Children With Appendectomy Have Increased Risk of Future Sepsis: Real-world Data in Taiwan

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What's known

Mounting studies have shown that the appendix plays an important role in human immunity. Our previous research suggests a correlation between appendectomy and future risk of sepsis in adults. To date, the association between appendectomy and future risk of sepsis in children remain unclear.

What's new

Appendectomy is associated with a 2.63-fold increased future sepsis risk in children, especially in children aged less than 6 years. We recommend that a need for thoughtful consideration should be taken before performing prophylactic or incidental appendectomy in children.

Abstract

Backgrounds

Appendectomy is one of the most commonly performed surgeries worldwide. Sepsis is an major etiology of morbidity and mortality in children. Our preliminary research revealed a positive correlation among appendectomy and future risk of sepsis in adults. However, to date, the relationship among appendectomy and future risk of sepsis in children remains unknown. The aim of this research was to investigate the relationship among appendectomy and hazard of future sepsis in children.

Methods

We applied a nationwide population-based cohort to assess whether children who received appendectomy were at increased risk of subsequent sepsis. Overall, 57261 subjects aged below 18 undergoing appendectomy as appendectomy group and 57261 matched controls were identified as non-appendectomy group from the National Health Insurance Research Database in Taiwan. We

use propensity score analysis to match age, sex, urbanization level, and parental occupation at the ratio to 1:1. Multiple Cox regression and stratified analyses were used to appraise the adjusted hazard ratio (aHR) for developing sepsis in children.

Results

Children who received appendectomy had a 2.63 times higher risk (aHR: 2.63; 95% confidence interval [CI]= 2.19, 3.16) of developing sepsis than those who did not, and the risk was even higher in children aged under 6 years (aHR: 4.25, 95% CI= 2.67, 6.77; aHR: 2.51, 95% CI= 1.78, 3.55; aHR: 2.29, 95% CI= 1.79, 2.94 in children aged < 6 years, 7-12 years, and 13-18 years, respectively). Patients with <1 year follow-up showed a 5.64-fold risk of sepsis in the appendectomy cohort (aHR: 5.64, 95% CI= 3.50, 9.07). Patients with 1–4 and ≥5 years' follow-up showed a 2.41- and 2.02-times risk of sepsis (aHR: 2.41, 95% CI= 1.78, 3.27; aHR: 2.02, 95% CI= 1.53, 2.65 in 1-4 years and > 5 years, respectively).

Conclusion

Appendectomy was correlative to a 2.63-fold increased future sepsis risk in children, and the risk in younger patients aged <6 years was even higher. More studies to interpret the possible biological mechanisms of the associations among sepsis and appendectomy are warranted.

Introduction

Appendectomy is one of the most frequently performed surgeries worldwide. The appendix is traditionally considered to be a useless organ. However, in recent years, numerous research have been illustrated that the appendix plays an indispensable role in human immunity.[1] The existence of the appendiceal biofilm in particular has shown to have a beneficial effect on the entire gut.[1,2] Many researches have proved that a previous appendectomy is related to inflammatory bowel disease,[3,4] recurrent *Clostridium Difficile* infection,[5] antibiotics-associated diarrhea, liver abscess,[6] and colorectal cancer.[7]

Sepsis in children is defined as a clinical syndrome complicated with severe infection and is characterized by systemic inflammatory reaction, immune dysfunction, microcirculatory derangements, and end-organ dysfunction, a complication of infectious disease which is associated with a high mortality rate and long-term morbidity.[8] It remains a considerable challenge in clinical practice and research.

Our preliminary study revealed appendectomy confers a 1.29-fold increased risk of developing subsequent sepsis regardless of sex or comorbidities in adults.[9] We speculated that appendectomy might affect future risk of sepsis in children. To date and to our best knowledge, there has been no previous research on this issue in a pediatric population. In order to determine whether appendectomy increases the risk of sepsis in children, we conducted a large scale national population retrospective cohort study using health information obtained from the National Health Insurance Research Database in Taiwan and analyzed the relationship among appendectomy and future risk of sepsis in children.

