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Comprehensive genomic analysis in sporadic early-onset colorectal adenocarcinoma patients

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Abstract

Background The incidence of colorectal cancer (CRC) in young adults has increased worldwide. Our study aimed to evaluate genomic alterations in early-onset (aged 15–39 years) sporadic CRC.

Methods Formalin-fixed, paraffin-embedded tissue samples from 90 patients with histologically confirmed colorectal adenocarcinoma with proficient mismatch repair status from Siriraj Hospital (Bangkok, Thailand) were extracted. Patients with clinically suspected familial adenomatous polyposis were excluded. A 517-gene mutational analysis was performed by next-generation sequencing using the Oncomine Comprehensive Assay Plus kit. The previously reported molecular data in adult-onset CRC from our group were used as a comparator group.

Results The five most frequently mutated genes were *APC (66%), TP53 (51%), KRAS (47%), ARID1A (31%), and KMT2B (31%)*. When compare with adult-onset, *NOTCH1 (11.1% vs. 1.9%), FBXW7 (23.3% vs. 14.8%), PIK3CA (20% vs. 12.1%), and FGFR3* (8.9% vs. 3.7%) mutations were more prevalent in early-onset. No differences were observed in other common mutations, such as *TP53, EGFR, KRAS, NRAS and BRAF* mutations. An increased prevalence in *KRAS* codon 12 mutations was also observed in early-onset patients compared to the adult-onset group (38.9% vs. 29.6%).

Conclusions Overall, the genomic landscape between early- and adult-onset CRC appears similar. However, our study revealed the enrichment of *NOTCH1, FBXW7, PIK3CA*, and *FGFR3* along with *KRAS G12* mutations, were more frequent in early-onset compared to adult-onset cases. Further studies with a larger cohort of patients on the comprehensive analysis of genetic/epigenetic signatures are required.

Keywords Genomic alterations, Molecular characteristic, Early onset, Adolescent and young adult, Colorectal cancer

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Background

Colorectal cancer (CRC) is the third most common cancer and is second in cancer mortality worldwide, contributing almost 1 million deaths in 2020 [1]. Most CRCs were diagnosed in people 65 years and older, while 13% were diagnosed in people 50 years or less. However, there has been a global increase in incidence CRC in early-onset patients, including countries in Asia, such as Taiwan, Korea, Japan, and Thailand, with age-standardized CRC incidence rates ranging from 5.4 to 12.9 per 100,000 [2–4]. Increased rates were observed in both sexes and organ sites. Although the precise etiology of the increased rates of CRC is not fully understood, several factors may contribute to the increase in incidence in younger people. These include the changes in dietary patterns to more processed foods, increased consumption of meat with less dietary fiber, increased prevalence of obesity, increased use of antibiotics in childhood that disrupt gut microbiota, and the evolving recommendations for the detection of CRC at an earlier age [5–10].

Several studies have evaluated the genetic landscape in early-onset patients with CRC, showing differences in tumor mutation burden, genomic instability, and enrichment in certain genetic mutations such as *MYCBP2, BRCA2, PHLPP1, TOPORS*, and *ATR*. However, these were conducted in western countries and included mainly Caucasian patients [11–13]. It is still unclear whether young Asian CRC patients have a distinct genetic landscape compared to patients older than 50 years. Therefore, this study was conducted to investigate genomic alterations in adolescent and young adult (AYA)-onset CRC patients (age 15–39 years) to determine if there are mutational differences compared to adult patients with CRC.

Methods

Patient selection

This study included consecutive cases early-onset CRC patients with histologically confirmed diagnoses of colorectal adenocarcinoma at Siriraj Hospital between January 1, 2008 to December 31, 2017. The details of the early-onset cohort were described separately in the previous study [14]. Inclusion criteria included (i) age at diagnosis between 15 and 39 years, (ii) available formalin-fixed paraffin-embedded (FFPE) tumor samples for DNA sequencing, and (iii) confirmed proficient mismatch repair protein by the immunohistochemical test. Patients with confirmed or clinically suspected familial adenomatous polyposis were excluded. The study protocol was approved by the Siriraj Institutional Review Board of the Siriraj Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand (EC1 No. 515/2561, Si 538/2018).

