RESEARCH ARTICLE

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# Detection of Risk Groups for Carcinogenic Liver Fluke Infection by Verbal Screening Questionnaire Using a Mobile Application

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## Abstract

The carcinogenic liver fluke, *Opisthorchis viverrini*, is a serious health problem in Southeast Asia where infection is associated with cholangiocarcinoma, a major cause of death in Thailand. This cross-sectional study aimed to screen for *O. viverrini* infection among a Thai rural population of 560 individuals from Nakhon Ratchasima, Khonkaen, and Chaiyaphum provinces with a verbal screening test with a mobile application (OvApp). Faecal samples were also processed with a mini-parasep sf parasite faecal concentrator. The infection rate of *O. viverrini* was found to be 2.86%. The majority of infections were detected in males aged 41–50, with primary school being their highest education level, and who were engaged in agricultural occupations. In screening for *O. viverrini* infection, the OvApp had a high sensitivity (87.5%), specificity (94.6%), negative predictive value (98.9%), and accuracy (98.6%). The positive predictive value was 70.0% for the OvApp. The observed agreement was substantial for this application (k-value = 0.64) indicated that it is a potentially useful tool for decreasing the cost of large-scale *O. viverrini* screening.

**Keywords:** *Opisthorchis viverrini*- OvApp- verbal screening questionnaire- mobile application -Thailand

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## Introduction

*Opisthorchis viverrini* remains a major public health problem in Southeast Asia, particularly in Thailand, the Lao People's Democratic Republic (PDR), Cambodia, and Vietnam (Sithithaworn et al., 2012). *O. viverrini* infection is associated with hepatobiliary diseases including hepatomegaly, cholangitis, cholecystitis, and gallstones (Harinasuta et al.,1960; Thamavit et al., 1978; Harinasuta et al., 1984). In addition, epidemiological and animal studies have demonstrated that *O. viverrini* infection is strongly correlated with cholangiocarcinoma (CCA), a bile duct cancer (Sripa et al., 2007; Shin et al., 2010). Presently, *O. viverrini* infection has been classified as a Type 1 carcinogen by the International Agency for Research on Cancer, World Health Organization (International Agency for Research on Cancer, 2011). CCA is responsible for a major proportion of the burden of disease and death in Thailand, apart from causing hundreds of millions of people to surrender their rights to healthy and dignified lives (Andrews et al., 2008). *O. viverrini*-induced CCA ranks the first in mortality among cancers for men and second among cancers in women in the Mekong Basin sub-region (Andrews et al., 2008; Sithithaworn et al., 2012; Sripa et al., 2012). In Thailand, *O. viverrini* is a common parasite found in rural areas located near natural fresh water reservoirs and constitutes a major public health problem (Wongsaroj et al., 2014), particularly in rural areas of Thailand, and eradication of fluke populations is urgently required in these areas. A low-cost and effective tool is needed for active surveillance among the risk groups.

From the study by Sievers by 2014, based on data gathered from the control of other known infections, the risk groups have been screened by questionnaires and effective diagnostic assessments performed.

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Participants were evaluated using a self-administered and self-report questionnaire on infectious diseases and on the use of health care facilities for feasibility and validity. The results indicate that infectious disease screening is a good and reliable tool to measure related risk factors and outcome in general (Sievers et al., 2014). In addition, self-administered questionnaires, distributed by existing administrative channels to village party chairmen, head-teachers and schoolchildren, showed good diagnostic performance for the qualitative assessment of urinary schistosomiasis endemicity (Lengeler et al., 1991). Our previous study investigated the population at risk of CCA in Nakhon Ratchasima province, Northeastern Thailand using the Korat-CCA verbal screening test. The population could be classified as low risk, moderate risk, and high risk for CCA. When CCA was screened using ultrasonography, four of 32 high risk participants had an abnormal biliary tract with dilated bile ducts. This study indicates that verbal screening test is a potentially useful tool which decreases the cost of large-scale CCA screening (Kaewpitoon et al., 2016b).

