Clinical Decision Support System for Acute Leukemia Classification in Coo-Development

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Abstract. This paper provides a review of Clinical Decision Support System (CDSS) with a focus on set up a “Bridge” between system developer and clinical staff. Acute Leukemia will be brief decision tree example be mentioned for Acute Leukemia Classification. For the purpose of improve in medical domain with I.T. technique. Clinical staff and system developer build up CDSS in Coo-Development plan. Also Explanation system in CDSS provides feedback “Channel”.

1. Introduction
Leukemia is one of top ten of cancer-related deaths in global world. According the Hong Kong Hospital Authority Statistical Report 1999 -2008, incidence of Leukemia was 4,000 and mortality of Leukemia was 2500. [1] As improving technique of medical, cure rate increasing year by year, it is necessary to increase the accuracy and speed of leukemia diagnosis. There are different types of leukemia, like Chronic Lymphocyte Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Acute Lymphocyte Leukemia (ALL), Acute Myelogenous Leukemia (AML). Also there are many subtypes like AML M1, M2, M3, L1, L2 and so on. In this paper, we will focus on how to use Clinical Decision Support System to classify the types of Leukemia. Without focusing on accuracy improves in Clinical Decision Support System, it is also important increase the rate of spread of Clinical Decision Support System by Coo-Development and explanation system.

2. Development in Clinical Decision Support System
Clinical Decision Support System (CDSS), first documented in the 1950s, are designed to assist individuals at the point of care. [2] CDSS have almost 40 years of history; many scholars have made few definitions. Geissbuhler [3] defined a CDSS providing diagnostic decision support as a computer-based algorithm that assists a
clinician with one or more component steps of the diagnostic process. Musen[4] defined a CDSS as any piece of software that takes information about a clinical situation as inputs and that produces inferences as outputs that can assist practitioners in their decision making and that would be judged as “intelligent” by the program’s users. CDSS is an intelligent system which able to analysis muti-symptoms of patient according to professional knowledge database and give a reliable diagnosis result for clinical staff referred. CDSS is a system just wants to release the pressure from high density of clinical duty from clinical staff, also decrease the error diagnosis rate.

3. Clinical Decision Support System Module

3.1 CDSS Module

Clinical Decision Support System is a complex system that contains many parts. Different users will interact with systems with different purpose. In that case, CDSS must be designed in different module.

**Figure 1** Clinical Decision Support System Design Module

**Human-Machine Interaction Interface:**

Interface is the front of the system. Clinical Staff are able to enter information of patient or view the record of patient. Normally, clinical staff need face mass of patients; they need to look monitor most of their working hour, however, most of developers are not take enough attention in this part. Since the one of the purpose of CDSS development is to release the pressure from clinical staff heavy work load. Interaction interface should be designed simple and look comfortable.

Database Module
**Electrical Patient Record:**

EPR is a new idea that replaces the paper—from patient records. It is easy for patient information searching. It can keep records longer and prevent data loss because of backing up easily. EPR records patients’ names, ID, sex, address, contact number, history, and drug allergy. Combining the information of patients in EPR, it can increase the correct rate of diagnosis results.

**Professional Knowledge Database:**

Professional Knowledge Database contains many international diagnosis standards which are settled by many researching cases. We can check the guideline of sickness diagnosis in *National Comprehensive Cancer Network*. It contains the medical knowledge in form of logical rules (Decision Tree). According to the logic method of western medical knowledge, it is very similar to programming design structure (IF-THEN-ELSE). Details will be shown in the following chapter. Though the function of knowledge base Editor, data will be entered by some professional staff in Clinical.

**Treatment database:**

According to different symptoms, different patients (sex, age, history or drug allergy), and different treatment plans will be shown after the result of diagnosis comes out. In western medicine, different treatment plans have already been settled up though different kinds of situations.

### 3.2 CDSS Diagnosis processing

![Process of Diagnosis](image-url)

**Figure 2** Process of Diagnosis
Clinical Decision Support System tries to simulate the process of human diagnosis. When patient have **general symptoms** of leukemia, doctor will sent information of patient and his/her blood sample to lab and have **Complete Blood Count (CBC)** for abnormal checking. While CBC comes out abnormal result, **CBC Alert** will give out alert to doctor for patient detail checking. To confirm whether is leukemia or not, Bone Marrow Smear classification is one of the most acceptable method in clinical domain.