A previous cohort of 108 patients with stage II-III adult-onset colon cancer from our group was also included as a comparator to the early-onset group, along with additional cases of colorectal cancer from the Cancer Genome Atlas (TCGA) database [15]. The details of the adult-onset colon cancer cohort were described separately in the previous study [16].

Determination of gene mutations

DNA was extracted from FFPE tissue using an automated DNA extraction platform (Chemagic™ MSM I Instrument, PerkinElmer, Inc., Waltham, MA, USA). The targeted sequencing of DNA samples was done using a next generation sequencing (NGS) platform with the 517-gene Oncomine Comprehensive Assay Plus panel (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Variant calling and annotation were performed using Torrent Suite software v5.6 (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Only variants with allele fraction of 5% or more were included, and variants present in the gnomAD database v2.1.1 were excluded. Suspected variants were subsequently assessed for pathogenicity using the Ensembl Variant Effect Predictor (VEP) version 109.3 [17]. Only variants with VEP-predicted high and moderate severity were included. To facilitate comparison with our previously reported work [16], a filtered set of 22 genes was also used, including *EGFR, ALK, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, MET, DDR2, KRAS, PIK3CA, BRAF, AKT1, PTEN, NRAS, MAP2K1, STK11, NOTCH1, CTNNB1, SMAD4, FBXW7* and *TP53*.

Statistical analysis

Patient characteristics and gene mutation frequencies were described using descriptive statistics. Categorical variables were presented as number and percentage, while continuous variables were reported as mean or median and associated ranges. Pearson's chi-square test was used to evaluate the difference between gene prevalence between early-onset and adult-onset cases. P-value adjustments with Benjamini-Hochberg correction were performed for multiple testing. Statistical calculations were performed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA) and R version 4.3.2 (Vienna, Austria). *P*-values less than 0.05 were considered statistically significant.

Results

Patient characteristics

The clinicopathological characteristics of 98 patients with early-onset CRC were described in the previously reported study [14]. Eight of the patients did not have adequate tumor tissue, leaving a total of 90 patients for genomic analysis. Table 1 represents the baseline characteristics of patients with early-onset CRC included in this study. Most of the patients were diagnosed with stage

Table 1 Patient baseline characteristics

Variables	Early-onset CRC	
	Number	%
Number of patients	90	100
Median age (years, range)	35 (21–39)	
Sex	48	53.3
Female	42	46.7
Male		
Site	12	13.3
Ascending	7	7.8
Transverse	11	12.2
Descending	24	26.7
Sigmoid	35	38.9
Rectum	1	1.1
Synchronous		
Sidedness	19	21.1
Right-sided	71	78.9
Left-sided		
Stage at diagnosis	3	3.3
I	17	18.9
II	42	46.7
III	28	31.1
IV		
Histology	85	94.4
Adenocarcinoma	5	5.6
Mucinous		
Differentiation	2	2.2
Well	79	87.8
Moderately	8	8.9
Poorly	1	1.1
No data		
LVI	51	56.7
No	35	38.9
Yes	4	4.4
No data		
PNI	38	42.2
No	46	51.1
Yes	6	6.7
No data		

Abbreviations CRC, colorectal cancer; LVI, lymphovascular invasion; PNI, perineural invasion

III-IV disease (78%) and had primary tumor sites in the rectosigmoid area (66%).

Genetic alterations in sporadic early-onset CRC

Using the full panel of 517 genes, the top 25 genomic alterations were exhibited in Fig. 1 that show the mutations in *APC, TP53, KRAS, ARID1A*, and *KMT2B* as the top five genes. To compare the prevalence of mutations in the early-onset group with the adult-onset group [16], a focused analysis on 22 genes which used in adult-onset cohort was performed and illustrated in Supplement Fig. 1. The most frequent gene mutations included *TP53* (51%), *KRAS* (47%), *FBXW7* (23%), *PIK3CA* (20%), and *SMAD4* (13%) genes. *FBXW7, PIK3CA, FGFR3, ERBB2* and *PTEN* mutations were more commonly found in cases of early-onset than in adult-onset, but this did not reach statistical significance. Only *NOTCH1* was significantly more prevalent ($P=0.016$). No differences were observed in other common mutations, such as *TP53, KRAS, NRAS, and BRAF* mutations between the two groups (Fig. 2; Table 2). When comparing our cohort with the TCGA dataset, increased frequencies of mutations *FBXW7, FGFR3* and *NOTCH1* were observed, while *NRAS, BRAF*, and *ERBB4* mutations were less seen (Fig. 2).

