IAES International Journal of Artificial Intelligence (IJ-AI)
Vol. 12, No. 2, June 2023, pp. 704~713
ISSN: 2252-8938, DOI: 10.11591/ijai.v12.i2.pp704-713

Cross-checked screening application for reliable categorisation of familial hypercholesterolaemia: design and development of the prototype

Marshima Mohd Rosli[1, 2], Muthukkaruppan Annamalai[1], Noor Alicezah Mohd Kasim[2,3], Chua Yung-An[2,3], Hapizah Mohd Nawawi[2,3]
[1]Faculty of Computer and Mathematical Sciences, Universiti Teknologi MARA (UiTM), Shah Alam, Malaysia
[2]Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM), University Teknologi MARA (UiTM), Sungai Buloh, Malaysia
[3]Faculty of Medicine, University Teknologi MARA (UiTM), Sungai Buloh, Malaysia

Article Info

Article history:

Received Feb 4, 2022
Revised Nov 8, 2022
Accepted Dec 5, 2022

Keywords:

Automated scoring and categorisation application
Familial hypercholesterolemia
Familial hypercholesterolemia diagnostic criteria

ABSTRACT

The paper describes the development of a computer-based familial hypercholesterolemia (FH) screening application (FH CatScreen©). The application facilitates automatic scoring and categorisation of patients by medical practitioners based on four well-known FH diagnostic criteria. In the absence of a FH diagnostic criterion for Malaysian population, these four diagnostic criteria are commonly used criteria to classify patients FH severity levels to manage early interventions. We applied an adaptive software development approach comprising planning, development and validation phases to develop FH CatScreen©. A user study involving thirty medical practitioners was conducted to evaluate the effectiveness and usability of FH CatScreen©. The study showed that FH CatScreen© was able to provide a more correct, faster and better-informed assessment compared to the traditional paper-based method. The study further showed that FH CatScreen© has a good degree of performance and acceptance by the participants. The participants indicated that the simultaneous use of the four diagnostic criteria in FH CatScreen© has assisted them to compare the outcomes of each of the criterion side-by-side. It allowed them to decide on the severity of patient condition with high confidence. FH CatScreen© has demonstrated its expediency and efficacy in collecting the data on FH incidence and prevalence in Malaysia.

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Corresponding Author:

Marshima Mohd Rosli
Faculty of Computer and Mathematical Sciences
Universiti Teknologi MARA, 40450 UiTM, Shah Alam, Selangor, Malaysia
Email: marshima@fskm.uitm.edu.my

1. INTRODUCTION

Familial hypercholesterolemia (FH) is the most common and serious form of inherited hyperlipidaemia that results from genetic mutations in genes that regulate the metabolism of low-density lipoprotein cholesterol (LDL-C), which leads to severe increase in blood LDL-C level, and ultimately causing premature coronary artery disease [1]. FH is treatable with low cost lipid lowering therapies, leading to a substantial reduction in premature coronary artery disease (CAD) if detected and treated early [2]. Hence, screening for FH is of utmost importance due to its substantial socio-economic impact.

There are handful of FH diagnostic criteria used to classify individuals into different severity of FH, namely dutch lipid clinic network criteria (DLCC) [3], Simon Broome (SB) [4], Japanese FH management

criteria (JFHMC) [5] and US-make early diagnosis to prevent early deaths (US-MEDPED) [6], [7]. Despite these established guidelines, the reports of FH in Malaysia are highly diversified in term of diagnostic method [8], for a couple reasons. First, there is no consensus guideline on how to screen FH in Malaysia. Even according to the Malaysian national standard practice guideline for management of dyslipidaemia, the clinicians may freely use DLCC, SB, JFHMC or US-MEDPED to diagnose the patients [9]. Second, the input variables and the outcome of each diagnostic criteria are different, therefore, any attempt to combine multiple diagnostic criteria into one diagnostic criterion is not possible. Before a population-based FH diagnostic tool is specifically designed for Malaysian FH patients, the healthcare workers in Malaysia have to content with the currently available FH diagnostic criteria, especially the DLCC and SB, which has been utilised by many Malaysian FH study groups since early 2,000 [10]–[13].

