RESEARCH ARTICLE

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Association between the Number of Repeated Praziquantel Treatments and Kidney Parenchymal Change in Northeast Thailand

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Abstract

Background: In Northeast Thailand, Praziquantel (PZQ) is used to treat infection with the Opisthorchis viverrnini (OV). OV has highly prevalence in this area due to the traditional consumption of uncooked cyprinid fish. The nephrotoxic effects of PZQ metabolite excretion through the kidney have not been assessed yet. This study investigated the relationship between number of Praziquantel treatments and kidney parenchymal change. **Methods:** A study was carried out on participants from the Cholangiocarcinoma Screening and Care Program (CASCAP) between 2013 - 2018. The frequency of PZQ use was reported using a standardized questionnaire. Kidney parenchymal change (KPC) was defined as having a kidney abnormality based on ultrasonography diagnosed by well-trained general practitioners. Adjusted odds ratios (ORs) measured associations between PZQ frequency and KPC controlling for the effects of other extraneous factors using multiple logistic regression. **Results:** A total of 490,969 subjects with mean age of 55.2 (SD = 9.15) years were enrolled among them 62.1% were female. Prevalence of KPC was 1.2% while prevalence of KPC were 1.2%, 1.3%, 1.4%, and 1.5% for participants with one, two, three, and more than 3 PZQ treatment occasions respectively. Those dose-response relationship was statistically significant based on chi-square test for trend (p-value <0.001). After controlling for possible confounders, compared to non-treatment, subjects with more than 3 treatment occasions were 25% more likely to have a KPC positive result (OR = 1.25; 95% CI: 1.02 - 1.52; p-value = 0.028). **Conclusion:** The number of repeated PZQ treatments is statistically significantly related to KPC. This relationship could be included in health messaging for those who continue eating uncooked fish with an understanding that the OV infection can easily be cured by PZQ without any other health concerns. For positive OV cases, however, the known efficacy of PZQ could over-ride the small magnitude of the adverse effect.

Keywords: praziquantel treatment- kidney parenchymal change- ultrasonography- screening

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Introduction

Kidney disease is an important non-communicable disease with serious morbidity and mortality impacts (Choi et al., 2007; Brennan et al., 2011; Collaboration, 2020). This disease is rising markedly and becoming a worldwide health problem in both developing as well as in developed countries (Lysaght, 2002; Jha and Modi, 2018). The incidence of kidney disease in developing countries is higher than developed countries; there are about 100 cases per 1,000,000 population in the United Kingdom (Ravanan et al., 2011), around 336 per 1,000,000 population in the United States (Collins et al., 2005), and around 15% of the US adults were estimated to have the disease (Johansen et al., 2021). Previous studies found a high prevalence of kidney disease in the Thai population, at around 17.5% of the population having the condition and about 8% having the more serious stages 3-5 of the disease (Ong-Ajyooth et al., 2009; Kanjanabuch and Takkavatakarn, 2020), and 33.2% found in hypertension patients (Krittayaphong et

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al., 2017). Moreover, the prevalence of kidney disease in Thailand was higher than that being reported in the United States for individuals over 40 years, and higher than the reported incidence in Taiwan and Australia (Perkovic et al., 2008). Within Thailand itself, the highest prevalence of kidney disease was found in the northeastern region (Yanagawa et al., 1997; Ong-Ajyooth et al., 2009; Cha'on et al., 2020). Although several causes of kidney disease have been identified (Hosseinpanah et al., 2009; Takamatsu et al., 2009), there may be some unique factors that could explain why the incidence of the disease is higher in Thailand than in many other countries and particularly in the northeast region of Thailand.

A distinctive eating habit of people in the Northeast of Thailand is the consumption of raw, partially cooked and/or fermented fish, especially fish with scales (cyprinid species) which are the source of liver fluke infection (Pinlaor et al., 2013; Phyo Myint et al., 2020). The fluke is called Opisthorchis viverrini (OV) and is endemic throughout the Greater Mekong Sub-region including Thailand, the Lao People's Democratic Republic, Southern Vietnam, Cambodia, and Myanmar (Young et al., 2010). This parasite is a major cause of bile duct cancer or Cholangiocarcinoma (CCA) (Bhamarapravati et al., 1978; Young et al., 2010; Sripa et al., 2011). Praziquantel (PZQ) has been the main treatment used for treating liver fluke infection in Thailand since 1980 (Jongsuksuntigul and Imsomboon, 2003; Laha et al., 2007; Wongba et al., 2011), and is available over-the-counter.