Methods

Data Source

Taiwan's National Health Insurance Research Database (NHIRD) was established in 1995 and

contains the health records of approximately 99% of all residents in Taiwan. The single-payer National Health Insurance (NHI) program in Taiwan provides medical coverage for around 23 million residents, which is almost the entire population. In this study, we analyzed data from the NHIRD, which contains information related to the diseases, treatments, and medications of NHI beneficiaries. Diseases and conditions are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). All data were encrypted in accordance with privacy protocols. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115-CR4). Written consent from study subjects was not required and waived by the Institutional Review Board of Research Ethics Committee II of China Medical University and Hospital, because the NHIRD comprises de-identified data for research purposes. The study carried out in accordance with principles of Declaration of Helsinki.

Study Population

The target population of this study comprised subjects under 18 years old. Children who underwent appendectomy (ICD-9-CM: 47.0 and 47.1) between 2000 and 2012 constituted the exposed cohort and those without appendectomy were deemed to be the unexposed cohort. The index date was the date the appendectomy was performed. Patients diagnosed with sepsis before the index date were excluded from the study. The exposed and unexposed cohorts were matched according to age, sex, urbanization level, and parental occupation using a ratio of 1:1.

Main Outcome and Confounders

The primary outcome was sepsis (ICD-9-CM: 003.1, 036.2 and 038.x). Participators who died or withdrew from the NHI program were considered as censored. We followed the participants from the index date to the incidence of sepsis, censor, or 31 December 2013, which was the end of the study. The potential confounders included sex, age, urbanization level, and parental occupation.

Age was divided into three groups: 6 years old or younger, 7-12 years old, and 13-18 years old. Parents' occupation was categorized as white collar or blue collar, and parents who were primarily retired, unemployed, or had a low income were assigned to the "other" group.

Statistical Analysis

Chi-square test was applied to examine the distributions of age, sex, urbanization level, and parental occupation between the appendectomy cohort and non-appendectomy cohort. For the mean of age, Student's t-test was used to compare the difference. The incidence was expressed as the number of sepsis diagnoses per 1,000 person-years. Hazard ratios and 95% confidence interval (CI) were estimated by the Cox proportional hazard model. The cumulative incidence curves were obtained by Kaplan-Meier method and tested by the Log-rank test. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was set as a p-value less than 0.05.

Results

From 2000 to 2012, 57261 children underwent an appendectomy (see **Table 1**). The majority of patients were aged 13 to 18 years (53.6%) and the mean age was 12.0(±4.22) years. There were more male patients than female patients. Most patients are living in a highlyurbanized area (level 1: 27.2%, level 2: 29.8%). In addition, 54.6% of the subjects' parents were white-collar workers. Control subjects with similar baseline characteristics were included.

In **Figure**, the cumulative incidence curve of sepsis in the appendectomy cohort was higher than that of the unexposed cohort during the whole study period. The p-value of the Log-rank test was less than 0.001, which demonstrates the difference between the two curves was significant. The incidence rate of sepsis in appendectomy patients was 8.44 per 1,000 person-years, which was higher than that of the non-appendectomy patients (3.21 per 1,000 person-years), as shown in

Table 2. After adjusting for age, sex, urbanization level, and parental occupation, the risk of having sepsis in children whose appendix was removed was 2.63 times (95% CI =2.19, 3.16) greater than that of non-appendectomy patients. Compared to children in the 7 to 12 years age group, the risk of sepsis in children aged 6 years or younger was increased by 2.56 times (95%CI=2.00,3.27) and that for children who aged 13 to 18 years old, there was 1.31 times greater risk (95%CI=1.07,1.59). Girls were more likely to develop sepsis than boys. Patients living in areas with lowest urbanization level had a 1.31-fold (95%CI=1.03, 1.65) increased risk of sepsis compared with patients living in the highest urbanization area. Children whose parents were retired, unemployed, or had a low income had a higher risk of developing sepsis (aHR=1.79; 95%CI=1.42, 2.26) compared to those whose parents were white-collar workers.

Table 3 shows the risk of sepsis in children with appendectomy stratified by different variables. Appendectomy increased the risk of sepsis in all age groups, especially in the 6 years or younger age group (aHR=4.25; 95%CI=2.67, 6.77). Regardless of gender, the risk of sepsis in patients who underwent appendectomy was more than two times greater compared with the non-appendectomy patients. For patients living in urbanization level 3 area, the aHR of sepsis for appendectomy cohort relative to the unexposed cohort was 3.12 (95%CI=2.00, 4.88). Among the three different parental occupation groups, appendectomy appeared to confer the greatest increase in risk of sepsis in children whose parents were blue-collar workers. The hazard ratios of sepsis for children who received appendectomy with less than one year of follow-up, 1-4 years' follow-up, and five or more years' follow-up were 5.64 (95%CI=3.50, 9.07), 2.41 (95%CI=1.78, 3.27) and 2.02(95%CI=1.53, 2.65), respectively.