In any case, all the above-mentioned FH diagnostic criteria are being used in paper-based form. There are additional challenges due to the shortcomings of the current paper-based FH screening practice: paper forms are cumbersome to print and handled, require physical space for storage, easily damaged and lost, and it is inefficient to keep them updated with evolving needs. The current practice also has issues associated with form filling and scoring, such as incomplete or incorrect completion, illegible handwriting error, wrong calculation of the score and mistake in the determination of the severity of FH. In addition, manually scoring would generally take longer time, which would significantly add up in large cohort screening.

While there is a number of FH diagnostic tools available to facilitate FH screening [14]–[16] (see the Related Work section), these proprietary systems are not adaptable for local implementation. In healthcare practice, the screening data has to be captured and stored in an accessible space for future reference, which is not possible with the use of proprietary system. Whilst, a controllable online FH screening repository system will serve as a convenient tool not only for FH patient management, but also to collect data for future analysis. With the digitisation and computerisation of FH diagnostic tools [17], reliable FH screening and categorisation could be administered with fidelity to the affected people.

Therefore, our team has successfully developed a computer-based FH CatScreen© application to facilitate automatic scoring and categorisation of FH in patients based on the four well-known and commonly used FH diagnostic criteria in Malaysia, namely DLCC, SB, JFHMC and US-MEDPED. Because these diagnostic criteria apply similar and different diagnostic inputs to detect FH in individuals [13], the application uses an inclusive form without redundancies to capture the inputs of each of the diagnostic criterion and presents the diagnostic result of each, side by side. FH CatScreen© also captures additional clinical information that is required beyond the diagnostic assessment for future reference and analysis. Further, the computerisation offers many advantages: detecting missing or incomplete responses, checking consistency of responses, compacting through use of interface elements like drop-down lists, automatically capture responses and calculate the FH diagnostic risk scores, and options to generate report and export the data; all of which are more effective and efficient than the present paper based screening [18]–[26].

In addition to all above, the simultaneous use of the DLCC, SB, JFHMC and US-MEDPED diagnostic criteria in FH CatScreen© and the side-by-side presentation of the diagnostic results, leads to corroborative outcomes on the severity of FH patient condition with high confidence. A user study involving thirty (30) medical practitioners showed that FH CatScreen© has a good degree of performance and acceptance by the participants: around 90% of the participants agreed or strongly agreed on the usefulness, satisfiability and learnability of FH CatScreen© and 84% of them agreed or strongly agreed on its ease of use. Moreover, FH CatScreen© has the cost advantage for scaling to larger cohorts in local population and the comprehensive diagnostic data collected over time will be useful in formulating a standard criterion for detecting FH in a Malaysian population.

2. RELATED WORK

Computerised diagnostic scoring are replacing the traditional paper-and-pencil forms because of their advantages: the possibility to detect missing responses and check consistency, compact through use of interface elements like drop-down lists, cost advantages for scaling to a large number of local population, and the possibility to adapt the interface for tailored feedback on health, and automatically capture responses and analyse results with powerful reporting and export of data, and giving immediate feedback; all of which are more effective and efficient than paper based diagnostic scoring [21], [27]–[29]. A significant number of disease diagnostic or screening applications have been developed over past years, including in the recent COVID-19 pandemic. The disease screening applications aim to provide early detection of the disease as well as effective treatment before the occurrence of the disease. For example, screening for comorbidities, such as diabetes [30], cardiovascular risk [31], high blood pressure [32] and coronary heart disease [33].

There are online FH diagnostic tools specifically to facilitate diagnostic scoring and categorisation of FH such as FH-Diagnosis by FH-Foundation [14], FH-Calculator by FH Australia network [15] and MDCalc by MD aware LLC [34]. Many FH risk calculators are equipped with a specific diagnostic criterion

(e.g., FHScore and FH-Calculator execute the DLCC criteria), while some others are equipped with more than one diagnostic criterion even though they execute only a selected criteria at a time (e.g., FH-Diagnosis, FH-Foundation and MDCalc are equipped with DLCC, SB and US-MEDPED diagnostic criteria). Some of these FH risk calculators such as FHScore that uses the DLCC diagnostic criteria require DNA testing data to determine the FH risk category, while other calculators such as MDCalc only utilised US MEDPED as diagnostic criteria and require simple evidence data to determine the FH category. However, all the above-mentioned proprietary computer-based FH screening and categorisation applications applies only a single FH diagnostic criterion at any one time, uncustomisable, and do not support data collection on the user's end.

