Designing and Evaluating a Decision Support System on Childhood Leukemia to Improve Medication Management

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Abstract

Aim: To design, develop, and evaluate a clinical decision support system (CDSS) to decrease the adverse effects of treatment in Childhood Leukemia.
Method: To achieve high accuracy, a knowledge base CDSS was designed based on the viewpoints provided by experts and clinical references. The system has the capability of medical report documentation, drug prescription, dosage determination, and displaying patients' medical history. It is also able to eliminate the problems caused by prescription and drug dosage errors by considering the patient's status.
Results: By documenting the patients' medical report, the system can provide comprehensive information and precise recommendations about the future readmission and drug dosage accuracy. The system achieved 94.5% sensitivity, 93% accuracy, and 80% specificity in the evaluation phase.
Conclusion: Application of such systems in the process of prescribing drugs can improve the quality of patient care by reducing the probability of pharmaceutical errors.
Keywords: Leukemia, Medication, Decision support system, Pediatrics

Although cancer is rare in children, childhood cancer is defined as the second cause of death after accidents (1, 2). Fortunately, most leukemic children can be treated given the latest advancements in oncology. However, complications and risks of medication remain controversial (3-6). Considering that adverse drug effects are common among children, prescribing appropriate medications is important in children, especially those involved with cancer (7, 8). Furthermore, leukemic children suffer from a large number of psychological and economic problems due to the side effects of their medication (9).

Historically, Adverse Drug Events (ADE) are still a therapeutic important tragedy in pediatric oncology. Evidence showed that 6.8% of patients admitted to one of the pediatric care centers were exposed to Adverse Drug Reaction (ADR) from chemotherapy (10). Another study concluded that among 2104 pediatric medication errors. 3% were related to pediatric chemotherapy (11). Clinical decision support systems (CDSS) and Computerized Provider Order Entry (CPOE) are two aspects of the information technology with the potential to reduce errors and improve decision making with the aid of clinician and decision-makers in the process of care (12).

The CDSS can provide the required knowledge about patient-specific information for physicians and other care providers (13, 14). In pharmacology related fields, CDSS can provide the basic and advanced information such as suggestions about indication, contraindications, drug-drug interaction, as well as checking and providing the basic dosing guidance for medication based on the patient's medical records and history (15, 16). In this regard, Jonathan Bury implemented a web-based decision support system for trial management of childhood acute lymphoblastic leukemia in 2005. The findings of this study showed acceptable results in reducing ADE with 100% accuracy and less than 0.0001 errors (17). Similarly, George R. Kim et al. conducted a computerized provider order entry system to order the chemotherapy drugs in leukemic children in order to reduce the ordering errors in the pediatric chemotherapy section (4).

Diagnosis methods stand on the powerful databases to achieve accurate diagnosis with high sensitivity and accuracy in patients' information processes. In addition, molecular specificity was performed for cancer patients by CDSS for delivering an accurate diagnosis (18). According to the recent experiments, CDSS was effective in drug prescription and improved the lives of children up to two or three years of age (19).

Despite all these similar systems, the main objective of this study was to design a system that can suggest chemotherapy orders based on the patient medical history and demographic information. Given the importance of pediatric chemotherapy, the final goal was to suggest the proper chemotherapy drug dosage by minimizing the side effects and comorbidities.

Method

This developmental study was carried out in three phases as follow:

In the first phase, the required data sets were identified based on a literature review and interviews with experts. Later, a researcher-made questionnaire was developed. The reliability of the tool was confirmed by a panel of experts containing five oncologists from medical centers and two experts in health information management. The questionnaire included the demographic and clinical dimensions using a five-point Likert- scale. In the next stage, a two-round classical Delphi study was conducted with 20 oncologists to determine and classify the minimum data sets (MDS). In this phase, the questionnaire was completed using face to face interviews in the first round and sent via email in the second round. The findings were analyzed by SPSS v.20. The consensus was defined as 75% agreement. Descriptive and analytical statistics were performed to determine the items' importance.

