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Original Article

Epidemiology, Seasonal Variability, and Factors Associated with Increased Mortality in Patients with Acute Appendicitis in Thailand: A Study Using Data from the National Health Security Office

Natthapon Khongcharoen, M.D.[1,2], Nattaya Khiawthuam[3], Pongsakorn Chouchuen, M.D., Ph.D.[1,2], Komwit Surachat, Ph.D.[1,2], Kulpreeya Sirichamratsakul, M.D.[4], Surasak Sangkhathat, M.D., Ph.D.[1,2,4]

[1]Department of Biomedical Sciences and Biomedical Engineering, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

[2]Translational Medicine Research Center, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

[3]Mahavajiravudh Songkhla School, Mueang, Songkhla 90000, Thailand.

[4]Division of Surgery, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Objective: The study aimed to study the spatiotemporal distribution of acute appendicitis in Thailand, using a reimbursement dataset from the National Health Security Office, and also analyze for mortality and factors associated with mortality after an appendectomy.

Material and Methods: The study used data mining to analyze a reimbursement data set from the Thailand National Health Security Office (NHSO), focusing on the diagnosis of acute appendicitis (K35.2-K35.9). The analysis looked for the incidence trend and seasonal variation of the incidence. The study also analyzed mortality and factors associated with the mortality. A prediction model for mortality was constructed using a decision tree.

Results: During the 4 fiscal years of the study period, from October 2016 - September 2020, a total of 287,449 individuals were diagnosed with acute appendicitis, and 272,850 appendectomies were performed, which gave an annual incidence (AI) of 10.8/10,000 person-years. The peak age incidence was in the second decade of life, which had an age-specific AI of 28.4/10,000 person-years. Using a multiplicative model of time series detrending and a decomposition model and a seasonal variation of acute appendicitis, with the highest incidence from May to October, linear regression showed a significant correlation between the incidence of appendicitis and precipitation (r^2=0.28, p-value<0.001). The AI of

Corresponding author: Prof. Surasak Sangkhathat, M.D., Ph.D.
Translational Medicine Research Center, Faculty of Medicine,
Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
E-mail: surasak.sa@psu.ac.th
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appendicitis was declining and showed an especially large decline in the year 2020, when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began. The overall mortality was 2.3%. A significantly higher mortality rate was found in cases with extreme age (pediatric or geriatric), those with co-morbidities (diabetes, hypertension, dyslipidemia, chronic pulmonary disease, chronic kidney disease), and those with complications, especially generalized peritonitis, sepsis, and acute kidney injury. A decision-tree prediction model suggested that sepsis and renal complication were key nodes determining mortality risk in pediatric and geriatric appendicitis.

Conclusion: A mortality risk from appendicitis remains in Thai patients, especially the elderly with co-morbidities and those with generalized peritonitis, sepsis, or renal complications. Early diagnosis and improvement in perioperative care in the extreme age groups might improve the mortality figure.

Keywords: acute appendicitis; mortality risk; seasonal variation

INTRODUCTION

Appendicitis is one of the most common surgical emergencies throughout human life[1]. The lifetime risk of having appendicitis in South Korea is approximately 16%[2], while the figure is 6.7-8.6% in the US[3]. The peak incidence is in the second decade of life, and appendicitis occurring in patients older than 40 has a higher chance of being associated with right-sided colorectal cancer[4]. Although antibiotic therapy has become an alternative choice for simple appendicitis, an appendectomy remains the standard treatment for acute appendicitis. The laparoscopic appendectomy has gained increasing popularity due to its shorter postoperative recovery period[5]. Currently, the general mortality rate of appendicitis is less than 1% in non-perforated cases, rising to more than 5% in complicated cases.

Several recent studies have proposed seasonal variations in appendicitis. Most of these studies found that the incidence of appendicitis cyclically increased in summer and declined in winter[2,6,7]. This phenomenon might be explained by a positive correlation between increased temperature and the incidence of gastrointestinal tract infection[8]. A study from Nigeria reported the highest incidence in their rainy season. Thailand is a tropical country where the average high temperature during the summer rises to 33-36 degrees Celsius[9], together with an increase in precipitation. An annual cyclical change in the incidence of acute appendicitis is then possible. Furthermore, if the incidence of acute appendicitis is indeed associated with climate variability, it raises another question: Is the change in the incidence rate related to the long-term trend of climate change?

This study was a data mining work that used a country-wide reimbursement dataset from the Thailand National Health Security Office (NHSO). The analysis focused on the epidemiology of acute appendicitis, its seasonal variations, mortality rates, and factors associated with mortality.

MATERIAL AND METHODS

Design and data sources

This was a retrospective study that used publicly available data from the Thai Hospital Information Portal, which is a joint project between the Institute of Research and Development for Health of Southern Thailand and the National Science and Technology Development Agency (NSTDA) that archived reimbursement data from the NHSO. The dataset spanned a four-year period, from October 2016 to September 2020, and consisted of basic demographic data (age, sex), diagnosis (principal diagnosis, secondary diagnosis), length of hospital stay, month and year of admission, discharge type, discharge category, treatment procedure(s), death date (if any), and health region where the patient was treated. Each patient's dataset was obtained during the same medical visit in which they received a diagnosis and treatment for appendicitis. Case identification used the ICD-10 (version 2519) keys K35.2-K35.9, which encode acute appendicitis. The dataset was requested through the website https://thip.nbt.or.th/ on June 2022 and deposited as a Supplementary Data file 1.