<table>
<thead>
<tr>
<th>Complete Blood Count List</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Myeloblasts</td>
</tr>
<tr>
<td>● Auer Rods</td>
</tr>
<tr>
<td>● Structure of Nucleoli</td>
</tr>
<tr>
<td>● Peroxidase</td>
</tr>
<tr>
<td>● Percentage of Myeloblasts or Promylocytes in Marrow Cells</td>
</tr>
<tr>
<td>● Lysosome concentration in the serum</td>
</tr>
<tr>
<td>● Esterase Staining[specific or unspecific]</td>
</tr>
<tr>
<td>● PAS Staining</td>
</tr>
<tr>
<td>● Erythroblasts in the blood</td>
</tr>
</tbody>
</table>

**Table 1**  Condition of CBC Alert

### 4. Briefly Introduction in Leukemia

Leukemia is a cancer of the bone marrow and blood (also name blood cancer). The two primary types of leukemia are lymphocytic leukemia, which involves an increase of white blood cells called lymphocytes; and myelogenous leukemia (also known as myeloid or myelocytic leukemia), which involves an increase in white blood cells called granulocytes. Leukemia can be acute or chronic. Acute forms of leukemia progress rapidly, whereas chronic forms of leukemia progress slowly, leading to different approaches to diagnosis and treatment. [5]

### 4.1 Leukemia Classification

Normally, international society leukemia classifications have 2 types, FAB and WHO. We focus on FAB classification. [6]

Leukemia classify as 4 types

<table>
<thead>
<tr>
<th>Full Name</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lymphocyte Leukemia</td>
<td>ALL</td>
</tr>
<tr>
<td>Acute Myelogenous Leukemia</td>
<td>AML</td>
</tr>
<tr>
<td>Chronic Lymphocyte Leukemia</td>
<td>CLL</td>
</tr>
<tr>
<td>Chronic Myelogenous Leukemia</td>
<td>CML</td>
</tr>
</tbody>
</table>

**Table 2** Types of Leukemia in FAB classification
In this paper, we try to focus on Acute Leukemia (ALL and AML)

**Acute Myelogenous Leukemia (AML) FAB Classification**

<table>
<thead>
<tr>
<th>AML Types</th>
<th>Feature</th>
</tr>
</thead>
</table>
| M0        | • Myeloblasts without granula or Auer rods  
            • All cytochemical reactions negative  
            • Incidence < 5% |
| M1        | • Myeloblasts with no or few Auer granula and/or Auer rods  
            • The majority of cells have a rim of pale to slightly basophilic agranular cytoplasm  
            • Nuclei with one or more nucleoli  
            • Few blasts are peroxidase positive  
            • Incidence 15-20% |
| M2        | • Maturation more distinct and beyond the promyelocytic stage  
            • 50% of bone marrow cells are myeloblasts or promylocytes  
            • Numerous leukemic cells with azurophilic granula, partially with Auer rods  
            • Numerous leukemic cells are peroxidase positive  
            • Incidence 25-30% |
| M3        | • The majority of bone marrow cells are pathologic promyelocytes, packed with large purple granula  
            • Single cells with Auer rods (Pathognomonic)  
            • Nucleus in variable form and size, frequently kidney-shaped or bilobed  
            • Incidence 10% |
| M4        | • Granulocytic or monocytic differentiation  
            • Percentage of monocytic cells in bone marrow and blood >20%, percentage of myeloblasts and promyelocytes usually also >20%  
            • Leukemic cells partially with specific or unspecific, esterase staining  
            • Lysosome concentration in the serum is elevated  
            • Incidence 15% |
| M5        | M5a (little differentiation)  
            • 80% of bone marrow cells are monoblasts, whose nucleus contains one to three large, bullous nucleoli  
            • Nonspecific esterase reaction is positive and lysosomal reaction in the serum is elevated  
            • Incidence 5%  
            M5b (differentiated)  
            • 20% of leukemic cells show maturation (promonocytes!), nucleus is convoluted or notched  
            • Number of monocytes in the blood higher than in bone marrow  
            • Nonspecific esterase and lysosomal reactions are the same as in M5a |
| M6        | • 50% if the bone marrow cells are megaloblastic erythrocyte precursors, some with a bizarre-shaped nucleus |
30% of the bone marrow cells are myeloblasts and promyelocytes, some with Auer rods
- Erythroblasts in the blood
- PAS staining of erythroblasts is positive
- Incidence < 5%