In the second phase, after system features were confirmed by Delphi method, the system model was designed using technical consultation based on the predefined concepts in Visual Studio IDE by C# language. The software included features of drugs prescribed for pediatric leukemia. The items were in accordance with the standards set by FDA and WHO for prescribing proper drug dosage with least comorbidity. The SQL Server was also used as a database management tool that created the relationships between entities.

This type of CDSS is based on the Knowledge that includes rules with interference reasoning agents called interference engine. This engine acts as a module that uses communication rules based on data entered by the user. The interference mechanism includes a formula that integrates the relationship between the knowledge base and data from actual patients. The If-Then-Else rules were used for modeling the knowledge base of the system (19, 25).

In the third phase, system usability, sensitivity, accuracy, and specificity were evaluated. The questionnaire of user interaction

satisfaction (QUIZ) was administered for evaluating the system usability. This standard questionnaire is available in German, Italian, Portuguese (Brazilian), and Spanish (20, 21). It contains 27 questions with 9 points Likert-scale. The reliability of this scale was reported as a=0.94. In the evaluation phase, the experts were provided with the final version of the system and were asked to respond to the questionnaire. The results of this phase were analyzed by SPSS v.20 and reported using descriptive statistics (median and mean scores) and confidence intervals. As a result, the system usability was determined. The sensitivity and accuracy of the system were also measured based on the data of children with leukemia who referred to the health centers. We compared the drug dosage suggested by the system with the dosage prescribed by the physician for each patient. Accordingly, the sensitivity, specificity, and accuracy were calculated for the system. The Kappa test was performed to measure the compliance between the system suggestion and the prescribed dose-response. In this phase, seven oncologists participated as experts and 59 leukemic patients took part from medical centers.

Results

In the first phase of the study, MDS was identified and system requirements were conducted. Of physicians (n=20) who participated in identifying the required data sets, 55% were within 41 to 50 years and 80% were male. The majority of physicians (=75%) were oncologists and 50% of the specialists had 21 to 30 years' experience in pediatric cancers. (Table 1)

The MDSs were categorized into demographic and clinical groups determined based on the Delphi method by experts. These consensus statements were needed for identifying drug dosage in addition to defining the field of databases. After conducting the first round, the experts identified the patient's age and weight, as essential elements in the demographic aspect. In the clinical aspect, experts reached consus about the type of illness, kidney condition, drug type, and drug dosage. In the case that the experts did not reach an agreement in the first phase, they could not reach an agreement in the second phase too. The results of the first-round are represnted in Figure 1.

After consultation with the experts and based on the findings, the essential drug lists and their characteristics were identified. These items were used in the system. As a result, the following list was generated:

Vindesine Sulfate; Vincristine Sulfate; Teniposide; Nitrogen Mustard; Prednimustine; Adriamycin; Asparaginase; Cytarabine; Prednisolone; Mercaptopurine.

In the second phase, software was developed and designed. Furthermore, SQL server-based CDSS was applied to support the structural and semi-structured data. Semi-structured data included digital media formats such as pictures, formulas, and other required data. Some other features of the database included: 1) a relational database to record drug information; 2) the ability to create a trigger, view, and stored procedure, 3) development of XML; 4) development of OLAP; 5) no limitation in the size and record of numbers; 6) support of the full text searching to increase the speed of information retrieval and natural language processing.

Considerin that tables are the most important element in relational databases, they were determined in the first stage of software designing phase. In this study, some tables were created based on the information including drug prescription, drugs name and characteristics, as well as patients' demographic and clinical information. The system designed in this study provides drug selection from the list of existing drugs or even adds new items to the list of drugs in the system. The ability to revise the information, add new drugs, or omit previous

drugs depends on the users' input.

In the third stage, the user can select the type of leukemia: 1) Chronic Lymphocytic Leukemia (CLL); 2) Chronic Myeloid Leukemia (CML); 3) Acute Lymphocytic-Lymphoblastic Leukemia (ALL); 4) Acute Myeloid Leukemia (AML); and 5) Hairy Cell Leukemia. This possibility provides the ability to enter the prescribed drugs formulas by default.