The availability of mobile health applications for self-care continues to increase globally, and Thailand is no exception. A consumer's sustained engagement with a health application is dependent on the usability and functionality of the application. Numerous studies have attempted to use health applications for alleviating symptoms or increasing understanding of diseases (Akhbardeh et al., 2015; Anderson et al., 2016; Radovic et al., 2016). However, little evidence of impact or decision-making with respect to the liver fluke has been published to date, particularly for *O. viverrini*. Smartphone or mobile applications may assist individuals with health concerns in self-monitoring, and screening the diseases. For this reason, *O. viverrini* mobile application (OvApp) was developed for iOS and Android platforms, as well as paper questionnaires. Therefore, this study aimed to screen the population at risk for *O. viverrini* through verbal screening questionnaires using this mobile application, and then detect the infection using a faecal concentration technique.

## Materials and Methods

*Study site and Participants*

A cross-sectional study was conducted among the 560 participants who live in Nakhon Ratchasima (Bua Yai and Kang Sanam Nang district), Khonkaen (Waengnoi district) and Chaiyaphum (Khon Sawan district) province, in the Northeastern region of Thailand during October 2016 to June 2017, and who were enrolled in the study. All participants provided informed consent before participating in the study. Participants were invited to be verbally screened through the mobile application during mobile unit activities for parasitic infection in the community areas.

*Development of questionnaire and mobile application*

The questionnaire for screening the risk group of *O. viverrini* infection was developed and then added to the mobile application. The questionnaire was selected based on the risk factors related to *O. viverrini* infection that were published in online databases which could be retrieved via PubMed. The questionnaire contains two main parts (1); general information including gender, age, education, marital status, and (2); a question with yes/no choices related to past histories as shown below:

| No. | Risk factors | References |
|---|---|---|
| 1 | consumption of raw spicy salad cyprinoid fish | Migasena, 1982: Chavengkun et al., 2016 |
| 2 | consumption of raw minced cyprinoid fish | Prakobwong et al., 2017; Saiyachak et al., 2016 |
| 3 | consumption of raw prickled cyprinoid fish | Aukkanimart, 2016 |
| 4 | consumption of raw preserved small cyprinoid fish | Migasena, 1982: Chavengkun et al., 2016 |
| 5 | consumption of raw fermented cyprinoid fish | Migasena, 1982: Chavengkun et al., 2016 |
| 6 | diagnosed with opisthorchiasis | Chaiputcha et al., 2015 |
| 7 | family member who had been diagnosed with opisthorchiasis | Chaiputcha et al., 2015; Chudthaisong et al., 2015 |
| 8 | family member who had consumed various dishes containing raw cyprinoid fish | Dao et al., 2016; Painsing et al., 2016; Vonghachack et al., 2017 |
| 9 | trend to consume various cyprinoid fish | Dao et al., 2016 |
| 10 | family relative who had been diagnosed with a cholangiocarcinoma | Sriamporn et al., 2004; Ayé Soukhathammavong et al. , 2015; Sriraj et al., 2016 |

The screening questionnaire was tested prior to the study, and then analysed for reliability, the Cronbach alpha coefficient was 0.75.

The mobile application (OvApp) for screening the risk group of *O. viverrini* infection was developed for iOS and Android platforms. It includes (1) a knowledge module; which is a dynamic content listing from offline and online media for basic knowledge of *O. viverrini,* (2) personal information module, which is used to collect user information (gender, age, body mass index, occupation, educational level, income), (3) screening module; this contains a quiz module (for O. viverini screening) (Figure 1).

To initialize data collection, the user can register themselves by using a simple authentication form. They then check for the existing account to obtain their existing data; if they do not have such data, the system creates new data on Apache CouchDB that hosts on the cloud, and the data is then synced to local PouchDB in this application. The user can store their data in offline mode and automatically synchronise such data as soon as the device is connected to the internet. The application user is required to insert some personal information by using the Personal Information module. Then they can start to screen themselves for the risk of liver fluke by using the screening module with some yes/no questions. For basic knowledge of liver fluke, we also provide some of the contents under the knowledge module, which can be used to test their knowledge in a quiz format.