For associated co-morbidities, the codes 'E11.X'-'E14.X' were used for diabetes mellitus, 'I10' for hypertension, 'E78.X' for dyslipidemia, 'J44.9' for chronic obstructive pulmonary disease, 'N18.9' for chronic kidney disease, and 'I25' for ischemic heart disease. Regarding complications, the codes 'R65.1', 'R57.2', and 'A41.9' were used for sepsis, 'T814' for surgical site infection, and 'N17.8'-'N17.9' for acute kidney injury.

To calculate the incidence rate, population numbers in each Health Region used the publicly available data from the Department of Health, Ministry of Public Health, Thailand through the URL: http://dashboard.anamai.moph.go.th/. Meteorological data were downloaded from the Climate Change Knowledge Portal (World Bank Group) through the URL: https://climateknowledgeportal.worldbank.org/download-data. This research was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC. 65-284-10-1).

Data management

Data analysis was performed with Python version 3.8.2. The Python code used in this study is available at the URL: https://github.com/sasurasa/THIP/blob/main/Package%201.1/SURPY/thip.py' or available as a package 'thip' from the PyPi repository, module name 'SURPY' (release 1.4.15)[10]. Calculations of lifetime risk used the current probability method[11] and the most recent life expectancy of Thai people as reported by the National Statistical Office (2022). To test the associations between each co-morbidity and mortality, univariable logistic regression was used. Death status was defined as having a date of death ('death_date') recorded in the database.

To visualize the patterns of seasonal variations of incidence, the multiplicative model of time series detrending and a decomposition model (setting the parameter 'period' at 12) were used. The packages involved were statsmodels and scipy. The dataset used for these analyses was separately deposited as the Supplementary Data file 2.

Prediction model construction

To construct a prediction model for mortality a 'decision tree' method was used. In-hospital mortality was used as a label when age group, sex, co-morbidities (diabetes, hypertension, ischemic heart disease, chronic kidney disease (CKD), chronic obstructive pulmonary disease), and complications (sepsis, surgical site infection, and acute kidney injury (AKI)) were assigned as attributes. The decision-tree analysis was performed with the Rapidminer studio program version 10.1 (Rapidminer GmbH, Germany), with a maximum depth set at 5 and the criteria 'information gain' used for tree construction.

The performance of the prediction tool was evaluated with a cross-validation technique with a 10-fold sampling and using the seed number 2001 on the Rapidminer program.

RESULTS

General demographic data

During the period from October 2016 to September 2020, the total number of appendicitis cases in the database was 287,449 individuals or an average of 71,862.3 cases per year, giving a crude incidence of 10.8 diagnoses per 10,000 persons annually. The male-to-female sex ratio was 1.11. When stratified by age group, the peak incidence was in the second decade of life (10-19 years old), which had a crude incidence of 28.4 diagnoses/10,000 person-years and contributed up to 31.4% of all appendicitis cases in the study period, followed by the age group of 20-29 years old (10.6 diagnoses/10,000 person-years). The incidence was rather stable, around 7.6-10.00 diagnoses/10,000 person-years) in the following age groups until it dropped to 4.6 diagnoses/10,000 person-years) in the group of 90–99-year-olds (Figure 1). The incidence trend had a downward direction during the four-year study period. Calculating the incidence with the life-expectancy of Thai people at 79.27 years in 2020, the lifetime risk of having acute appendicitis in Thai people is estimated at 17.0%. Interestingly, the number of appendicitis cases diagnosed during the year when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (2020) appeared was significantly reduced from the preceding years (2017-2019). The average cases per month dropped from 6,128.7 cases (S.D. 369.8 cases) before 2020 to 5,381.0 cases (S.D. 381.2 cases) in 2020 (p-value<0.01). The decrease in the incidence of appendicitis in the year 2020 occurred simultaneously with the reduction in the monthly diagnoses of the common cold (J00) from 2,939.4 (S.D. 643.4 cases) to 1,944.1 (S.D. 937.1 cases) in the same period (p-value<0.01).

Of the 283,293 cases whose principal diagnosis was acute appendicitis in the four years, 129,990 cases (45.9% of 283,923 cases) were recorded as 'unspecified acute appendicitis' (K35.8), 123,473 cases (43.5%) of 'appendicitis with localized peritonitis (K35.8)' and 28,745 cases (10.5%) of 'appendicitis with generalized peritonitis (K35.2)'. Other diagnoses were recorded in 4,156 cases, of which the five most common were 'diseases of the digestive system complicating pregnancy, childbirth or puerperium (O99.6)' (1,062 cases), 'other and unspecified ovarian cysts (N83.2)' (143 cases), 'salpingitis and oophoritis, unspecified (N70.9)' (100 cases), 'other specified diseases and conditions complicating pregnancy, childbirth, and the puerperium (O99.8)' (93 cases), and 'other and unspecified intestinal obstruction (K56.6)' (93 cases).