M7
- Positive reaction with thrombocytes peroxidase and antibodies against thrombocytes
- Incidence 3%

Table 3  Symptoms of different type of AML

<table>
<thead>
<tr>
<th>Detail of AML classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0: Myeloblastic leukemia without maturation</td>
</tr>
<tr>
<td>M1: Myeloblastic leukemia with minimal maturation</td>
</tr>
<tr>
<td>M2: Hypergranular leukemia with maturation</td>
</tr>
<tr>
<td>M3: Hypergranular promyelocytic leukemia</td>
</tr>
<tr>
<td>M4: Myelomonocytic leukemia</td>
</tr>
<tr>
<td>M5: Monocytic/ Monoblastic leukemia)</td>
</tr>
<tr>
<td>M6: Erythroleukemia</td>
</tr>
<tr>
<td>M7: Megakaryoblastic leukemia</td>
</tr>
</tbody>
</table>

Table 4  Full name of different type of AML

4.2 Leukemia Similar Sickness
Before System enters the processing of Leukemia Decision Tree, we need to distinguish the similar sickness from leukemia. It is able to

4.2.1 General Symptoms of Leukemia
Before we classify the type of Leukemia, we need to classify whether the patient are doubted in leukemia or not. Here is General Symptoms of Leukemia.

- Fever or chills
- Persistent fatigue, weakness
- Frequent infections
- Losing weight without trying
- Swollen lymph nodes, enlarged liver or spleen
- Easy bleeding or bruising (Blood Platelets decrease)
- Tiny red spots in your skin (petechiae)
- Excessive sweating, especially at night
- Bone pain or tenderness
- Anaemia
- Immature White Blood Cell and Lymphocyte Increase
4.2.2 Similar Symptoms Sicknesses of Leukemia

<table>
<thead>
<tr>
<th>Name</th>
<th>Similar</th>
<th>Different</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>• Anaemia</td>
<td>• No enlarged liver or spleen</td>
</tr>
<tr>
<td></td>
<td>• Bone pain or tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• White Blood Cell Increase</td>
<td></td>
</tr>
<tr>
<td>Infectious Lymphocytosis</td>
<td>• White Blood Cell and Lymphocyte Increase</td>
<td>• Most of White Blood Cell is immature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No Anaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood platelet decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• *Easy to check in bone marrow examination</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>• White Blood Cell decrease</td>
<td>• blood platelets decrease</td>
</tr>
<tr>
<td></td>
<td>• Fever</td>
<td>• No enlarged liver or spleen</td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
<td>• No Immature White Blood Cell increase</td>
</tr>
<tr>
<td>Infectious Mononucleosis</td>
<td>• Enlarged liver or spleen</td>
<td>• No Blood platelets decrease</td>
</tr>
<tr>
<td></td>
<td>• Enlarged liver or spleen</td>
<td>• No Immature Lymphocyte increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paul-Bunnell test Positive</td>
</tr>
</tbody>
</table>

Table 5 Similar Sickness of Leukemia [6]

5. Decision Tree of Acute Leukemia classification

With the improvement of medical technique, leukemia is no longer can’t be cured. Probability will increase if the type of leukemia can be classification early. For the mass of patient, it is necessary to build up a system that improves the diagnosis speed. According the brief diagnosis, particular test can be done in early period of leukemia. For future develop, direction of research will be improve the rage and complexity of decision tree. It can though data mining to generate more complex and accuracy of decision tree if leukemia patient case can be collected. Furthermore, we can combine the knowledge of image retrieve in future research. Decision Tree is one of the logical thinking for programming design. [8]

- Each internal node tests an attribute value
- Each branch corresponds to attribute value
- Each leaf node assigns a classification

The logic of Decision Tree is very similar to western medical structure. When patient have A, B, and C symptoms, then they will be diagnosed as Disease X. Structure if (IF-THEN ELSE) is very easy to apply in programming. In decision support system decision tree structure is very high speed even there are mass of node.
Acute Myelogenous Leukemia (AML)

Auer rods
Available

AML M0, M2, M3, M5, M6, M7

Cell Nucleus Shape and Size
Similar

AML M1

None Or Fewness

Acute Myelogenous Leukemia M1

Different or Kidney Shape

Acute Myelogenous Leukemia M3

Amount of Cell Differentiation
High

AML M2, M4

Low

Non-special Esterase Stain Positive/Lysosome Increase

Vacuoles Nucleolus
Distortion or Notch Nucleolus

Acute Myelogenous Leukemia M5a
Acute Myelogenous Leukemia M5b
Plastocyte Peroxidase Test Positive

Acute Myelogenous Leukemia M2
Acute Myelogenous Leukemia M4

Part of Special or Non-special Esterase Stain Positive

Figure 3 Initial Decision Tree of Acute Leukemia

Decision Tree supposes made by the data mining and generate automatically. In this paper, decision tree is decided by Leukemia FAB classification according to medical reference book instead. [6] It is necessary to increase the level of complexity of tree in future research.