The architecture of the Ov database system and data communication is shown in Figure 2. The data is hosted on the cloud using Apache CouchDB, which is a NoSQL database that is used in web technologies by storing the document based in JSON format, using JavasScript as the query language and being implemented in the Erlang using HTTP for an API. We use PouchDB, which is also a NoSQL database inspired by Apache CouchDB that runs well on mobile devices. PouchDB helps web developers to build offline applications. The Ov hybrid mobile applications store data locally while offline by using PouchDB, and then synchronize data to the cloud using the Apache CouchDB host when the application is back online. This Ov hybrid mobile application is developed by using an ionic-framework. This framework is free, open-source, and all components have been optimized for hybrid mobile application development built with web technologies such as HTML5, CSS, and JavaScript for multiple platforms and many devices. The users can store their data anytime and anywhere by NoSQL database syncing from the local PouchDB to the Apache CouchDB cloud. The overall system architecture is defined as presented above, particularly with respect to how the data from this application reaches the Apache CouchDB as the remote site for authentication, initializes the application and synchronizes the data from the local PouchDB to the remote side. OvApp is now available for free download. A screenshot of this application is shown in Figure 3.

*Diagnosis of O. viverrini infection*

Faecal specimens were collected, processed and examined following the manufacturer's instructions for the mini-parasep sf faecal parasite concentrator (MPFC) (DiaSys Europe Limited, formerly Intersep Ltd). The tubes and sedimentation cones were labelled with the specimen identification numbers. A level faecal sample was introduced into each tube containing 3.3ml of 10% formol-saline using a spoon on the end of the Mini Parasep SF filter. The MPFC was sealed by screwing in the filter/sedimentation cone unit. This was then vortexed for emulsification with the sedimentation cone pointing upwards. The MPFC was then inverted and centrifuged at 1,500 rpm for two minutes. The mixing chamber and the filter were then unscrewed and discarded for incineration while the supernatant in the sedimentation cone was decanted. The deposit was then examined microscopically using physiological saline and iodine for the eggs and larvae of intestinal parasites. Each of the preparations was examined systematically under the microscope for a minimum of five minutes. All preparations were initially screened with a low-power (10x) objective lens. Suspected parasitic objects were subsequently examined under a high-power (40x) objective. Stool samples were examined by two laboratory technologists and then confirmed by an expert parasitologist. Finally, the data were analyzed and interpreted accordingly. Patients who were infected with other known parasites were treated with anti-parasitic drugs and also attended health education.

*Calculations and statistical analysis*

Data entry and analysis were performed using Excel and SPSS version 22.0 statistical software for descriptive statistics. This was partly achieved by summing the total points of ten questions, 1 question/point, and then interpreted as high risk (8–10 points), moderate risk (4–7 points), low risk (1–3 points), or no risk (0 points). Faecal diagnosis results based on the faecal concentrator kit were used as the gold standard. Infection rate, sensitivity, specificity, positive and negative predictive values (PPV, NPV), and accuracy were analysed using SPSS version 22 and a kappa estimator was employed to determine the strength of the agreement of each method with the combined result. Kappa values were interpreted as follows: 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–0.99 perfect agreement (Landis and Koch, 1977).

*Ethical approval*

This study was approved by the Ethics Committee for Research Involving Human Subjects, Suranaree University of Technology (EC- 59-38, Date: August 4, 2016).

## Results

Five-hundred and sixty participants were enrolled in this study. The majority of participants were male (58. 39%), aged 41–50 (37.32%), had their highest education at primary school level (61.07%), and were involved in agricultural work (84.46%). The *O. viverrini* infection rate was 2.86%. The majority of *O. viverrini* infections were identified in each general characteristic, and it was found that males (3.08%) aged 31–40 (4.78%), with their highest education level being primary school (3.81%), and working in agriculture (3.17%), were determined as being egg positive. In terms of differences between provinces, *O. viverrini* infections were detected in Chaiyaphum (5.56%) followed by Nakhon Ratchasima (1.64%) and Khonkaen (0.62%) provinces (Table 1).