3. RESEARCH METHOD

3.1. Adaptive software development method

This section presents the software development method and the system architecture of FH CatScreen©. We applied an adaptive software development method to develop FH CatScreen©, which consists of three phases: planning, development and validation. The process is iterative, incremental and it focuses on improvement during development as Figure 1 [35].

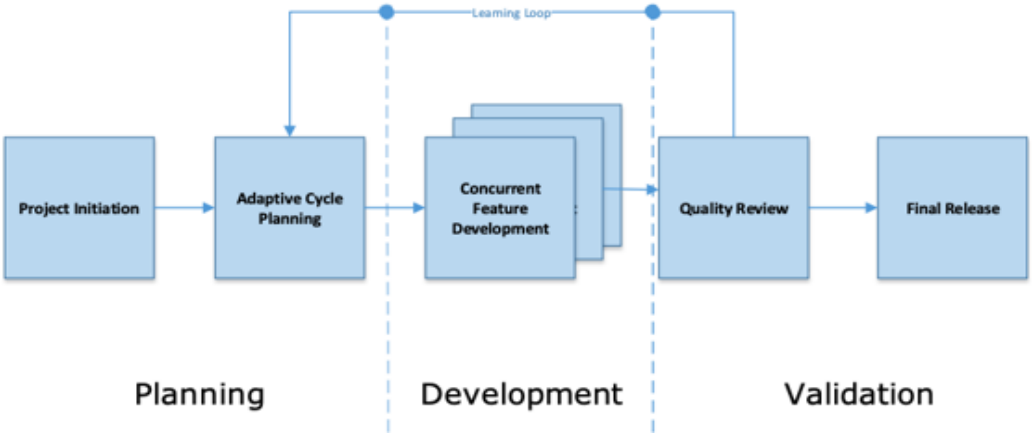

Figure 1. Phases of FH CatScreen© development

The Planning phase consists of two steps: project initiation and adaptive cycle planning. In the first step, the project objective and constraints are understood, and the functional requirements are outlined. The next step creates the application designs and the delivery plan that determines the number of iterations and the deliverables for each iteration. The development phase involves concurrent development activities between the application developers and the stakeholders such as knowledge sharing and decision making. The decision-making ability depends on the knowledge learnt continuously through incremental feature adaptation after each development cycle, and the quality review of the prototype unit that follows in the validation phase. The learning loop between the validation and planning phases dealt with the concomitant changes in the requirement specifications, design and development of the application. The tested application is ready to be deployed once the results are acceptable.

3.2. Functional requirements

The functional requirements describing the application's functionalities and the supporting user interfaces were specified. The use case diagram of FH CatScreen© is Figure 2. There are two user roles and six use cases. A medical practitioner (normal user) can register a new patient's information, enter the diagnostic assessment information (from which the FH risk under each of the four diagnostic criterion is calculated), and view and edit his/ her patients records. An administrator can view the information of all patients recorded in the system and generate a dataset (in CSV file format) for analysis.

3.3. System architecture

The FH CatScreen© system architecture consists of three components: i) user input, ii) assessment and categorisation, and iii) data management as Figure 3. The process starts with a medical practitioner registering his/ her patient to the system before entering the patient's diagnostic assessment information (user

input) and concludes with the computation of the FH risk category (assessment and categorisation). The risk scores are calculated based on the respective FH diagnostic criteria, to which a set of decision rules is applied to determine the patient's FH risk category.