The northeastern region of Thailand has the highest global and national prevalence of liver fluke infection. OV affected 17% of the regional population in 2009 and 23% in 2014. This means PZQ use is widespread (Sithithaworn et al., 2012; Thaewnongiew et al., 2014), and attachment to regional eating habits leads to a high rate of re-infections and hence repeated PZQ treatments (Hinz et al., 1994; Saengsawang et al., 2016). Studies have reported that OV re-infection and repeated PZQ treatments were both associated with an increased risk of hepatobiliary diseases including CCA (Tao et al., 2010; Kamsa-Ard et al., 2015; Thinkhamrop et al., 2019). Indeed, there is a common understanding among people in the northeast of Thailand that OV infections can easily be cured by PZQ, hence, they continue eating uncooked fish disregarding infection risk. Thus, health promotion regarding dietary habit modifications of "not eating raw fish" has not been effective. In addition, pharmacokinetic studies have found that repeated use of PZQ resulted in concentration levels, especially in the liver and kidneys (Olliaro et al., 2014). For the kidney, parenchymal change is a focus for early sign of renal abnormalities.

Renal parenchyma is the internal part of the kidney that is responsible for blood filtration and urine formation. Renal disease occurs predominantly due to the deposition of trace mineral salts that steadily stop the normal functioning of kidneys resulting in chronic kidney disease. Causes of renal parenchymal disease have been identified including regular intake of junk food, diabetes mellitus (DM), hypertension (HT), and high blood pressure (Bailey et al., 2014; Ladi-Akinyemi and Ajayi, 2017). Another major cause is medication such as non-steroidal anti-inflammatory drugs (NSAIDs) (Abd ElHafeez et al., 2019; Lefebvre et al., 2020). However, evidence regarding the role of PZQ on kidney disease is limited. To our knowledge, there is only one study, which demonstrated that 80% of PZQ and its metabolites are excreted in the kidneys resulting in abnormalities, eventually leading to serious health consequences (Patzschke et al., 1979). Therefore, our study aimed to investigate whether there was a relationship between the number of repeated PZQ treatments and kidney parenchymal change (KPC) based on renal ultrasonography (USG) in a real world setting under controlled conditions.

Materials and Methods

Design overview

This retrospective cohort study recruited 3,936 participants at primary- and 424 participants at secondary-hospitals in 22 provinces of Northeastern Thailand as part of the Cholangiocarcinoma Screening and Care Program (CASCAP) (https://cloud.cascap.in.th/), which is the first large project for CCA screening in a high-risk population (Khuntikeo et al., 2015). The data were obtained from the CASCAP database called Isan Cohort. Participants were recruited from the high risk area for OV infection based on routine data of the Ministry of Public Health of Thailand. They were either selected by the village health volunteers or were purposively attending participating hospitals for CCA screening due to their perceived risks of the cancer. Recruitment was limited to those aged over 40 years. All cohort members who were enrolled between February 2013 and December 2018 were eligible. For this paper, participants whose baseline data, including history of using PZQ, and US findings were available, were included into the analysis.

Primary outcomes and study factors

The primary outcome for this study was KPC based on renal USG findings, classified as positive or negative by either well-trained general practitioners or radiologists who were working for CASCAP. Figure 1 illustrates an example of A) left KPC, and B) right KPC. Another study variable of interest was the lifetime frequency of PZQ treatment, categorized as none, one time, two times, three times, and more than three times. This was based on a face-to-face interview using a standardized questionnaire conducted at the date of enrolment ofthe baseline visit. After providing informed consent, participants were asked to recall the number of occasions they had ever used PZQ. To ensure data quality and to assist the participants in recalling the medication, an image of a PZQ tablet was shown to the participants during the interview. Other independent variables include gender, age at enrollment, highest achieved education level (primary or lower, secondary, certificate, or higher), main occupation (unemployed, farmer, other), cigarette smoking history (yes or no), alcohol consumption history (yes or no), whether they had been diagnosed with DM, and whether they had been diagnosed with HT. These were incorporated into the analysis to control for their effects on the relationship between frequency of PZQ used and KPC.