The populations at risk for *O. viverrini* infection were classified into varying risk and no risk groups;

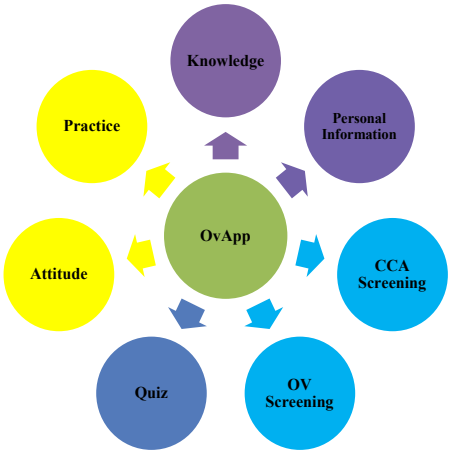


Figure 1. The Modules of Mobile Application (OvApp) for Screening the Risk Group of *O. viverrini* Infection was Developed for iOS and Android Platforms.

Table 1. General Characteristic and *O. viverrini* Infection Among 560 Participants from Nakhon Ratchasima, Chaiyaphum, and Khon Kaen Provinces, Northeast Thailand during October 2016 and June 2017.

| General characteristics | No. of participants | O. viverrini infection | % |
|---|---|---|---|
| Gender | | | |
| Male | 327 | 10 | 3.08 |
| Female | 233 | 6 | 2.58 |
| Age (year old) | | | |
| 31–40 | 43 | 2 | 4.65 |
| 41–50 | 209 | 10 | 4.78 |
| 51–60 | 168 | 2 | 1.19 |
| >60 | 140 | 2 | 1.43 |
| Education | | | |
| Uneducated | 30 | 1 | 3.33 |
| Primary School | 342 | 13 | 3.81 |
| Secondary School | 102 | 2 | 1.96 |
| Undergraduate | 86 | 0 | 0.00 |
| Occupation | | | |
| Agriculture | 473 | 15 | 3.17 |
| Employee | 60 | 1 | 1.67 |
| House Keeper | 12 | 0 | 0.00 |
| Government officer | 5 | 0 | 0.00 |
| Other | 10 | 0 | 0.00 |
| Place | | | |
| Nakhon Ratchasima | 183 | 3 | 1.64 |
| Chaiyaphum | 216 | 12 | 5.56 |
| Khon Kaen | 161 | 1 | 0.62 |
| Total | 560 | 16 | 2.86 |

Table 2. *Opisthorchis Viverrini* Infection among the Population at Risk from Nakhon Ratchasima, Chaiyaphum, and Khon Kaen Provinces, Northeast Thailand During October 2016 and June 2017.

| Risk Group | No. of examined/ participants | *O. viverrini infection* | |
|---|---|---|---|
| | | No. of positives | No. of negatives |
| Risk | 20/56 | 14 | 6 |
| High | 10/56 | 10 | 0 |
| Moderate | 4/56 | 3 | 1 |
| Low | 6/56 | 1 | 5 |
| No Risk | 403/56 | 2 | 538 |
| Total | 560 | 16 | 544 |

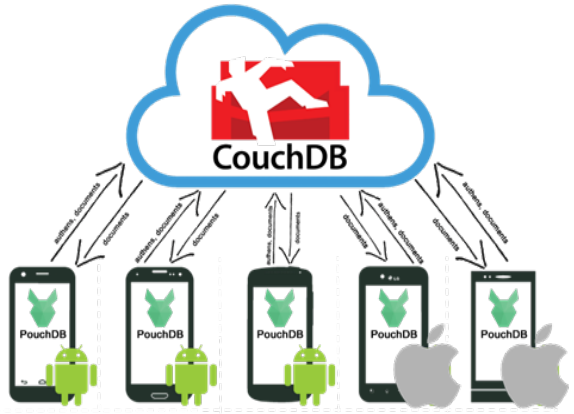


Figure 2. Architecture of OvApp Database System and Data Communications.

the largest group had no risk (71.96%), followed by high risk (1.79%), and low risk groups (1.07%). The stool samples of the populations at risk for *O. viverrini* infection were examined and we found 14 positive and six negative cases. Positive cases were classified as high risk (ten cases), moderate (three cases), and low risk (one case). Meanwhile, the no-risk group of 403 participants was tested and only two were found to have *O. viverrini* on examination (Table 2).