An important part of the DSS system is designing a convenient and proper user interface (UI) due to the importance of communicating with users. The user interface includes software and hardware aspects such as various means of display, input, and computation, which support communication between the user and computer. In this system, UI contains different features such as icon-based menu, drop-down menu, display different dosage of drugs, possibility of creating a file for each child, determination of medication dose based on demographic information, simple user interface, medication dictionary, and provision of the necessary instructions for working with the system. Some features of the system are shown in Figure 2.

For improving user interface usability, the main menu of the system was designed in the form of a cycled shape on the first page after logging in. The aim was to show support circular data flow (Figure 3). The user can achieve each arrow's information by positioning the cursor on each arrow. The physician can determine drug dosage for every age group by the system.

In the third phase, usability and user satisfaction of the final version of the CDSS were evaluated in collaboration with physicians as the main users. The result of the QUIS survey is presented in Table2.

For each question, a score of zero (lowest) to nine (most) was considered. The mean scores of 0-3 indicate a poor level, 3-6 represent the intermediate level, and 6-9 represent a good level.

As illustrated in Figure 4, the results of usability evaluation reveal that the overall performance system is at a good level (7.25 out of a scale of 9). Moreover, the mean of satisfaction in four dimensions (screen display, terminology, system information, learnability, and compatibility) were 7.41±0.5, 7.01±0.5, 7.76±0.5, and 6.92±0.5, respectively.

Later, perforative evaluation of the system was performed on 59 leukemic children who were under treatment from 2014 to 2015. The results showed that just 5 patients had appropriate drug dosage prescriptions and 5 other patients had inappropriate drug dosage prescriptions.

For calculating the accuracy, sensitivity, and specificity of CDSS, true positive, true negative, false positive, and false negative rates were calculated (TP=51; TN=4; FP=1; FN=3). The system sensitivity, accuracy, and specificity were calculated as 94%, 93%, and 80%, respectively.

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP}+\text{FN}} \times 100 = \frac{51}{51+3} \times 100 = 94.45\%$$

$$\text{Accuracy} = \frac{\text{TP}+\text{TN}}{\text{TP}+\text{TN}+\text{FN}+\text{FP}} \times 100 = \frac{51+4}{51+4+3+1} \times 100 = 93.22\%$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN}+\text{FP}} \times 100 = \frac{4}{4+1} \times 100 = 80\%$$

Kappa test was calculated to determine the compliance between suggested drug dosages with prescribed dose-response by oncologists. In this study, the scale was calculated by the following formula and the Kappa score was 0.52.

$$kappa = \frac{[pr(a)-\text{Pr}(e)]}{[1-pr(e)]}$$

$$pr(a) = \frac{51+4}{51+4+3+1} = \frac{55}{59} = 0.932$$

$$pr(e) = \left(\frac{54}{59} \times \frac{55}{59}\right) + \left(\frac{5}{59} \times \frac{4}{59}\right) = 0.853 + 0.005 = 0.858$$

$$kappa = \frac{[pr(a) - \text{Pr}(e)]}{[1 - pr(e)]} = \frac{[0.932 - 0.858]}{[1 - 0.858]} = 0.52$$

The kappa rate of 1 indicates perfect agreement; whereas, a kappa rate of 0 indicates that the agreement is attributed to chance.

According to Landis and Koch kappa index, the score represents the average compliance between the professionals' prescriptions with the output of this system.