Considering the distribution of cases among the 13 health regions in the country, District 1 (the northern part of the country) had the highest number of cases (average of 8,513.5 cases annually), followed by District 9 (the upper central part, 8,166.8 cases) and Region 8 (the northeastern part, 6,289.5 cases) (Figure 2). When adjusted by the number of registered persons in each region, Region 1 had the highest incidence at 14.5 diagnoses per 10,000 population annually. In comparison, the Bangkok Metropolitan area had the lowest incidence figure at 7.4 diagnoses per 10,000 population.

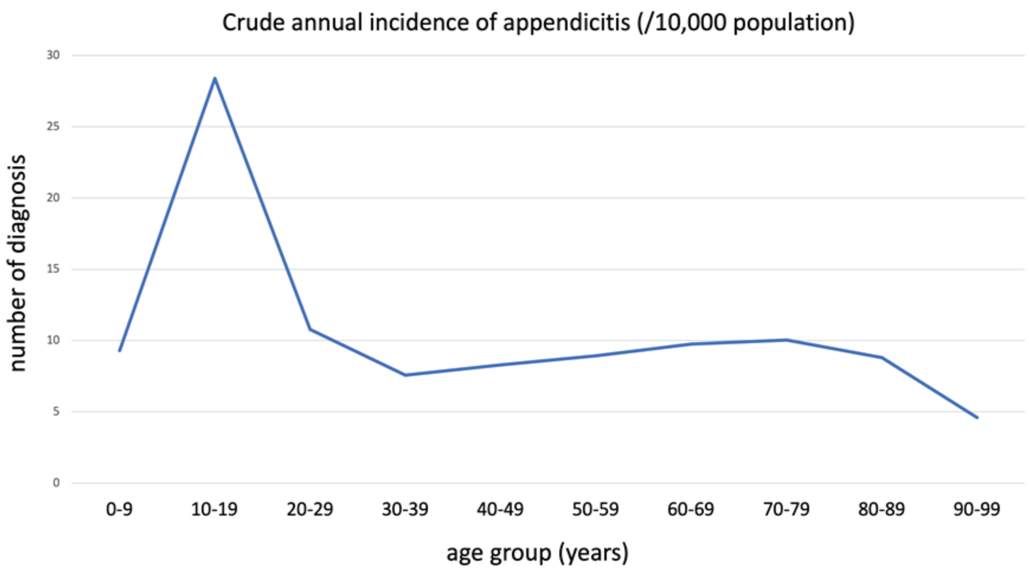


Figure 1 Crude annual incidence of appendicitis in Thailand according to age group

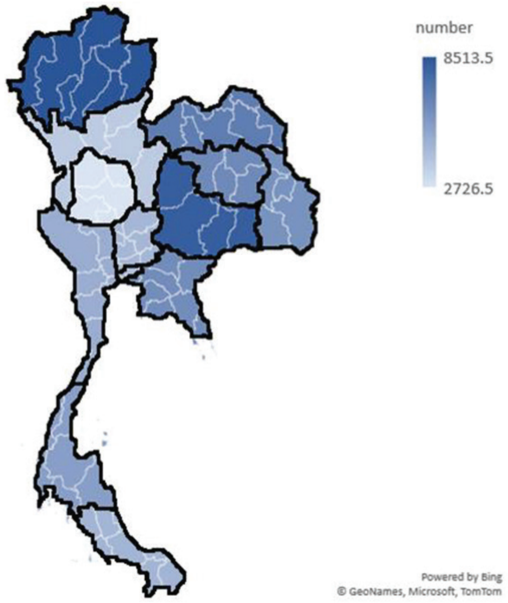


Figure 2 Number of appendicitis cases per year in each health district in Thailand