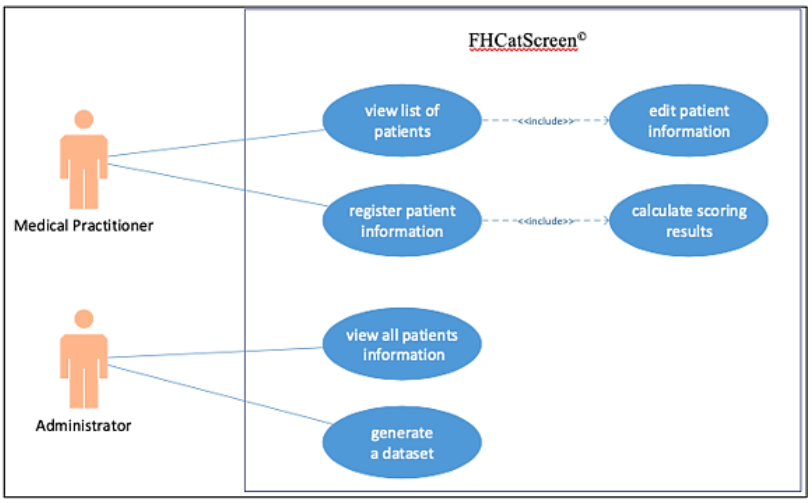

Figure 2. Use case diagram for FH CatScreen©

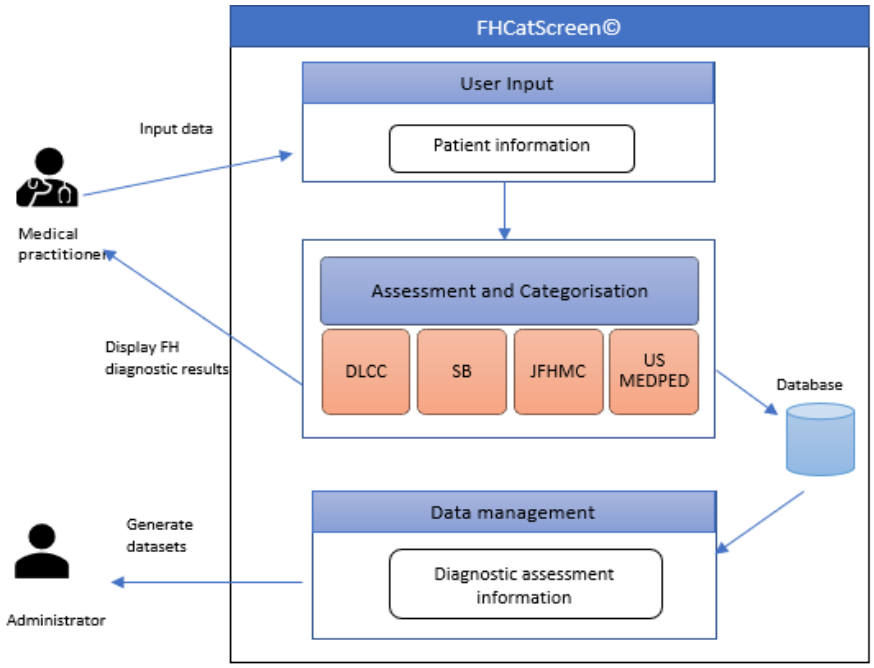

Figure 3. FH CatScreen© architecture

In essence, each of the FH diagnostic criterion refers to a set of implicit rules and requirements used to assess FH risk in affected people. These rules are explicated and captured in the application as rule-based categorisation conditions: IF-THEN statements. An example of a rule in the DLCC criteria is "If patient is diagnosed having premature CAD, then add 5 marks to score."

The patient details (input data) and the screening results are stored a database for further reference. The data management component in FH CatScreen© manages the diagnostic assessment information. The administrator can extract selected data from the database and view them or export them as a CSV file.

4. EVALUATION

We conducted a user study to evaluate the effectiveness and usability of FH CatScreen© using thirty (30) voluntary participants, which consists 13 medical practitioners, 10 postgraduate students, 4 academicians and 2 researchers who are affiliated with the UiTM Sg. Buloh hospital. The study involved participants completing paper-based FH diagnostic scoring, online diagnostic scoring and usability questionnaire. Before participants started performing the study, they were asked to follow the instructions written on the task list and the questionnaire.

4.1. Test case selection

We selected the three (3) patient cases from the health screening programme datasets and transcribed into the evaluation document (labelled as Test Case 1, Test Case 2 and Test Case 3). We took two factors into consideration: a) whether a patient is on lipid lowering medication or not, and b) whether a patient has performed genetic testing or not. For patients who are on lipid-lowering therapy, there is need to adjust their LDL-C level to obtain the baseline level based on the lipid-lowering medication type and dosage. The genetic testing information is necessary for test cases selection because it helps to identify the FH cases. If the genetic test result is positive, then FH is highly probable. In addition, the specified test cases need to satisfy the following requirements: a) Patient has family history of CAD or tendon xanthomata, and b) Patient has family history of hypercholesterolaemia. These two requirements are essential for our test case selection because FH is an inherited disease where the presence of the aforementioned conditions in close family members contributes strong evidence of family inheritance disease. The considerations and requirements produced variation of the diagnostic outcomes across four different diagnostic criteria, which minimises potential threat for cases bias.