Faecal diagnosis results based on the faecal concentrator kit were used as the gold standard to estimate the sensitivity, specificity, NPV and PPV, and accuracy of

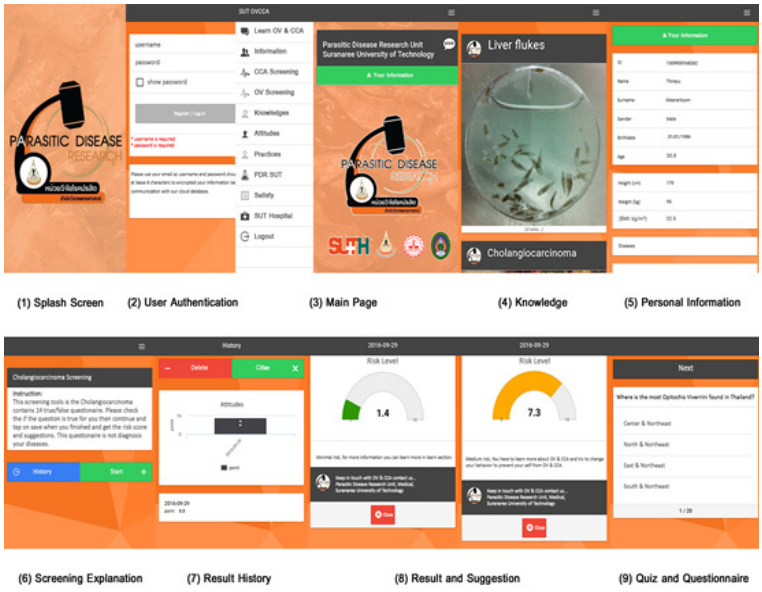


Figure 3. OvApp was Used for Screening the Population at Risk for *O. viverrini* Infection.

Table 3. Parameters of OvApp for *O. viverrini* Screening among 560 Participants from Nakhon Ratchasima, Chaiyaphum, and Khon Kaen Provinces, Northeast Thailand During October 2016 and June 2017.

| Parameters | % | 95% CI |
|---|---|---|
| Sensitivity | 87.50 | 87.37-92.42 |
| Specificity | 98.90 | 93.89-99.25 |
| Negative predictive value | 99.63 | 97.32-99.95 |
| Positive predictive value | 70.00 | 61.45-75.14 |
| Accuracy | 98.57 | 91.22-99.14 |
| Kappa | 0.64 | 0.51-0.74 |

the OvApp method for screening the population at risk for *O. viverrini* infection (Table 3). The parameters measured for the OvApp were as follows; sensitivity (87.50%), specificity (98.90%), PPV (70.00%), NPV (99.63%), and accuracy (98.57%). The agreement of OvApp with the comparison between screening results and faecal detecting results was calculated by the MPFC method. The observed agreement was substantial for the OvApp (k-value = 0.64, mean rank =0.51-0.75).

## Discussion

Mobile health application use for self-care is steadily increasing in Thailand namely Kaewkungwal et al., (2010) assessed the application of cell phone integrating into the healthcare system to improve antenatal care and expanded programme on immunization services for the under-served population in border area. This study indicates that the module integrated and functioned successfully as part of the healthcare system; it is proved for its feasibility and the extent to which community healthcare personnel in the low resource setting could efficiently utilize it to perform their duties. In addition, Kiranantawat et al., (2014) developed and evaluated a new free flap monitoring system: SilpaRamanitor. Software was developed for Android-operated mobile phones. Forty-two normal subjects were recruited to assess its effectiveness. This study was developed a new, accurate, and reliable diagnostic system for postoperative microsurgery monitoring using a smartphone application. SilpaRamanitor is inexpensive and easy to use, making it applicable in many microsurgical settings. Numerous studies have attempted to use health applications for alleviating symptoms or increasing understanding of diseases (Akhbardeh et al., 2015; Anderson et al., 2016; Radovic et al., 2016). Here, we describe a mobile application for screening *O. viverrini* risk groups. OvApp was developed and created for iOS and Android platforms, as well as paper questionnaires. Faecal diagnosis results based on the faecal concentrator kit were used as the gold standard and revealed that OvApp had a reliable performance for prediction the risk of *O. viverrini* infection which show high sensitivity, specific, PPV, NPV, accuracy and k-value. OvApp is able to identify the populations at risk for *O. viverrini* infection, as it successfully detected 14 positive cases but only had two false negative cases. Of six participants who had scores in the risk group but were negative for *O. viverrini* infection, they possibly had treatment before participating in the screening project or they had consumed raw fish that did not contain the infective stage of *O. viverrini*. This result confirms that a verbal screening test for populations at risk of diseases facilitates early detection, and is similar to a previous study regarding CCA screening using a verbal screening test in rural areas (Kaewpitoon et al., 2016b). This result indicates that using OvApp for screening for *O. viverrini* infection is both very simple to use and provides rapid analytical results. Participants took only approximately two minutes to answer the questions and they were then able to calculate their own risk using the test.