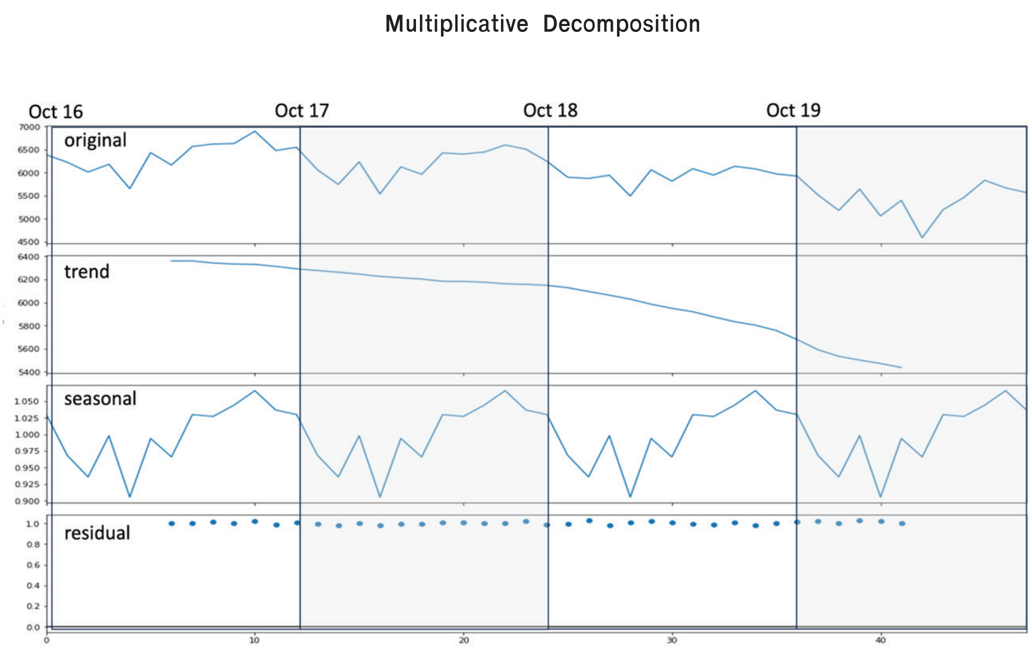


Figure 3 Multiplicative decomposition curves showing the seasonal variations of the incidence of acute appendicitis in Thailand during the study period

Seasonal variation of the incidence

The multiplicative decomposition of the incidence data clearly showed a seasonal variation in the incidence of acute appendicitis (Figure 3), which increased between May and October of each year during the four-year period. When linear regression was performed to examine correlations between the incidence and the four climate parameters, including precipitation, minimum temperature, mean temperature, and maximum temperature, precipitation had the best correlation to the incidence of acute appendicitis, considering the least root mean square error, and the highest r-square (Figure 4). The correlation between the seasonal variations of precipitation and incidence is demonstrated by co-linearity in their detrended curves (Figure 5).

Surgical procedures and hospital stay

Of 308,756 hospital admissions in 287,449 cases, an open appendectomy (ICD-9 ‘4709’) was recorded in 270,253 admissions, while a laparoscopic appendectomy (ICD-9 ‘4701’) was performed in 2,597 admissions. The average length of hospital stay in cases whose principal procedure was an open appendectomy was 3.48 days while it was 3.53 days in cases of laparoscopic appendectomy. Sepsis or related conditions (R651, R572, or A419) were recorded in 3,217 admissions (1.01%), and cases with sepsis had a significantly longer hospital stay at an average of 10.99 days). Patients with generalized peritonitis had a significantly higher chance of surgical site infection, with an odds ratio of 12.52 (95% CI 10.95-14.33). The length of hospital stay in cases with generalized peritonitis (6.1 days) was significantly higher than for patients with unspecified or localized peritonitis (3.04 days) (p-value<0.01).

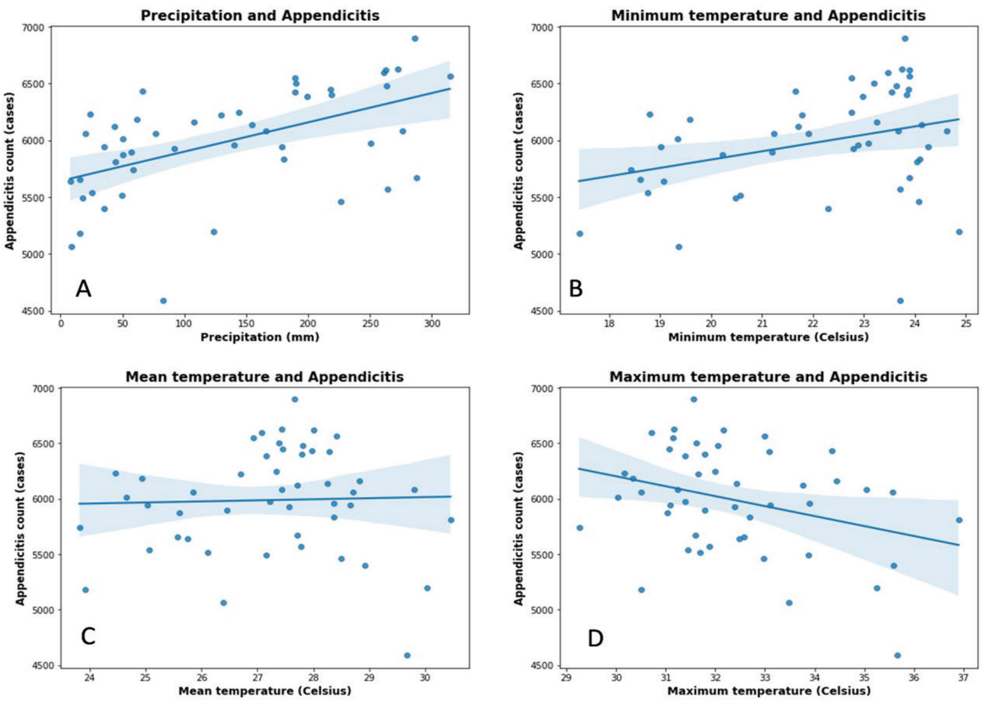


Figure 4 Scatter plots showing correlations between the appendicitis case numbers and A) precipitation (r^2=0.28, p-value<0.001); B) minimum temperature (r^2=0.10, p-value=0.028); C) mean temperature (r^2=0.00, p-value=0.830); and D) maximum temperature (r^2=0.10, p-value=0.085)