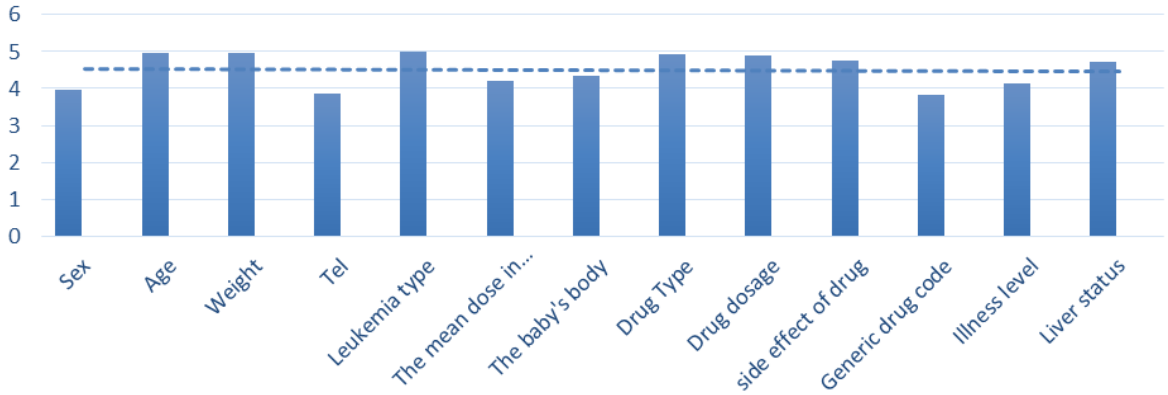
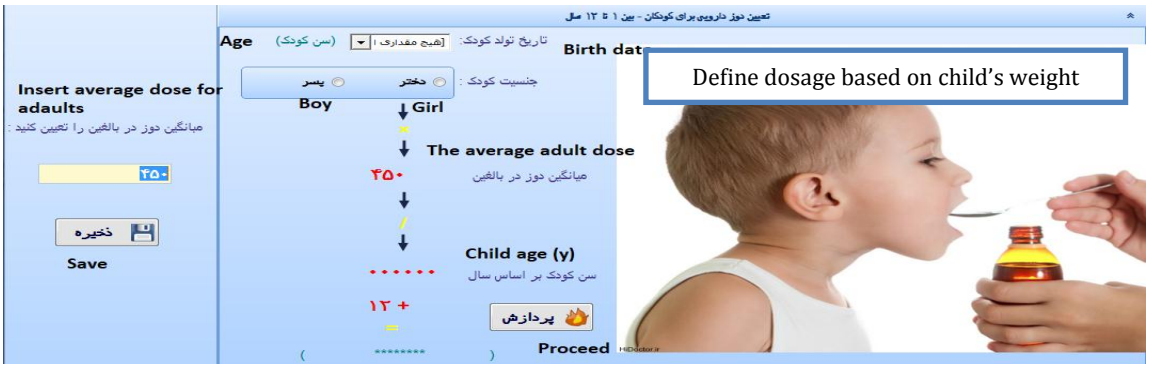


Figure 1: System features Mean in First round of Delphi survey



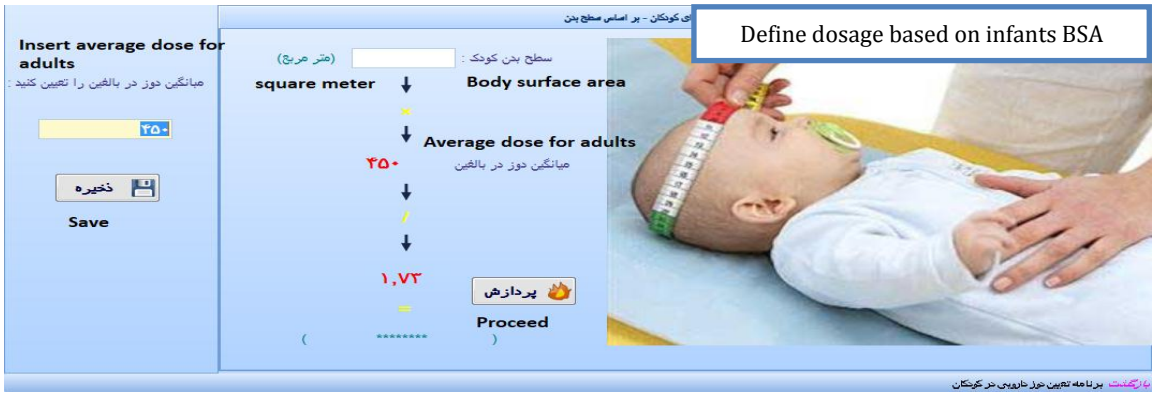


Figure 2: Views of CDSS environments. Selecting the proper dosage of the drug for a specific child based on his age, weight, height, and liver and kidney status are shown in these pictures.