Statistical analysis

Baseline characteristics of the subjects were presented as frequency counts and percentages for categorical data (i.e. gender, age groups, education levels, occupation, cigarettes smoking history, alcohol consumption history, history of diagnosed with DM, history of diagnosed with HT, and number of PZQ treatments). The continuous data, such as the age at enrollment in years were described using mean plus standard deviation (SD), and the minimum and maximum range.

The prevalence of KPC was estimated overall and separately for each category of factors including PZQ treatment frequency, gender, age groups, education levels, occupation, cigarette smoking history, history of diagnosed DM, and history of diagnosed HT. To investigate the association between PZQ and KPC, we first assessed the dose-response relationship between the two factors using chi-square test for trend. Then we explored for potential candidate variables to be included in the multivariate model for the further step of controlling for their effects on the relationship between PZQ and KPC. For this step, we estimated unadjusted odds ratios (OR) and their 95% confidence intervals (CI) to measure the association between the independent variables and KPC, one at a time, using bivariate logistic regression, for each of the following factors- gender, age, education levels, occupation, cigarettes smoking history, alcohol consumption history, history of diagnosed DM, history of diagnosed HT, and the number of repeated PZQ treatments- the factor of interest. Then we estimated the OR and its 95% CI for quantifying the relationship between PZQ and KPC adjusted for the candidate variables by inclusion of one factor at a time to allow assessment of which extraneous variables played a role in the adjusted OR of interest using multivariable logistic regression. The final model containing all important covariates, while providing a valid and precise estimate of the OR, was then used for answering the research question. We used STATA version 13.0 (StataCorp, Collage Station, TX, USA) for the analysis. Statistical significance level was set as p-value <0.05.

Results

Study participants

A total of 1,133,136 participants were enrolled in the CASCAP database. We excluded 555,788 subjects due to missing data on USG examination results, 73,487 subjects due to not being residents of Northeastern Thailand, and 11,893 subjects due to other incomplete data. Thus, a total of 490,969 subjects were included in the analyses (Figure 2). Of those, about a quarter (27%) reported they had been treated with PZQ (n = 132,561); from this amount, around three-quarters (74.2%) were treated only once (n = 98,408) whereas about 5.4% were treated more than 3 times (n = 7,192).

Demographic characteristics

Among 490,969 subjects in the analysis set, mean age was 55.2 years (SD = 9.15) and age ranged from 40 to 100 years old (Table 1). Participants were mainly female (62.1%), had attained a primary school or lower education (76.8%), worked as farmers (81.7%) and had ever smoked cigarettes (79.6%). About 20% reported they had been treated with PZQ one time, 4.3% for 2 times, 1.2% for three times, and 1.5% for greater than three times (Table1).

Prevalence of Kidney Parenchymal Change (KPC)

Among 490,969 subjects who underwent renal ultrasonography, the overall prevalence of KPC was 1.2%. It was 1.4% in males and 1.0% in females (Table 2). The prevalence of KPC increased as the number of PZQ treatments increased. KPC prevalence was 1.1%, 1.2%, 1.3%, 1.4%, and 1.5% for those who had none, one, two, three, and more than three instances of PZQ treatment, respectively. This dose-response relationship was statistically significant based on chi-square test for

Table 1. Demographic Characteristics of Study Participants

Characteristics	Number	Percentage
Number of treatments with PZQ		
None	358,408	73.0
One time	98,408	20.0
Two times	20,883	4.3
Three times	6,078	1.2
More than three times	7,192	1.5
Gender		
Male	186,274	37.9
Female	304,685	62.1
Age (years)		
<50	151,213	30.8
50-60	202,939	41.3
>60	136,817	27.9
Mean (standard deviation)	55.20 (9.15)	
Range	40-100	
Education		
Primary and lower	377,027	76.8
Secondary	91,152	18.6
Certificate and higher	22,788	4.6
Occupation		
Unemployed	19,651	4.0
Farmer	401,316	81.7
Others	70,001	14.3
Smoking history		
No	390,665	79.6
Yes	100,304	20.4
Drinking history		
No	285,178	58.1
Yes	205,791	41.9
Diabetes mellitus		
No	456,201	92.9
Yes	34,768	7.1
Hypertension		
No	460,308	93.8
Yes	30,661	6.2