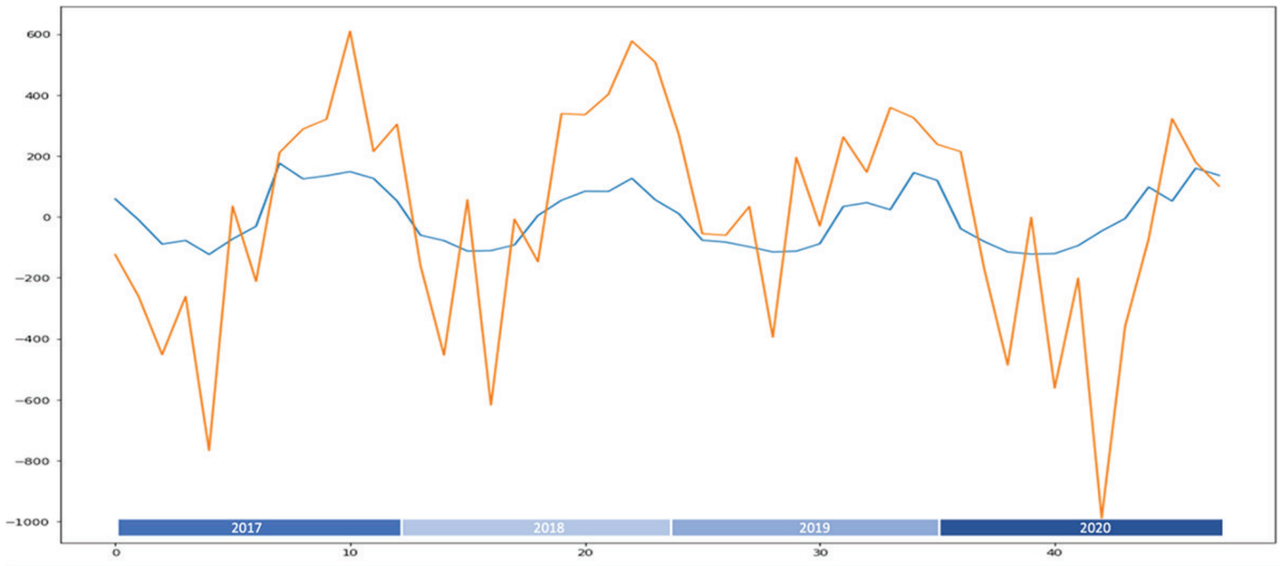


Figure 5 Linear plots showing co-linearity between detrended values of appendicitis incidence (orange line) and precipitation (blue line) in Thailand. The lower bar marks years (October to September)

Mortality and associated factors

The mortality was 6,531 cases or 2.27 percent of total cases in this study. Among these, the discharge status was documented as deceased in 998 cases. Age was positively correlated with an increased likelihood of mortality, as indicated by an odds ratio of 1.070 (95% CI 1.068-1.071). Regarding sex, males exhibited notably lower mortality rates in contrast to females (Table 1). The presence of generalized peritonitis was associated with a significantly higher chance of death, with an odds ratio of 5.93 (95% CI 5.33-6.60). The correlations between age, diagnostic group (peritonitis, sepsis), and mortality are shown in Supplementary Figure 1. On univariable logistic regression, co-morbidities and/or complications also increased the mortality risk. The differences in mortality rates among the health regions are shown in Supplementary Figure 2.