Discussion

The results of our cohort study disclosed that children who received appendectomy had a 2.63 timesrisk (aHR: 2.63; 95% CI= 2.19, 3.16) of developing sepsis than those who did not receive

appendectomy, and in the subgroup of children 6 years old or younger the risk was even higher (aHR: 4.25, 95% CI= 2.67, 6.77). We also observed that an increased incidence of sepsis persists over time, even 5 years after receiving appendectomy. As far as we know, this is the first population-based cohort study investigating the association between appendectomy and future sepsis risk in children.

The appendix is traditionally considered to be a residual organ. However, recent studies indicated it is an important immune organ.[1,2,10] The appendix has been shown to have an important interaction with the gut flora[11] and the chief site of manufacture of secretory immunoglobulin (Ig) A.[12] The IgA secreted by appendix has been shown to contribute to the formation, evolution, and balance of the gut microbiome and biofilms.[13,14] In human beings, biofilms are most prevalent in the appendix, decreasing in abundance towards the end of the colon,[1] which suggests that the appendix may be the "base camp" of the biofilms. The intestinal biofilms are considered the first-line of defense on the mucosa. Once the appendix is removed, the stability and recovery capability of the biofilms are influenced,[15] and these changes affect the function of the gut mucosa layer and increase the risk of intestinal infections and systemic inflammation.[16]

Previous studies also indicated that the gut microbiome in children is still developing and in a relatively unstable status.[17] Compared with older age children, children 6 years old or younger have the highest risk of developing sepsis with prior appendectomy. We speculate that this may be associated with the immaturity of the gut microbiome and immune system. The development of the microbiome is generally believed to begin from birth, with the various life events causing chaotic shifts in the microbiome, which is considered highly variable with continuous development before adulthood.[17] The duration of microbial colonization triggers and accompanies the maturation of the mucosal immune system.[13] Overall, the gut microbiome is considered to be stable and mature in adulthood. Once the appendix is removed, the development and stability of gut microbiome is affected due to the loss of the 'safe house' after infectious diarrheal events. The

formation and development of the gut epithelium and biofilms are also influenced by the loss of the appendix. It is conceivable that the earlier the removal of the appendix, the greater the impact is on the gut. The immune system becomes mature and adaptable after being exposed to a variety of foreign antigens and microbes.[18] The antigen exposure is needed the presentation from the secondary lymphoid tissue,[19] such as lymph nodes, tonsils, spleen, and mucosa-associated lymphoid tissues. The gut epithelium is always exposed to a large amount of microorganisms so our gut is equipped with specialized gut-associated lymphoid tissue (GALT), which is the largest peripheral lymphoid tissue in the body.[20,21] Therefore, GALT and the gut microbiome dominate the maturation of the human immune system. The appendix is a member of GALT,[2] so appendectomy induces a negative effect on the maturation of the immune systems, especially in younger children. Appendectomy might induce gut dysbiosis,[15,22] which affects the maintenance of gut-barrier function and modulation of the immune system. Sánchez-Alcoholado et al. indicated that appendectomy is associated with profound long-term dysbiosis due to a reduction of the richness and diversity of the gut microbiome.[22] It has been found that the composition of the intestinal flora of patients with sepsis is severely distorted.[23] The gut is believed to be a motor of sepsis and multiple organ dysfunction syndrome in recent research.[24] It is hypothesized that the gut mucosa increases permeablility and apoptosis in critical illness, which perhaps lead to intestinal flora leaking into the systemic circulation and resulting in sepsis and systemic inflammation.[25] Hence, the risk of future sepsis in children undergoing appendectomy is increased.[26,27] The greater fragility and immaturity of the gut microbiome in younger children may explain why the risk is greater in younger children.

The incidence of sepsis in the sub-analyses stratified by years of follow-up showed a significantly higher risk in all subgroups, especially in the group within the first year of follow-up after undergoing appendectomy, which might be partially related to surgical complications, such as perforation, abscess formation, and wound infection.[28] Nevertheless, the risk of sepsis is still

markedly higher even 5 years after receiving appendectomy. We speculate that appendectomy may have a negative effect on immunity and gut flora, thereby increasing the incidence of sepsis with time. The downward trend in the incidence of sepsis is thought to be related to the maturation of a child's immune system over time.