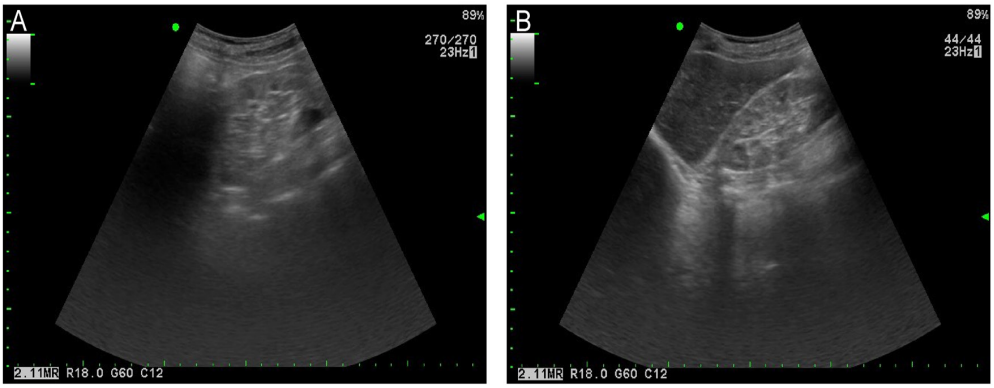

Figure 1. Ultrasound Images of Kidney Parenchymal Change. (A), Left kidney parenchymal change; (B), Right kidney parenchymal change.

Table 2. Prevalence of KPC by Risk Factor and Crude Odds Ratios with 95% Confidence Intervals Measuring Associations between Risk Factors and KPC.

Factors	Number	KPC positive		Crude OR	95% CI	p-value
		n	%			
Overall	490,969	5,672	1.2	NA	NA	NA
PZQ treatments						<0.001*
None	358,408	3,990	1.1	1		
One time	98,408	1,219	1.2	1.11	1.04 - 1.19	
Two times	20,883	273	1.3	1.18	1.04 - 1.33	
Three times	6,078	86	1.4	1.27	1.03 - 1.58	
More than three times	7,192	104	1.5	1.3	1.07 - 1.59	
Gender						<0.001
Female	304,685	3,013	1	1		
Male	186,274	2,659	1.4	1.45	1.38 - 1.53	
Age (years)						<0.001
<50	151,213	617	0.4	1		
50-60	202,939	1,706	0.8	2.07	1.89 - 2.27	
>60	136,817	3,349	2.5	6.12	5.62 - 6.68	
Education						<0.001
Certificate and higher	22,788	144	0.6	1		
Secondary	91,152	617	0.7	1.07	0.89 - 1.29	
Primary and lower	377,027	4,911	1.3	2.08	1.76 - 2.45	
Occupation						<0.001
Others	70,001	609	0.9	1		
Unemployed	19,651	493	2.5	2.93	2.60 - 3.31	
Farmer	401,316	4,570	1.1	1.31	1.21 - 1.43	
Smoking history						<0.001
No	390,665	4,217	1.1	1		
Yes	100,304	1,455	1.5	1.35	1.27 - 1.43	
Diabetes mellitus						<0.001
No	456,201	4,832	1.1	1		
Yes	34,768	840	2.4	2.31	2.15 - 2.49	
Hypertension						<0.001
No	460,308	4,949	1.1	1		
Yes	30,661	723	2.4	2.22	2.05 - 2.40	

*Indicated p-value based on score test for trend of odds; KPC: Kidney parenchymal change; PZQ, Praziquantel; NA, Not applicable; OR, odd ratio from simple logistic regression; 95% CI, 95% confidence interval of crude OR