Decision-tree mortality prediction model for mortality

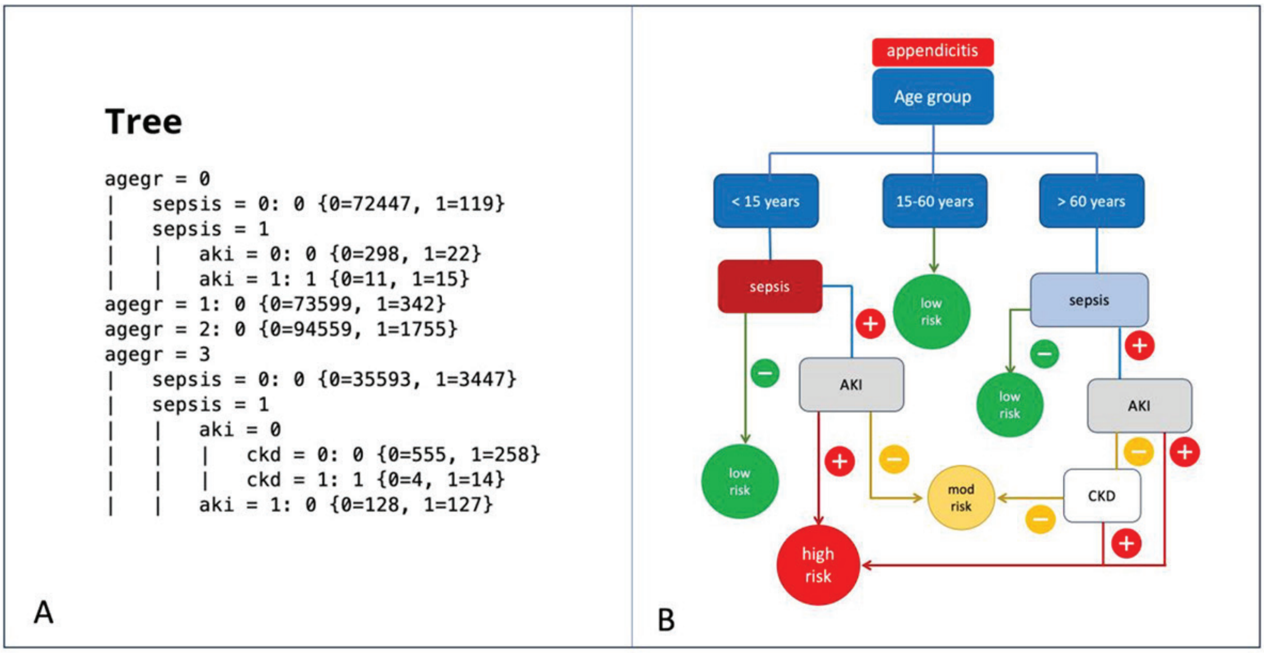
Using a decision-tree prediction modeling technique, a prediction model was constructed as shown in Figure 6. When tested with a cross-validation technique, the prediction accuracy was 97.87%, the negative class recall rate was 99.97%, and the positive class recall was 1.13%.

The decision-tree model used age, complications (sepsis, acute kidney injury), and co-morbidity (chronic kidney disease) as decision nodes. High mortality risks were found in the extreme age groups, i.e. pediatric patients less than 15 years and patients older than 60 years. For pediatric cases, sepsis and AKI were the nodes determining the risk of mortality. Pediatric appendicitis without any of those two risk factors had a chance of mortality of 0.16%, while those with sepsis had a mortality rate of 10.69%, and the mortality rate increased to 57.69% when they had both factors. In patients aged more than 60 years, mortality rates in cases with and without sepsis were 36.74% and 8.82%, respectively. In patients with sepsis, the mortality rate increased to 49.80% when they had AKI, and the figure increased to 77.78% if the patient also had underlying CKD.

Table 1 Factors associated with in-hospital death in study appendicitis patients

Parameter	Number (%)	Mortality (%)	OR	95% confidence interval
All	287,449 (100.0)	2.27	–	–
Sex				
Female	15198 (52.6)	1.99	ref	–
Male	136251 (47.4)	2.47	1.251	1.19–1.31
Age group				
<15 years	73,324 (25.5)	0.24	ref	–
15–29 years	72,697 (25.3)	0.48	1.982	1.66–2.37
30–60 years	100,509 (35.0)	1.86	7.882	6.76–9.19
>60 years	40,919 (14.2)	9.87	45.488	39.14–52.85
Marital status*				
Single	57,180 (35.0)	1.97	ref	–
Married	108,350 (64.5)	4.10	4.813	4.53–5.11
Divorced/Widow	2,413 (1.4)	11.69	15.109	13.21–17.29
Diagnostic code**				
Appendicitis, unspecified	129,990 (45.2)	1.92	ref	–
Localized peritonitis	123,473 (43.0)	1.93	1.005	0.95–1.06
Generalized peritonitis	29,830 (10.4)	4.10	2.185	2.03–2.34
Others	4,156 (1.5)	10.39	5.930	5.33–6.60
Co-morbidity				
Diabetes mellitus				
Absent	277,567 (96.6)	2.00	ref	–
Present	9.882 (3.4)	10.00	5.451	5.08–5.85
Hypertension				
Absent	268,421 (93.4)	1.81	ref	–
Present	19,028 (6.6)	8.82	5.256	4.96–5.57
Dyslipidemia				
Absent	280,132 (97.5)	2.17	ref	–
Present	7,317 (2.5)	6.37	3.073	2.79–3.39
COPD***				
Absent	286,557 (99.7)	2.22	ref	–
Present	892 (0.3)	19.17	10.449	8.83–12.37
Chronic renal failure				
Absent	286,639 (99.7)	2.21	ref	–
Present	810 (0.3)	25.56	15.216	12.97–17.85
Ischemic heart disease				
Absent	286,767 (99.8)	2.24	ref	–
Present	682 (0.2)	15.84	8.212	6.68–10.10
Complications				
Sepsis/SIRS				
Absent	284,525 (99.0)	2.04	ref	–
Present	2,942 (1.0)	25.14	16.147	14.97–17.62
Surgical site infection				
Absent	285,534 (99.3)	2.24	ref	–
Present	1,915 (0.7)	6.63	3.096	2.57–3.71
Acute kidney injury				
Absent	285,671 (99.4)	2.11	ref	–
Present	1,178 (0.6)	27.78	17.821	16.01–19.83

*Marital status=analyzed only for those aged >20 years; **Used ICD-10=code recorded in the principal diagnosis ('PID'); ***COPD=chronic obstructive pulmonary disease; OR=odd ratio