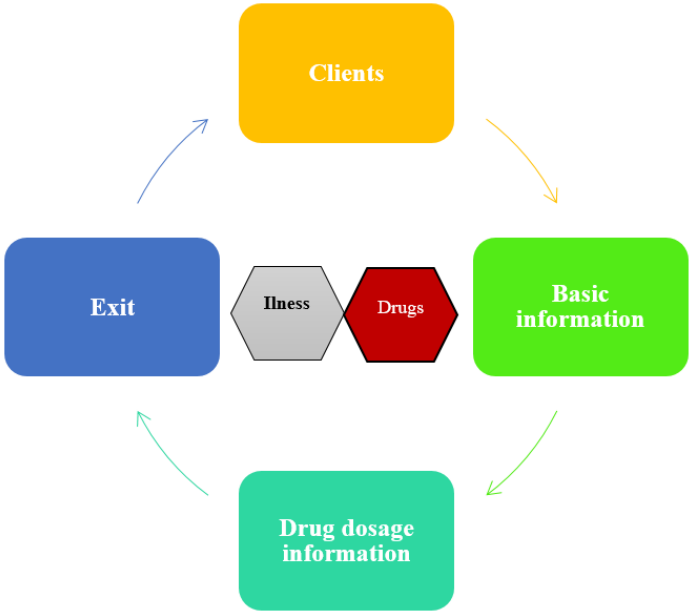


Figure 3: Cycle view of the main page

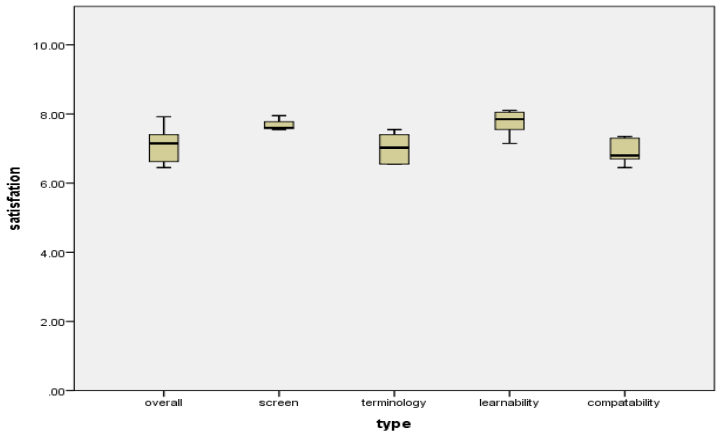


Figure 4: User satisfaction results

Table 1: Demographic properties of experts in Delphi survey (n=20)

Properties	Percentage	Numbers
Age		
<30 years	1	5%
30-40	1	5%
41-50 years	11	55%
51>years	7	35%
Clinical expertise		
<10 years	1	5%
11-20 years	7	35%
21-30 years	11	55%
>30 years	1	5%
Expertise		
Internal Medicine	5	15%
Oncology fellowship	15	75%

Table 2: Different part of Questionnaire

Part of the Questionnaire	Subject
The first part with 4 questions	Demographical information
The second part with 6 questions	Overall system performance
The third part with 4 questions	Questions related to display features and screen
Fourth part with 6 questions	Questions related to terminology and system information
Fifth part with 6 questions	Questions related to learnability of system
Sixth part with 5 questions	Questions related to compatibility features of the system

Discussion

As mentioned previously, many computerized systems were implemented for medication management in different fields of medicine. Several studies were conducted over drug prescription from stored databases. However, the question is that 'why do we need a new system to manage the medications used by leukemic children? In this regard, a study developed and investigated the pharmacokinetic software package MW/Pharm. The researcher provided rapid answers in clinical practice using this software (26). This kind of systems use a large stored database in all fields of medicine; meanwhile, our CDSS can provide a high volume of drug information in the field of pediatric cancer drugs, cancer-related drug dosage, and even clinical information about different types of cancers in children. Despite other similarities in terms of information management in the database, CDSS also provides the ability to edit information for the users, which can be considered as one of its benefits.