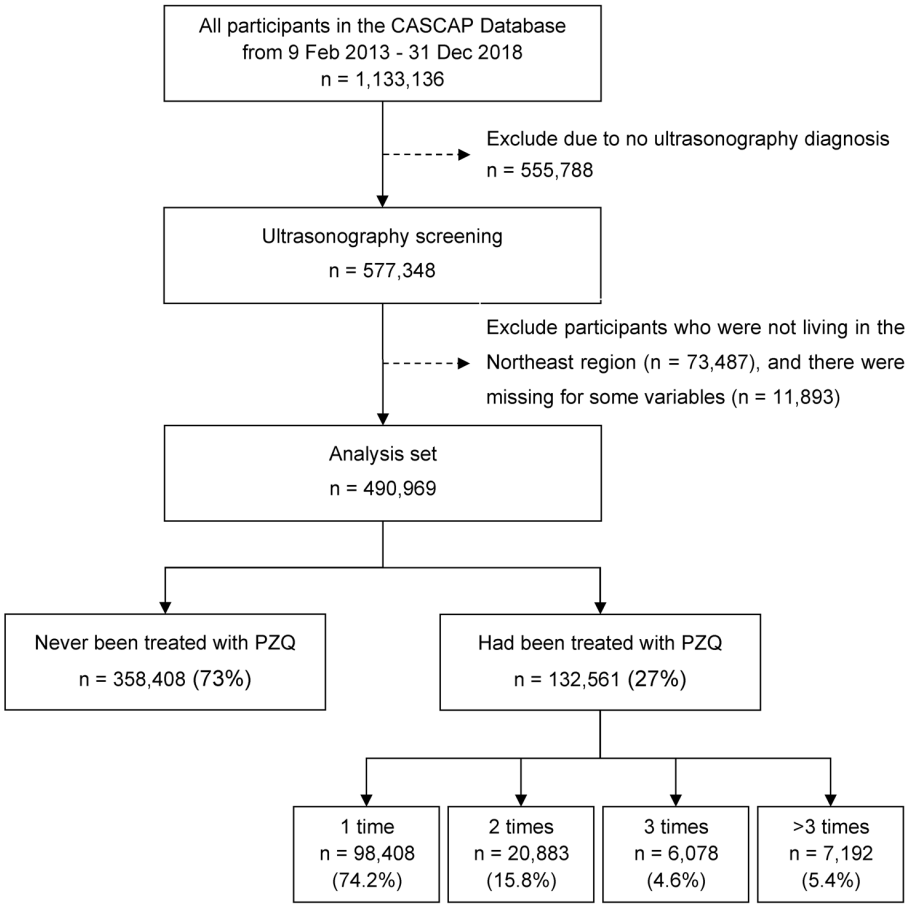

Figure 2. Sample Selection Process

trend (p-value <0.001).

The prevalence of KPC was consistently higher in males than in females (Figure 3). The highest prevalence of KPC positive was 1.9% (58/3,076) found in males who used PZQ 3 times, and the lowest was 0.9% found in females who also used PZQ 3 times (28/3,002). The number of KPC positive cases in subjects who used PZQ 1 time was highest among subjects aged about 65 years old (Figure 4).

Associations between PZQ and KPC
Bivariate analysis

The results from bivariate analysis using simple logistic regression show a statistically significant association between the number of PZQ treatments and KPC. Compared to no PZQ treatment, the odds