AKI=acute kidney injury; CKD=chronic kidney disease; mod risk=moderate risk

Figure 6 A) Decision tree analysis of factors associated with mortality in patients with appendicitis (picture from the RapidMiner program), and B) Schematic summarization of the decision tree constructed from the results of the analysis

DISCUSSION

The study mined a large dataset from the key governmental healthcare resource agency and found that the incidence of acute appendicitis in Thailand was around 11 cases/10,000 person-years, and the lifetime risk of having acute appendicitis in Thai people was 17.0%. There was a downward trend in the incidence during the 4-year study period, especially in the year when the SARS-CoV-2 pandemic began. Our study also demonstrated seasonal variations in the incidence of appendicitis in Thailand, which peaked during the period from May to October. The incidence variations were correlated with the average seasonal rainfall in the country.

Seasonal variations of acute appendicitis have been suggested by various reports[6-8]. Most studies used hospital-based datasets and found that the incidence increased during the summertime[6,7,12-15]. Some studies also found a correlation between the incidence of appendicitis and other environmental parameters such as the rainy season[16], humidity[17], air pollution[18], and atmospheric pressure[15]. In our study, the data clearly demonstrated seasonal variations in the incidence of appendicitis, with a peak occurring during Thailand's rainy season, from June to September. The variations of the incidence fitted more with the precipitation pattern in the country, and overall the variations in the incidence of appendicitis seemed to follow the precipitation changes. Plausible explanations for this correlation might be the fluctuation of some viral diseases that are also more common in the rainy season[19]. Another factor that could be noted is that the first school semester in Thailand runs from late May to mid-October, which increases the spreading ability of viral diseases. The reduction in the incidence of appendicitis in the year 2019 might be explained by governmental strategies to control the SARS-CoV-2 pandemic, including school closings and the promotion of remote working.

In the US, the figures for the lifetime risk of acute appendicitis were reported at 6.7% in females and 8.6% in males[19]. Our figures were rather high compared to those. However, our lifetime risk at 17% was comparable with that of Korean people, which reported a figure of 16.3%[2]. Our study also found that mortality in patients diagnosed with appendicitis in Thailand was rather high at 2.2%. Factors that were associated with higher mortality in our patients were extreme age and co-morbidities. Infantile appendicitis was an uncommon condition but had a high risk of perforation and sepsis when it occurred. Our study found that the overall mortality in infants with appendicitis was 3%, and the figure rose to 6.5% if the patient had generalized peritonitis. After the age of 1 year, the overall deaths in each age were lower than 1.0% until the age of 34, which might imply that the presence of a co-morbidity, which was more common in the older age groups, had an impact on outcomes. The evidence was more obvious in the age groups of more than 60 years, in which general mortality increased to almost 10%. Our data showed that various co-morbidities and complications, especially sepsis and acute kidney injury, were significantly associated with higher mortality rates. The co-morbidity that had the highest odds of mortality risk was chronic kidney disease. Consistently, our study found that chronic kidney disease was associated with a poor outcome in the elderly with sepsis. In a recently published hospital-based pediatric case series including 122 patients with acute appendicitis, 7.38% of the cases developed acute kidney injury[20]. A multicenter data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) found that an appendectomy alone had a 0.2% risk of acute kidney injury, and the appendectomy cases with acute kidney injury had a significantly higher adjusted 30-day mortality prediction at 8.3%, compared to 0.04% in those without the complication[21]. Taken together with our study, the data emphasize the importance of adequate hydration and prevention of sepsis, which would prevent the development of renal complications.

The strength of our study was the size of the NHSO dataset that represented the picture of appendicitis in the whole country, which meant that figures derived from the analysis were population-based. Moreover, a large data set provides a high correlation power. However, this type of data has limitations as well. As the data were submitted to the NHSO for reimbursement purposes, it might include cases who underwent an appendectomy, but without histologically confirmed appendicitis. In addition, causes of death could not be traced from this limited data, which might include death following an appendectomy, but unrelated to appendicitis.

Another limitation in our study is the fact that there exist numerous subtypes or levels of severity within comorbid conditions. For instance, the severity of acute kidney injury can be categorized by AKIN based on various criteria levels or urine output, and this severity significantly impacts patient death. In our study, the datasets we used lacked information regarding the severity or subtypes of the comorbid diseases included in our analysis. Knowing these factors would have enabled us to clarify the particular coexisting health issues and formulate a more precise version of our decision tree.