6. Coo-Development in CDSS

“Coo-Development” means cooperation in CDSS development between clinical staff and system developers.
Figure 4 Coo-Development Processes

Brief Decision Tree of System was settled up in System Developing period according the data, which is provided by Clinical Decision Standard. In this period, decision tree only can fit the situation of normal case. However, there is mass of special case in clinical practical. There are mass of factor will effect the result of diagnosis. It is impossible to drop it all in Clinical Decision Standard. It is one of the reasons that clinical decision support system are not fit the real clinical cases.

Demo version of CDSS is built up and delivers to clinical department for real case testing. It also can be called as Real Case Fitting Period. In this period developers are able to check the accuracy of brief decision tree. In the view of system developing, system developing plan cost can be reduced if discover the problem and fix it in early period. Suggest Diagnosis results are not suggested to use as reference in this period. Feedbacks that come from clinical staff will be use for brief decision tree amended.

After a certain period of time, System enters a new period of application. In this period, suggest diagnosis result can be reference in real clinical case because of the cases fitting are become more accuracy. It also means that the number of feedback will be reduced normally. Decision Tree will be amended when new feedback give out or new clinical standard update.

In Coo-Development in CDSS, clinical staffs and system developers develop CDSS. The process of “Feedback ” like a bridge of developer and clinical staff, it can improve the accuracy of diagnosis analysis and the acceptation rate.
7. Explanation System in CDSS

“Explanation facilities are typically included in knowledge-based information systems, where their purpose is to provide system users with the underlying reasons for why the system reaches a particular conclusion or makes a particular recommendation.” [9]

Explanation system is a function, which makes users, clinical staff; understand why the system has such result. It also helps clinical staff to give a feedback to system developers to amend the diagnosis structure in system.

7.1 Demand in Explanation function for CDSS

Clinical Decision Support System has been developed many years. However, it still can’t be accepted by most of clinical staff. One of the reasons is that they doubt the accuracy of diagnosis result coming from system. They cannot accept the result without a detail explanation. To increase the rate of acceptation, function of explanation is necessary. Without the reason of increase the rate of acceptation, it also decreases the error rate cause of special case. Clinical staff is able to check the explanation how system is running.

7.2 Reason of Explanation function CDSS

Since the suggest diagnosis result analysis is according the Decision Tree. In that case, explanation can show the “Paths” how the decision runs. Also it provides evidence about the leukemia classification. Clinical Staffs are able to figure out how the systems run; also they can point out the singularity of the decision tree. It can help to improve the accuracy of the system in very short period. In the early period of the system release, clinical staff and developers are work together because of explanation system. Since clinical staff have participle in process of developing. They will accept the system more easily when the system final release and use in real case. One study concluded that not the expert advice given, but the ability to explain that advice, was the single most important factor in user acceptance of expert system application. [10]

7. Conclusion

With the improvement in medical domain, many diseases are no longer being uncured. Also the pressure and workload of clinical staff are become heavier in this year. A system support is essential to staff who is working in clinical domain. However, there is great gap between clinical staff and system developers. No matter how many new versions of CDSS have been developed, system is unable to wide spread. Coo-Development plan is able to set up “Bridge” though Feedback function. Structure of diagnosis analysis is amended according feedback come from clinical staff. It also will be amended if the diagnosis standard update. For feedback function in CDSS, explanation system is built up for clinical staff for reference. According the information of
explanation system, clinical staffs are able to express their feedback to system team more easily. Since Coo-development, clinical staff and system developer builds system together; the acceptation rate of system can increase.

Reference
[1] Hong Kong Hospital Authority, Hong Kong Hospital Authority Statistical Report in WWW’ 10, 2011

[2] Emily J. Vardell, Mary Moore PhD, Isabel, a Clinical Decision Support System, 1, University of Miami, Scholarly Repository, 1-1-2011