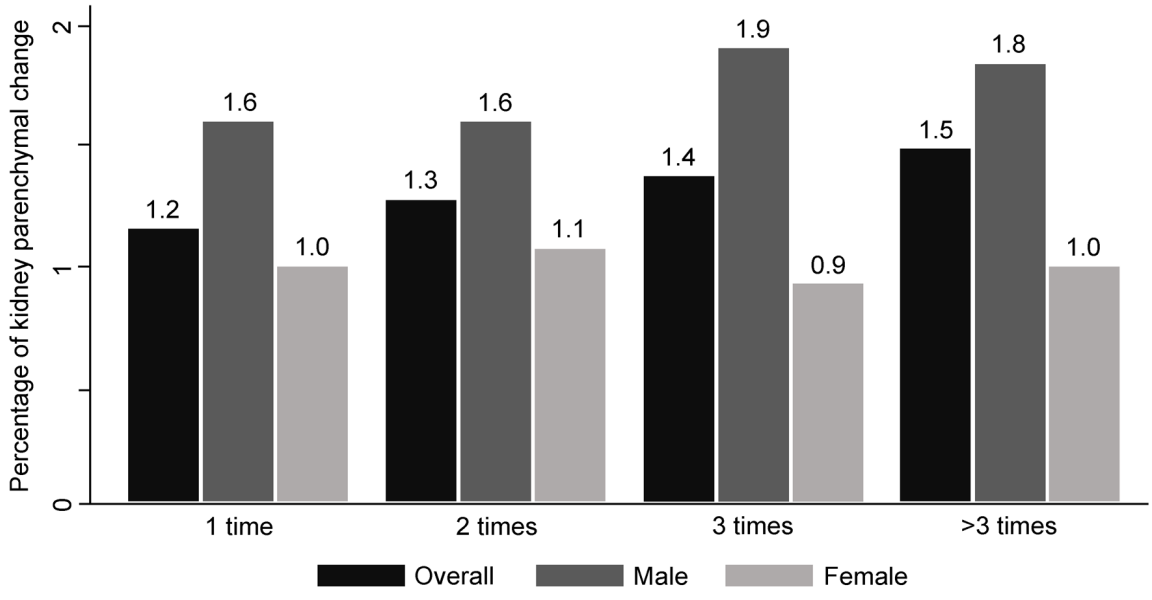

Figure 3. Percentage of Positive Kidney Parenchymal Change by Sex According to Number of Praziquantel Treatments.

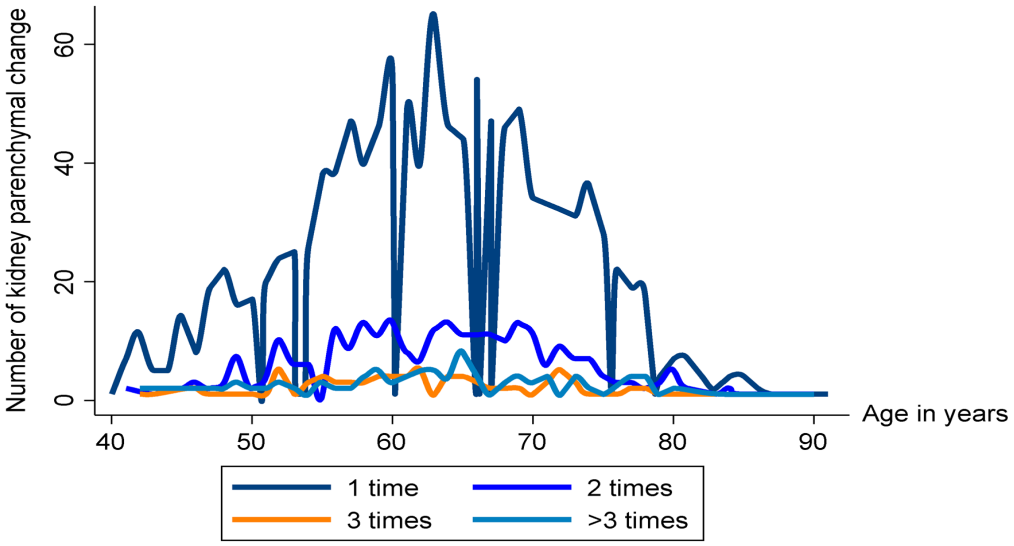

Figure 4. Number of Cases Positive for Kidney Parenchymal Change by Frequency of Praziquantel Treatments and Age.

