[26] The practical guidance on medication safety in patients with hepatic impairment was published in English, yet only integrated in CDSS in the Netherlands.[10] This study provides valuable insights for other countries that want to integrate decision support for safe use of medication in hepatic impairment. To make optimal use of clinical decision support, the exchange of the diagnosis and severity of hepatic impairment between healthcare professionals needs to be improved. Pharmacotherapy meetings between GPs and pharmacists can help. These meetings could be used to discuss practicalities limiting the exchange of the diagnosis and severity of hepatic impairment and to improve

involvement and knowledge among participants. Previous studies have shown the positive impact of high-quality pharmacotherapy meetings in optimizing pharmacotherapy.[32,33]

Medication-related problems are very common in patients with cirrhosis. A recent single-centre trial showed that more than half of medication-related problems could be resolved by a pharmacist-led medication review.[5] These results are promising and the guidance we developed can support pharmacists. However, for large-scale implementation of pharmacists-led medication reviews in these patients, there are still some barriers to overcome as we demonstrated in this study.

5 | CONCLUSION

We showed that the level of knowledge of community pharmacists on medication safety in patients with hepatic impairment is low and that additional education is needed and wanted. The majority of pharmacists encounter patients with hepatic impairment regularly; however, when providing care in these patients they frequently experience difficulties in the contact with other healthcare professionals and lack essential patient information. If these issues are resolved, pharmacists can play a more active role in ensuring safe and optimal medication use and prevention of medication-related problems in patients with hepatic impairment.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

R.W. and M.A. drafted the manuscript. A.B., K.T. and S.B. participated in data analysis and interpretation and critically revised the manuscript. Supervision was done by A.B. and S.B. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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