Test Case 1 is a "Definite Yes" FH risk case where the patient does have premature CAD, tendon xanthomata, family history of premature CAD and tendon xanthomata and have performed genetic testing. Test case 3 is a "Definite No" FH risk case where the patient does not have premature CAD, stroke, corneal arcus, tendon xanthomata, lipid lowering medication, even if genetic testing has not been performed. Test Case 2 lies in between them, is an "Indefinite" FH risk case where patient does not have tendon xanthomata, which is a cardinal clinical sign of FH. While patient is also without premature CAD, the presence of corneal arcus and family history of tendon xanthomata, and the calculated baseline LDL-C of 4.4 mmol/L, does not contribute sufficient scores to conclude either it is a "Definite Yes", or a "Definite No" FH risk case. The FH risk outcomes according to the diagnostic criteria for each of the test cases are summarised in Table 1. Note that we have applied the risk category label provided by each criterion.

Table 1. Test case selection

	FH Diagnostic Criteria			
Test Case	DLCC	SB	JFHMC	US-MEDPED
1	Definite	Definite	Yes	Yes
2	Probable	Unlikely	No	No
3	Unlikely	Unlikely	No	No

4.2. Task execution

The participants are required to complete three tasks. The first task is to assess patient cases using the paper-based FH diagnostic scoring and assessment forms, and the second task is to assess patient cases using the online diagnostic scoring and assessment form on FH CatScreen©. The third task is to answer the usability questionnaire.

At the start of the session, each participant was given a set of evaluation document, which consists the three transcribed patient cases, the paper-based DLCC, SB, JFHMC and US-MEDPED diagnostic scoring and assessment forms and the usability questionnaire. Before they started performing the tasks, the procedure was explained to the participants, and were asked to follow the printed instructions provided to them. Participants were asked to return the set of evaluation document when they finished.

In the first task, participants need to score and assess three stratified patient cases using each of the FH diagnostic scoring and assessment form, manually using paper and pencil. In total, the four diagnostic forms consist of 33 questions (Yes/No, Multiple-choice response items and short answer items), some of which are repeated in the forms. Out of 33 questions, one question required calculation that is to calculate the pre-treatment LDL-C level for patient on lipid-lowering therapy.

In the second task, participants need to log in to the FH CatScreen© and register the three patient cases using online patient registration forms. The same patient cases that were used in the first task were reused. To minimise the case selection bias, we randomly assigned the patient cases to the participants. It

ensures that the selection of the patient cases in the second task is not biased toward that of the first task. The online patient registration form consists of 47 unique assessment questions, supported by graphical user interfaces (GUI). The activity was conducted in a computer laboratory and the participants used common type of personal computers when scoring the cases on FH CatScreen©.

The paper-based assessment (using four individual FH diagnostic scoring and assessment forms), and the online assessment (using FH CatScreen©) differ not only in terms of the number of questions but also in the way in which the participants are required to score the assessments. Compared to the second task there are fewer diagnostic questions to score in the first task. Nevertheless, unlike the auto-determination of the FH diagnosis result in second task, the participants determine the diagnosis result manually in the first task; they apply the FH diagnostic criterion rules for scoring the responses, then use the item-score to determine the decision outcome.

In the third task, the participants are required to answer 14 questions, i.e., 2 questions related to participant's background and 12 questions related to the usability of FH CatScreen©. The usability questions focused on the four usability requirements, namely, usefulness, ease of use, ease of learning and satisfaction. Usefulness refers to participant's perception on the usefulness of FH CatScreen© in helping him/ her to accomplish the task effectively. Ease of use refers to the effort required to use FH CatScreen© and how easy the participant thinks it is to use. Ease of learning refers to how fast the participants who have not seen FH CatScreen© before this session, learnt and understood to use the application effectively. Satisfaction refers to how pleasant the participant experienced when using FH CatScreen© [36].