Table 3. Unadjusted and Adjusted Odds Ratios together with 95% Confidence Intervals between Number of Praziquantel Treatments and Kidney Parenchymal Change based on Multiple Logistic Regression

Praziquantel treatments	OR	95% CI	p-value
Unadjusted			<0.001
None	1		
One time	1.11	1.04 - 1.19	
Two times	1.18	1.04 - 1.33	
Three times	1.27	1.03 - 1.58	
More than three times	1.3	1.07 - 1.59	
Adjusted for gender, age, education, occupation, smoking, drinking alcohol, diabetes mellitus, and hypertension			0.099
None	1		
One time	1.03	0.97 - 1.10	
Two times	1.06	0.94 - 1.20	
Three times	1.17	0.94 - 1.45	
More than three times	1.25	1.02 - 1.52	0.028

OR, odd ratios; 95% CI, 95% confidence interval of OR

of having KPC increased according to the increasing number of PZQ treatments- one treatment (OR = 1.11; 95% CI: 1.04 - 1.19), two treatments (OR = 1.18; 95% CI: 1.04 - 1.33), three treatments (OR = 1.27; 95% CI: 1.03 - 1.58) and more than three treatments (OR = 1.30; 95% CI: 1.07 - 1.59). This relationship was statistically significant (p-value <0.001). Other extraneous factors that were also found to be significantly associated with higher odds of KPC include male gender, higher age group, lower education level, farming or unemployed as main occupation, smoking cigarettes, subjects diagnosed with DM, and subjects diagnosed with HT (Table 2).

Multivariable analysis

The multivariable analysis using multiple logistic regression revealed that the odds of having KPC according to each group of PZQ use did not change considerably when extraneous factors were included into the model. For example, the OR for the group with more than 3 instances of PZQ treatment ranged between 1.25 and 1.3 (Table 3). We therefore decided that the final model

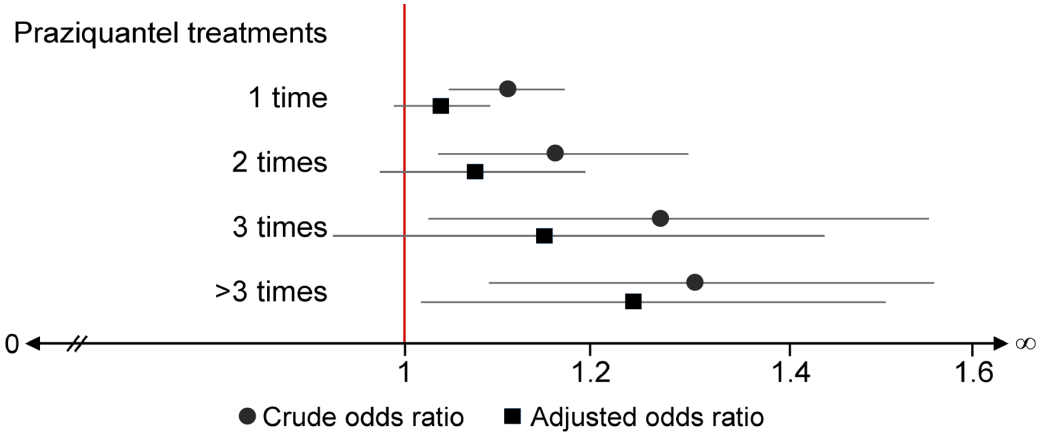

Figure 5. Forest Plot of Crude Odds Ratio and Odds Ratio adjusted for gender, age, education, occupation, smoking, drinking alcohol, diabetes mellitus, and hypertension measuring associations between repeated praziquantel treatments and kidney parenchymal change.

for answering the research question would include all covariates. After adjusting for all covariates, having being treated with PZQ more than three times statistically significantly increased the odds of having KPC by 25% compared to no PZQ treatment (adjusted OR = 1.25; 95% CI: 1.02 - 1.52; p-value = 0.028). Figure 5 shows the crude OR from bivariate analyses compared to adjusted OR in multivariable model.