To implement our findings in a clinical context, the clinician can integrate the understanding of the comorbid conditions that increased the mortality rate in our decision tree analysis, considering the numerous predictive tools available in clinical practice. As an illustration, healthcare practitioners have the option to employ tools like the Systemic Inflammatory Response Syndrome (SIRS) or SOFA score to anticipate the likelihood of sepsis. Acute kidney injury (AKI) manifests as an elevation in serum creatinine of 0.3 mg/dL or more within 48 hours, or an increase of 1.5 times or more compared to the baseline within the preceding 7 days. Additionally, AKI can be evaluated by monitoring urine volume, which is indicated if urine volume remains below 0.5 mL/kg/h for a minimum of 6 hours. Consequently, doctors could assess creatinine levels or urine output to further check for' AKI. In summary, armed with knowledge about substantial risk-elevating conditions, the establishment of protocols or guidelines for the early detection of these conditions becomes feasible. For example, considering the insight we gain from the decision tree, older individuals aged over 60, who present with sepsis and acute kidney injury alongside appendicitis, have a higher mortality rate compared to typical appendicitis patients. Therefore, it becomes possible to enhance the intensiveness of vital signs monitoring in elderly patients. In instances where these patients develop fever or experience reduced urine output, proactive measures can be adopted. In the case of a fever, a septic workup or commencement of antibiotics might be appropriate. Similarly, if urine output decreases, assessing creatinine levels promptly and initiating early hydration can be beneficial to avoid acute kidney injury. It's worth noting that these decisions depend on the clinicians. This decision tree can function as reminders, prompting healthcare providers to remain vigilant about these conditions and take necessary steps for diagnosis, treatment, or prevention, as they could significantly elevate the risk of mortality. Moreover, many of the tools we have discussed can be gauged through signs and symptoms or basic laboratory tests, many of which are typically conducted as routine procedures in appendicitis cases.

In conclusion, over the 4-year period of the study there were 106 cases of appendicitis per 100,000 Thai person-years, with a decreasing incidence rate over the study period. The incidence of appendicitis in Thailand had seasonal variations, peaking in the rainy season. Extreme age, co-morbidities, and associated complications, especially renal complications, were associated with increased mortality in these patients.

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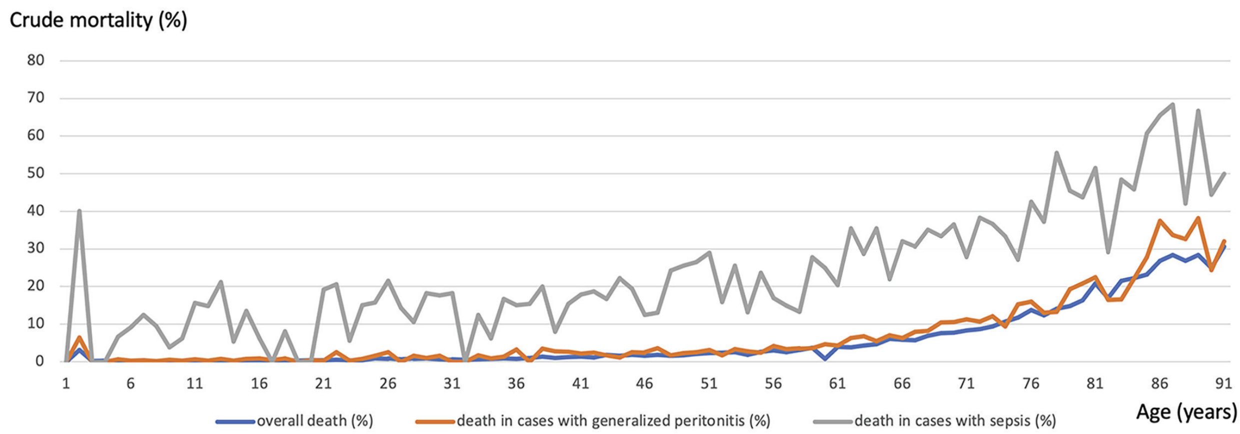
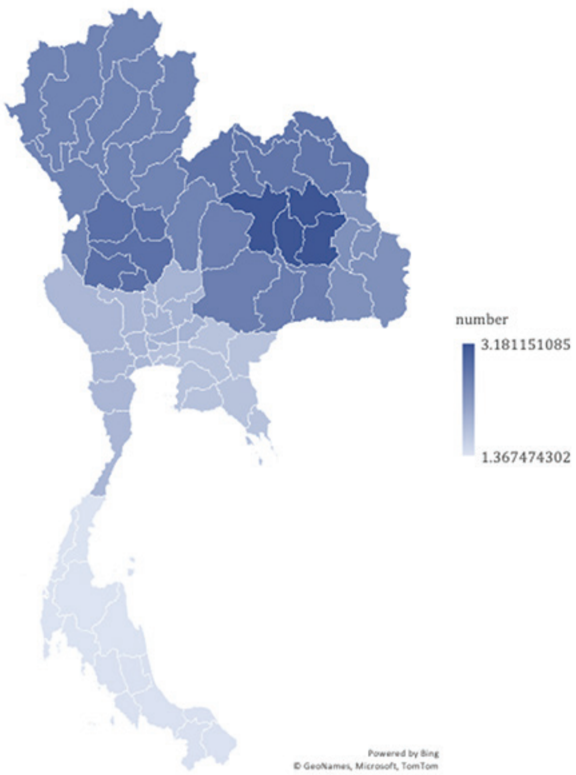


Supplementary Figure 1 Mortality in acute appendicitis in Thailand during the study period according to age and associated diagnoses



Supplementary Figure 2 Mortality of acute appendicitis in Thailand during the study period according to health region