5. RESULTS AND DISCUSSION

5.1. Paper-based vs. FH CatScreen© diagnostic scoring and assessment

The descriptive statistics for the correctness of assessment results and time spent to complete the paper-based FH diagnostic scoring and assessment forms and on FH CatScreen© in the user study is shown in Table 2. The maximum correct result for both forms of assessment was 12. FH CatScreen© automatically calculated the FH diagnosis results correctly for all cases correctly for all 30 participants. However, when the participants performed the FH diagnosis manually using the FH diagnostic scoring and assessment forms in the first task, the minimum and maximum numbers of correct results obtained by the participant were 9 and 12, respectively. Out of the 30 participants, twenty-one (21) determined all 12 results correctly, eight (8) determined 11 results correctly and one (1) only determined 9 results correctly.

Table 2. User study results-correctness and time spent

	Correct Results		Time Spent (in minutes)	
Statistics	Paper forms	FH CatScreen©	Paper forms	FH CatScreen©
Mean	11.63	12	28.33	13.30
SD	0.77	0.18	7.83	2.89
Min	9	12	17	10
Max	12	12	44	20

Given the distribution is normal, tested by using the Kolmogorov-Smirnov test, and the correctness of the assessment and the time spent are continuous variables, we used the Wilcoxon signed-rank test separately to check for difference in the time spent and in the correctness of the results between the paper-based and the computer-based scoring and assessment of FH diagnosis results; the latter using FH CatScreen©. The Wilcoxon signed-rank test is also used to compare the two sets of scores that come from the same participants and to investigate any change in scores when individuals are subjected to more than one way to evaluate the FH CatScreen©. We evaluated the effectiveness of FH CatScreen by comparing the correctness and time taken using the statistical Wilcoxon signed-rank test. In terms of correctness, the results indicated that there is no different of correctness for FH scoring calculation between FH CatScreen and paper-based questionnaire. Regarding the time taken to calculate the FH scoring, the results indicated that the time taken for the FH CatScreen to calculate FH scoring is effective than the time taken for the manual calculation. These results are consistent with the findings of other studies [37], [38]. Thus, we can say that FH Catscreen is successful in reducing the user time to calculate the FH diagnosed score.

5.2. Hypothesis testing for differences in correctness of participants FH risk assessment results

The paper-based FH diagnostic scoring and assessment was performed manually where the diagnostic scoring and calculation of the result are done by medical practitioners. In the computer-based assessment using FH CatScreen©, the system automatically calculates the result based on the diagnostic

scoring done by a medical practitioner. We noted there were difference in the number of correct results provided by the 30 participants. Subsequently, we conducted a hypothesis test to verify this observation.

The null hypothesis for the test is: there is no difference in the means of the correct results between the paper-based FH diagnostic scoring and assessment and the computer-based assessment using FH CatScreen©. We obtained a Z-value= -2.807 with p-value= 0.005. Since the p-value is less than 0.05, we reject the null hypothesis and we can conclude that there is a difference in the means of the correct results between the paper-based and computer-based FH diagnostic scoring and assessment. Thus, we can empirically corroborate that FH CatScreen© success to provide more correct assessments than paper-based assessment form.

5.3. Hypothesis testing for differences in time spent by participants to assess FH risk

We observed the difference in the time spent by participants to complete the user study. The null hypothesis for the test was: there is no difference in the means of the time spent between the paper-based FH diagnostic scoring and assessment and the computer-based assessment using FH CatScreen©. We obtained a Z-value= -4.785 with p-value= 0.000. Since the p-value is less than 0.05, we rejected the null hypothesis and we conclude that there is a difference in the means of the time spent between the paper-based and computer-based FH diagnostic scoring and assessment. Thus, we can empirically corroborate that FH CatScreen© is successful in reducing the user time to score and assess the FH risk in patients.

5.4. Participants usability responses

Participants are required to share their user experience and feedback by completing a usability questionnaire that aim to obtain information related to the four usability requirements. Usefulness, ease of use, ease of learning and satisfaction when using FH CatScreen©. The participants' responses are based on a 5-point likert scale (1 = strongly disagree, 5 = strongly agree).