Discussion

We investigated an association between PZQ, a medication used for treating OV (a major cause of CCA, a fatal cancer), and KPC which is a sign of kidney disease, one of the most common non-communicable disease globally (Perkovic et al., 2008; Brennan et al., 2011). This effort was based on half a million cohort members in northeastern Thailand where the prevalence of CCA is the highest in the world (Sripa and Pairojkul, 2008). All of them had undergone renal ultrasonography operated by well-trained physicians. We found a statistical significant association between the two factors, that is, the prevalence of KPC increased as the number of PZQ uses is increased. KPC prevalence was 1.1%, 1.2%, 1.3%, 1.4%, and 1.5% for those who had none, one, two, three, and more than three instances of PZQ treatment, respectively (p-value <0.001). This was also a statistically significant dose-response (p-value <0.001) relationship. Participants who reported having more than 3 treatment occasions were 25% more likely to have a KPC positive results (OR = 1.25; 95% CI: 1.02-1.52; p-value = 0.028). According to the Bradford Hill's criteria for causation (Hill, 1965), the dose response relationship is one of the nine criteria that suggest a cause-effect relationship. Another criteria is a strong association between the causative agent and the outcome. Our findings met the former criteria but not the latter. This result implies caution is needed regarding the frequent use of PZQ on more than 3 occasions, but not less frequent use. In addition, the KPC itself is an early sign of kidney disease but not the disease itself.

There are a number of factors that have been found in other studies to associate with KPC including age (Glassock and Rule, 2012), and DM and HT (Bailey et al., 2014; Ladi-Akinyemi and Ajayi, 2017). The effect of these 3 confounders was controlled in our study, meaning that we have likely found an independent effect of PZQ use. Other covariates such as body mass index, physical activity, and nutritional status, etc. are not available in the cohort database. However, this limitation might not cause a confounding effect on our findings. We've already adjusted the OR for the effects of gender, age at enrollment, education levels, main occupation, cigarette smoking history, diagnosis with DM, and diagnosis with HT. In addition, the large size of our study gives us confidence that the role of unknown confounders should be minimal. That is, their effects would have been random and thus we achieved a precise estimate of the OR with a sufficiently large sample size.

A limitation of our study was that the data relating to the history of repeated PZQ treatment was obtained by self-report in a face-to-face interview using a standardized questionnaire. Participants may have responded to the questionnaire by only estimating the number of times they had used PZQ treatment- not a precise figure. The socio-demographic, and some health data were also self-reported leading to potential bias in some confounders such as history of DM and HT. We implemented a careful method of data collection by training research assistants and requiring them to present the image of PZQ tablet while interviewing the participants regarding the PZQ repeated use to ensure their answers were correct. These are unlikely to be a source of a systematic error for our study. Regarding random error, our half-a-million sample size made it less problematic. Also, this study was conducted on selected subjects only in northeastern Thailand and may not reflect the whole Thai population. Further study is necessary in the region and elsewhere throughout Thailand to test the generalization of our results.

Our study reveals PZQ use of more than three occasions is associated with KPC prevalence in a dose response relationship. Although the magnitude of association is small, such effect is avoidable by promoting decreases in raw fish consumption rather than using the medications after raw fish consumption. Hence, warning messages regarding possible adverse results of repeated PZQ use might be beneficial for those who purchase it over-the-counter, and continue to eat raw fish. Once OV infection is detected, however, the small magnitude of the adverse effect and the known efficacy of PZQ mean treatment is still advised.

Author Contribution Statement

PP, BT, and KT initiated the idea, and provided constructive criticism and edited of the drafts of the manuscripts. NC and NK performed the ultrasonography and edit the drafts of the manuscripts. PP, KT, JT, and BT performed data management and data quality assurance, data analysis, and wrote all statistical methods and the results sections of the manuscript. PP, NK, NC, JT, KT, MK, and BT initiated the idea, provided feedback and edited the drafts of the manuscript. All authors have seen and approved the final version of the manuscript.

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Approval

This paper is a part of the dissertation submitted in fulfillment of the requirements for the degree of Epidemiology and Biostatistics Program, Faculty of Public Health, Khon Kaen University, Thailand.

Ethics considerations

The Khon Kaen University Ethics Committee for Human Research approved the research protocol, reference number HE621547 which requested the data from Cholangiocarcinoma Screening and Care Program (CASCAP). The CASCAP data collection was conducted according to the principles of Good Clinical Practice, the Declaration of Helsinki, and national laws and regulations about clinical studies. It was approved by the Khon Kaen University Ethics Committee for Human Research under the reference number HE551404. All subjects gave written, informed consent to participate in the study and for their anonymized data to be used for statistical analysis and dissemination.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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