Furst et al., (2012) estimated that 9.3 million people suffer from bile duct liver fluke infections in the Southeast Asian region (39% of the global number of cases), including 8.03 million cases of opisthorchiasis, mostly in the Lao PDR and Thailand. This study found that the *O. viverrini* infection rate was 2.86%, with the majority of *O. viverrini* infections being identified in each general characteristic, with males aged 31–40, educated to primary school level, and working in agriculture being found to be most susceptible. This result is similar to other studies reporting *O. viverrini* prevalence in community areas of Thailand. *O. viverrini* is a common parasite found in rural areas located near natural fresh water reservoirs and constitutes a major public health problem in rural populations (Kaewpitoon, 2016a,c). Rural communities continue to maintain the habit of extensively consuming raw or half-cooked fish, which are intermediate hosts (Chavengkun et al., 2016). Raw fish consumption is strongly associated with *O. viverrini* infection (Harinasuta et al., 1960; Sithithaworn et al., 1997; Kaewpitoon et al., 2007; Songserm et al., 2012). In addition, gender (male), being aged over 30, occupation in agriculture, highest education being primary school level, family member having been diagnosed with opisthorchiasis, and family relative having been diagnosed with cholangiocarcinoma, have all been associated with *O. viverrini* infection (Kaewpitoon et al., 2008; Manwong et al., 2013; Chaiputcha et al., 2015; Chudthaisong et al., 2015). Therefore, these risk groups should be concerned and be screened in order to decrease the incidence of this disease.

The using a mobile application to support healthcare providers in diagnosis and monitoring the diseases have been reported (Huang et al., 2017; Seneviratne et at al., 2018; Meyer et al., 2018). Huang et al., (2017) using a mobile device application to support emergency clinicians in diagnosing pulmonary embolism. Their study indicate that most physicians felt the application is easy-to-use, facilitates rapid decisions about ordering computed tomography or pulmonary embolism treatment. Finally, most physicians agree the application is helpful in diagnosing pulmonary embolism (77%). The mobile device application appears to be user-friendly and acceptable by emergency physicians that timely and accurate diagnosis of pulmonary embolism is clinically significant. In addition, the HealthNavigator application was developed to provide chronic disease risk assessments, linkage to local general practitioners and lifestyle programs. Assessments were

either self-administered or facilitated by community health workers through a Primary Health Network initiative targeting ethnically diverse communities. This study shows that mobile applications are promising tools to support chronic disease screening and linkage to health services. The mobile applications embedded into Primary Health Network programs may be a useful adjunct for the implementation of community screening programs (Seneviratne et at al., 2018). Meanwhile, we describe a mobile application for screening *O. viverrini* risk groups. OvApp has the potential to increase healthcare access for vulnerable populations. Growing popularity and use of commercial digital health applications in Thailand potentially affords opportunities to support disease detection and monitoring and rapid treatment mobilization.

In conclusion, OvApp is a simple, rapid and low-cost screening test for *O. viverrini* infection. This tool may be useful for *O. viverrini* screening for the large-scale prevention and control of the spread of this liver fluke.

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*Declaration of Conflicting Interests*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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