Due to the use of CDSSs in drug dosage settings in similar studies, the information and knowledge base of these systems is one of the important parts. Ammenwerth believes that any system that can manage the information can help users to make the right decision (27). The applied knowledge should be achieved from reliable sources, such as pharmacological and clinical references. It also should be confirmed by experts. Therefore, we conducted a literature review under experts' supervision for knowledge acquisition to increase CDSS reliability in the first phase of this research. Considering the features of CDSS, physicians will be independent from referring to pharmacological references.

In one of the famous studies concerning molecular drug modeling, Vinter believes that setting up this kind of system requires designing various subsystems that should have different features including high graphic

capabilities and searchable knowledge. On the other hand, designing simple and interactive user interfaces has a significant impact on user functionality (28). Therefore, capabilities of the C# programming language should be used to create the interface, so that the users are allowed to interact with the system, enter instructions into the DSS, and retrieve information. Thus, a two-way interactive interface was designed between the user and the system. In the study by Proost, a special interface was applied with the capability of customization according to the issue (26).

Ronal et al. developed a DSS for managing sick children at the pediatric oncology unit. The application was designed for monitoring some cancers in children between 7 to 12 years old. Their system recieves symptoms and problems of children and generates complete reports of their last medical status by the decision support system (29). This system can suggest an appropriate drug dosage for all leukemic children up to 12 years old with different types of leukemia based on their demographic information. This indicates universal application of this supporting system and its advantage in monitoring leukemic children to prevent comorbidity from birth.

In a similar study by Kim over error reduction in pediatric chemotherapy, CDSS was used in prescribing chemotherapy drugs with a 95% confidence level. This software can determine appropriate medication dosing regimens for all kinds of pediatric cancers with high confidence and alert medication errors in the drug administration phase before adverse drug error occurred (4). In comparison with this system, Kim's support system considers only weight and age to determine drug dosage, but this CDSS considers all data; so, it can be effective in drug administration, even from kidney and liver status.

Another advantage of this system is integrating all information of the patient to suggest the best medication with minimum complications. This means that the system combines all patient's data (such as gender, age, weight, body surface) with the patient's type of cancer initially and then represent the proper drug with a suitable dosage. Meanwhile, many other systems prescribe and suggest a medication regime with no consideration and attention to a specific patient's clinical status. This feature can provide the best response with the highest safety to ensure providing better care for the patient. This feature differs from other studies and invented systems.

In addition to all advantages of the system mentioned in comparison to other studies, its high accuracy and sensitivity has an effective role in preventing drug errors and managing leukemic children in the best way. Based on the systems' usability result, it can be used in pediatric oncology units' workflow to improve patient management.

Moreover, this study has some limitations. One of the most significant limitations is concerned with the software platform. This CDSS is a windows-based program. This means that the program needs to be installed in every application. Furthermore, it cannot be accessed through the web. Additionally, the drug dosages recommendations were provided based on the opinions of experts who participated in this study. Furthermore, this study focused only on a single medical center. Therefore, the findings may not be generalizable to all medical centers. A web-based version of CDSS can be developed in future studies. The research can be conducted in several medical centers instead of focusing on a specific medical center and the opinions of more experts can be utilized.

Conclusion

In this study, the CDSS was designed to suggest appropriate dosage of chemotherapy orders based on the patient medical records. The evaluation results showed that the system

usability was approved by the oncologists who participated in the survey. Capabilities such as creating medical records and suggesting dosage formulas have made this system usable by physicians. Ultimately, this system can be implemented in pediatric oncology departments to reduce adverse drug errors and improve medication administration in children with leukemia.

Disclaimer Statements

- **Conflict of interests:** None
- **Financial support or sponsorship:** This study was approved by the Tehran University of Medical Sciences (M.Sc. thesis, Code of Ethics: IR.TUMS.SPH.REC.1395.1787).
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- **Authors' contributions:** All of the authors have contributed to writing the article. The corresponding author made the final proofreading.

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