We also noted that children living in a lower urbanization area and those whose parents are primarily retired, unemployed, or have a low income had a higher risk of developing sepsis. This phenomenon may be associated with region-related medical convenience[29] and financial or familial support. That is to say, socioeconomic status affects the incidence of sepsis.[30,31]

There is growing evidence that shows conservative medical treatment with antimicrobials might be an appropriate and well-tolerated treatment for acute simple appendicitis in children.[32,33] Our research lends proof of an association among previous appendectomy and future risk of sepsis in children. Therefore, we suggest that the optimal treatment plan for appendicitis ought to be chosen with more careful and thoughtful consideration ought to be undertaken before performing prophylactic appendectomies in children.[34,35]

The NHIRD is a massive database which routinely collects huge amounts of clinical and administrative healthcare-related data. With respect to research, it provides the strength of large sample size, while avoiding selection, recall, and participation bias.[36] It is a large, powerful source of data for biomedical research.[37] The strength of our study is that the population-based data from the NHIRD is adequately representative of the oridinary population,[38] but the database still some inherent limitations. First, the NHIRD does not contain data on socioeconomic status, family history, birth history, lifestyle, and nutrition status, which may be risk factors in the development of sepsis. Although we adjusted for age, sex, urbanization level, and parental occupation, and performed propensity score-matching, these unmeasured confounders might have affected our results. Second, confirmation of the true sepsis incidence is difficult. The gold standard for sepsis diagnosis in children is clinical identification of life-threatening organ dysfunction caused by

infection.[8] At the nationwide population level, it is impractical to require a retrospective medical record review for conventional disease observation. As an alternative, routinely collected data are analyzed to estimate the prevalence of sepsis, mainly based on ICD coding of cases. The definition of sepsis was based on ICD-9-CM codes, rather than clinical diagnostic criteria,[39] which is an inherent limitation of the NHIRD. We believe that the diagnostic codes based on hospitalization diagnosis are accurate because the NHI in Taiwan has an ad hoc committee responsible for monitoring the accuracy of claims data to prevent violations. Although the accuracy of these codes has been demonstrated,[40-43] there may still be a tendency to underestimate the incidence of sepsis due to the explicit use of diagnosis by ICD coding.[44,45] Finally, the subjects are mainly Taiwanese which remains uncertain whether the findings in our studies can be apporpriate to other ethnic groups. More studies are also needed in patients from other ethnicities and districts to support our results.

Conclusion

Children who received appendectomy had a significantly greater risk of developing sepsis than those who did not undergo appendectomy, especially in children 6 years old or younger. Future research with metagenomic analysis of gut microbiota in children undergoing appendectomy is warranted to clarify the possible immunopathological mechanisms of these associations.

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Children With Appendectomy Have Increased Risk of Future Sepsis: Real-world Data in Taiwan is original. The authors hereby certify that none of the material in this manuscript has been or will be published and none is currently under consideration for publication elsewhere..

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Table 1. Baseline Characteristics of Children With and Without Appendectomy

	Appendectomy				*p*-value
	No		Yes		
	N = 57261		N = 57261		
	n	%	n	%	
Age (years)					0.001
≦6	5519	9.64	5519	9.64	
7−12	21637	37.8	21032	36.7	
13-18	30105	52.6	30710	53.6	
Mean (SD)	11.5	4.31	12.0	4.22	0.001
Sex					0.99
Girl	23076	40.3	23076	40.3	
Boy	34185	59.7	34185	59.7	
Urbanization level[†]					0.99
1 (highest)	15567	27.2	15567	27.2	
2	17074	29.8	17074	29.8	
3	10392	18.2	10392	18.2	
4 (lowest)	14228	24.9	14228	24.9	
Parental occupation					0.99
White collar	31283	54.6	31283	54.6	
Blue collar	18727	32.7	18727	32.7	
Others[‡]	7251	12.7	7251	12.7	

SD, standard deviation.

[†] The urbanization level was categorized into 4 levels by the population density of the residential

area: level 1 was the most urbanized region and level 4 was the least urbanized region.

‡ Other occupations included primarily retired, unemployed, and low-income populations.