Figure 4 shows the survey results for each usability requirements. The results of each corresponding three-question block were averaged to produce the bar chart. The results are positive. The majority (89%) of the participants agreed or strongly agreed on the usefulness of FH CatScreen© to screen FH risk, and on the ease of learning to use the application effectively, 93% of the participants agreed or strongly agreed that it was a satisfactory experience to use FH CatScreen©, and 84% of the participants agreed or strongly agreed that it was easy to use the application. In all questions, by far, the majority of participants answered that they agreed or strongly agreed, indicating the FH CatScreen© had a strong appeal, and was perceived to be highly usable, useful, easy learning and highly satisfied by our end users. The outcome on the ease of use is slightly lower than the other usability requirements because a senior participant felt somewhat uncomfortable using FH CatScreen© as the participant had difficulty adjusting to the computer-based form layout and is not familiar with certain features of the GUI controls.

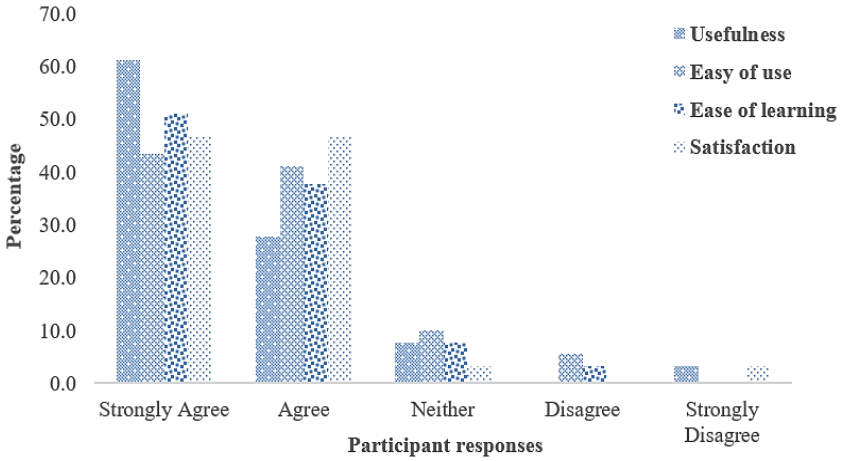

Figure 4. Usability results

5.5. Advantageous and benefits of using FH CatScreen©

FH CatScreen© has potential to facilitate the diagnostic scoring, categorisation and screening FH risk in patients in primary care, specialist lipid, cardiac clinics or in community health screening programme. The

computer-based application provides a platform for medical practitioners to rapidly categorise FH patients with only one-page data entry and the analysis outcomes are reported in four different diagnostic criteria: DLCC, SB, JFHMC and US-MEDPED. The built-in control features support consistency of scoring, able to prevent data entry errors and assuring data integrity. In terms of data digitisation, the online FH CatScreen© allows authorised users to capture FH clinical data from anywhere, anytime and any device, and store them in a secured database on the cloud. The stored data can be extracted for clinical audit and research analysis afterward.

Compared to relying on a single FH diagnostic criterion that is being practiced in diagnostic and screening areas currently [14]–[16], [32], [33], the use of multiple diagnostic criteria such as in FH CatScreen© allows a medical practitioner to easily compare the outcomes of each of the criterion and corroboratively decide the severity of FH patient condition with high confidence. It sheds more light on unclear previous results, especially when dealing with indefinite cases [39], which helps a medical practitioner to decide on the subsequent management of the FH patient such as referral to a specialist clinic (Lipid or Cardiology), conduct family cascade screening, perform genetic testing for FH candidate genes and consider starting lifestyle intervention and treatment with lipid-lowering medications early to target LDL-C levels.

The analysis of the data collected over time can help medical practitioners to better understand the concordance and discordance in the data. Furthermore, the results can assist medical practitioners to learn about the suitability and correlation among the criteria to screen Malaysians at risk of FH. The relationships between the assessment data and performance can be used to develop a FH diagnostic criterion specific for Malaysian population in future.