Table 2. The Incidence and Risk Factors for Sepsis Among Children

	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[&] (95% CI)
Appendectomy					
No	159	495455	3.21	1.00	1.00
Yes	395	468160	8.44	2.63(2.19, 3.16)***	2.63(2.19, 3.16)***
Age (years)					
≦6	113	99654	11.3	2.71(2.13, 3.46)***	2.56(2.00, 3.27)***
7−12	153	363661	4.21	1.00	1.00
13-18	288	500300	5.76	1.36(1.12, 1.66)***	1.31(1.07, 1.59)**
Sex					
Girl	281	395556	7.10	1.48(1.26, 1.75)***	1.45(1.23, 1.72)***
Boy	273	568059	4.81	1.00	1.00
Urbanization level[†]					
1 (highest)	130	261817	4.97	1.00	1.00
2	150	287002	5.23	1.05(0.83, 1.33)	1.00(0.79,1 .27)
3	101	175513	5.75	1.16(0.89, 1.50)	1.11(0.85, 1.44)
4 (lowest)	173	239283	7.23	1.46(1.16, 1.83)**	1.31(1.03, 1.65)*
Parental occupation					
White collar	254	527098	4.82	1.00	1.00
Blue collar	193	327228	5.90	1.23(1.02, 1.48)*	1.17(0.96, 1.42)
Others[‡]	107	109289	9.79	2.00(1.60, 2.51)***	1.79(1.42, 2.26)***

CI, confidence interval; HR, hazard ratio; PY, person-years.

[#] Incidence rate per 10,000 person-years.

[†] The urbanization level was categorized into 4 levels by the population density of the residential

area: level 1 as the most urbanized region and level 4 as the least urbanized region.

‡ Other occupations included primarily retired, unemployed, and low-income populations.

& Multivariable analysis including age, sex, urbanization level, and parental occupation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Incidence and Hazard Ratio of Sepsis for Children With and Without Appendectomy by Age, Sex, Urbanization Level, Parental Occupation

	Appendectomy						Crude HR (95% CI)	Adjusted HR[&] (95% CI)
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]		
Age (years)								
≦6	22	51376	4.28	91	48278	18.9	4.24(2.66, 6.75)***	4.25(2.67, 6.77)***
7−12	46	188858	2.44	107	174803	6.12	2.51(1.78, 3.55)***	2.51(1.78, 3.55)***
13-18	91	255221	3.57	197	245089	8.04	2.29(1.79, 2.94)***	2.29(1.79, 2.94)***
Sex								
Girl	76	203216	3.74	205	192340	10.7	2.87(2.21, 3.74)***	2.87(2.21, 3.74)***
Boy	83	292239	2.84	190	275820	6.89	2.41(1.86, 3.12)***	2.51(1.94, 3.25)***
Urbanization level[†]								
1 (highest)	36	134456	2.68	94	127361	7.38	2.78(1.89, 4.08)***	2.78(1.89, 4.09)***
2	44	147491	2.98	106	139511	7.60	2.54(1.78, 3.61)***	2.60(1.83, 3.70)***
3	26	90289	2.88	75	85223	8.80	3.06(1.96, 4.78)***	3.12(2.00, 4.88)***
4 (lowest)	53	123219	4.30	120	11606	10.3	2.40(1.74, 3.32)***	2.46(1.78, 3.40)***

Parental occupation								
White collar	76	270763	2.81	178	256335	6.94	2.49(1.90, 3.26)***	2.53(1.93, 3.31)***
Blue collar	49	168287	2.91	144	158941	9.06	3.11(2.25, 4.31)***	3.15(2.28, 4.36)***
Others‡	34	56405	6.03	73	52884	13.8	2.26(1.50, 3.39)***	2.33(1.55, 3.50)***
Follow-up years								
<1	20	57197	3.50	112	57128	19.6	5.60(3.48, 9.02)***	5.64(3.50, 9.07)***
1-4	59	208675	2.83	138	202155	6.83	2.41(1.78, 3.27)***	2.41(1.78, 3.27)***
≧5	80	229583	3.48	145	208877	6.94	2.02(1.54, 2.66)***	2.02(1.53, 2.65)***

CI, confidence interval; HR, hazard ratio; PY, person-years;

Incidence rate per 10,000 person-years;

† The urbanization level was categorized into 4 levels by the population density of the residential area: level 1 as the most urbanized region and level 4 as the least urbanized region.

‡ Other occupations included primarily retired, unemployed, and low-income populations.

& Multivariable analysis including age, sex, urbanization level, and parental occupation;

* p <0.05, ** p <0.01, *** p <0.001.

Figure caption

Figure. Cummulative Incidence of Sepsis Between Children With and Without Appendectomy