6. CONCLUSION

FH CatScreen© is a convenient application that substantially simplifies the scoring, categorisation and data storage of FH screening. It is one of the world's first web-based FH diagnostic screening application that combined the DLCC, SB, JFHMC and US-MEDPED FH diagnostic assessments. It allows corroborative comparison of the results of the different diagnostic criteria to decide on the severity of patient condition with high confidence. The evaluation study has revealed that the FH CatScreen© is usable, effective and efficient in terms of correctness and time spent for the assessment of FH risk in patients, and well-liked by the test users. Acknowledging the need to improve the performance of FH risk assessment, the I-PPerForM researchers have instituted additional questions (not found in the existing FH diagnostic criteria) that captures other related personal, clinical and oral medical history information. The idea is to collect a comprehensive diagnostic data that will be useful in formulating a FH diagnostic criterion specific for Malaysian population. Despite the need to answer more question items than the ones in a conventional paper-based form, the functionality and usability results attest to the utility of FH CatScreen©. Therefore, we believe FH CatScreen© can expedite the collection of data on FH incidence and prevalence in Malaysia. For being convenient, FH CatScreen© will enhance FH detection by encouraging more FH screening programmes in the community and cascade screening for relatives of index cases. The cloud data-sharing feature of FH CatScreen© eases centralised collection of FH data from the screening conducted on patients in hospitals, medical centre and multiple field-testing sites.

ACKNOWLEDGEMENTS

The authors would like to thank the Ministry of Education Malaysia and Universiti Teknologi MARA for their financial support to this project under REI Grant No. 600-IRMI/REI 5/3 (001/2019). We would also like to thank the Faculty of Computer and Mathematical Sciences, Universiti Teknologi MARA, Selangor, Malaysia for all the supports.

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BIOGRAPHIES OF AUTHORS

Marshima Mohd Rosli is a senior lecturer at the Department of Computer Science, Universiti Teknologi MARA, Malaysia, where she has been a faculty member since 2007. Marshima graduated with Bsc (Hons) Information Technology from Universiti Utara Malaysia in 2001 and an M.Sc. in Real Time Software Engineering from Universiti Teknologi Malaysia in 2006. She completed her PhD in Computer Science from the University of Auckland, New Zealand, in 2018. Her research interests are primarily in the area of software engineering, artificial intelligent and data analytics. She can be contacted at email: marshima@tmsk.uitm.edu.my.

Muthukkaruppan Annamalai is an Associate Professor in the Department of Computer Science at the Universiti Teknologi MARA. He teaches Philosophy of Computer science and Agent Technology. His research interests span a range of topics, from knowledge management, modelling and ontologies, information retrieval, logical reasoning and agent systems, with a focus on knowledge systems**.** He can be contacted at email: mk@tmsk.uitm.edu.my.

Dr Noor Alicezah Mohd Kasim is an Associate Professor at the Department of Pathology, Faculty of Medicine, Universiti Teknologi MARA (UiTM). She obtained her MBBS from the International Islamic Universiti Malaysia in 2005. After completing the houseman ship, she joined UiTM as a trainee lecturer in pathology. She successfully obtained the Master of Pathology (Chemical Pathology) in 2012. She is also actively involved in Familial Hypercholesterolaemia (FH) research and does provide consultation to FH and dyslipidaemia patients through the lipid clinic at Hospital Al Sultan Abdullah (HASA) UiTM. She is also an active member of the European Atherosclerosis Society, the Asian-Pacific Society of Atherosclerosis and Vascular Disease and the Malaysian Association of Clinical Biochemists. She can be contacted at email: noor202@uitm.edu.my.

Dr Chua Yung An is a pharmacogenetics scientist graduated from Universiti Sains Malaysia (2016). His field of interest is on biochemistry and genetics. Over five years of tenure as a Postdoctoral Researcher in Universiti Teknologi MARA, he has authored nearly 20 full papers and over 40 scientific presentations at various international conferences. His current field of specialisation is on genetic aspects of lipid disorders, especially familial hypercholesterolaemia (FH). He is one of the pioneer scientists in describing the genetic makeup of FH patients in Malaysia by employing targeted next-generation sequencing method, and the first to report the prevalence of FH in Malaysia. He can be contacted at email: yungan.chua@gmail.com.

Professor Datin Dr Hapizah Md Nawawi is a Professor and Senior Consultant in Chemical Pathology and Metabolic Medicine at the Faculty of Medicine, Universiti Teknologi MARA (UiTM), Malaysia; and Founding Director and Principal Fellow of the Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM), one of UiTM Centres of Excellence (CoE). The niches areas of this CoE are in Atherosclerosis, Coronary risk factors, Familial Hypercholesterolaemia (FH) and Coronary Heart Disease Prevention. She can be contacted at email: hapizah@uitm.edu.my.