Further exploring of *KRAS* mutations, we observed a significantly higher prevalence in codon 12 mutations in the early-onset cohort compared to metastatic CRC patients in the TCGA cohort (38.9% vs. 28.1%, $p=0.041$), but not for *KRAS* codons 13 and 146 (Fig. 3). Among those with *KRAS* mutations, *KRAS* G12D was the most common variant in the early-onset cohort, being present in 24 patients (26.7%). The number of patients with each *KRAS* mutation is shown in Table 3. Notably, no uncommon mutations, such as codons 59, 61, or 117, were found in the early-onset group (Fig. 3).

Discussion

Our study is one of the few studies to describe the genetic landscape in early-onset sporadic CRC. Overall, the genomic landscape between early and adult-onset CRC appears similar; however, we identified mutation enrichment in several genes, including *NOTCH1,FBXW7,PIK3CA*, and *FGFR3* in patients compared to cases with adult-onset and those of the TCGA data set.

CRC under the age of 50 is a problem that is increasing worldwide. Changes in the diet, physical activity, microbiome, or environmental toxic exposures have been proposed to be implicated as possible causes [10, 18, 19]. Approximately 20% of patients with early-onset CRC can be attributed to identifiable germline mutations in genes that cause familial cancer syndromes, including familial adenomatous polyposis and Lynch syndrome, however, about 80% of early-onset CRCs are sporadic cases. A variety of other genetic/epigenetic alterations have also been reported. Evidence suggests that CRC in the early-onset group may have a different molecular etiology than CRC diagnosed in older adults and may be more refractory to some treatment regimens than the adult-onset group [20, 21]. However, knowledge regarding the molecular features of sporadic early-onset CRC is limited, with few studies evaluating the genomic differences in this patient population.

In 2019, Lieu CH et al. [21] reported the comprehensive genomic landscape in early and later-onset CRC in 18,218 patients using a targeted NGS assay in 403 cancer-related genes. In the early-onset group (<40 years old) with microsatellite stable tumors, *TP53* (82%), *APC* (66%) and *KRAS* (46%) were the most common gene mutations. More recently, in a study, Busico A, et al. [22] reported

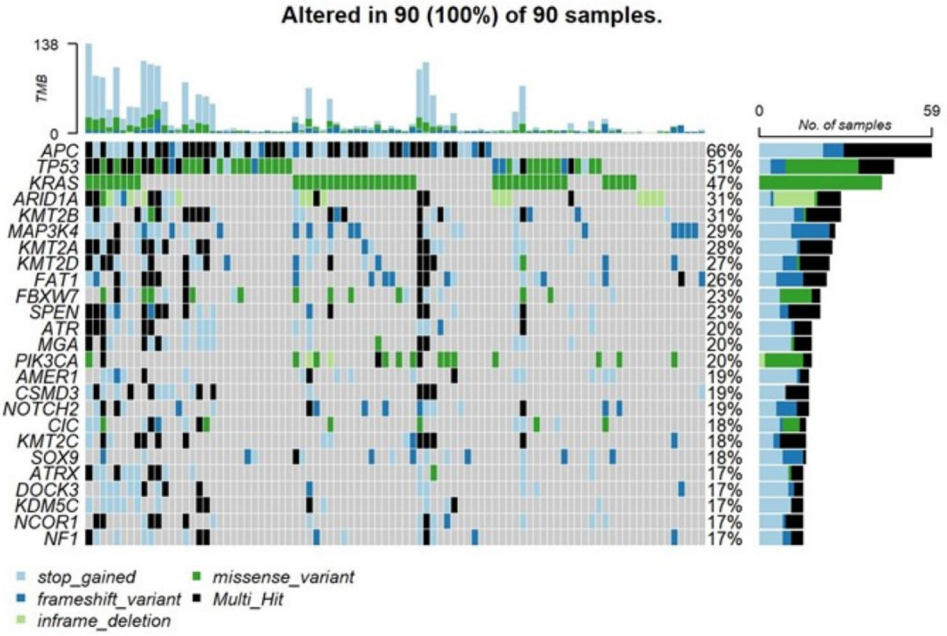

Fig. 1 Oncoplot of the top 25 genes from early-onset CRC using the comprehensive genomic

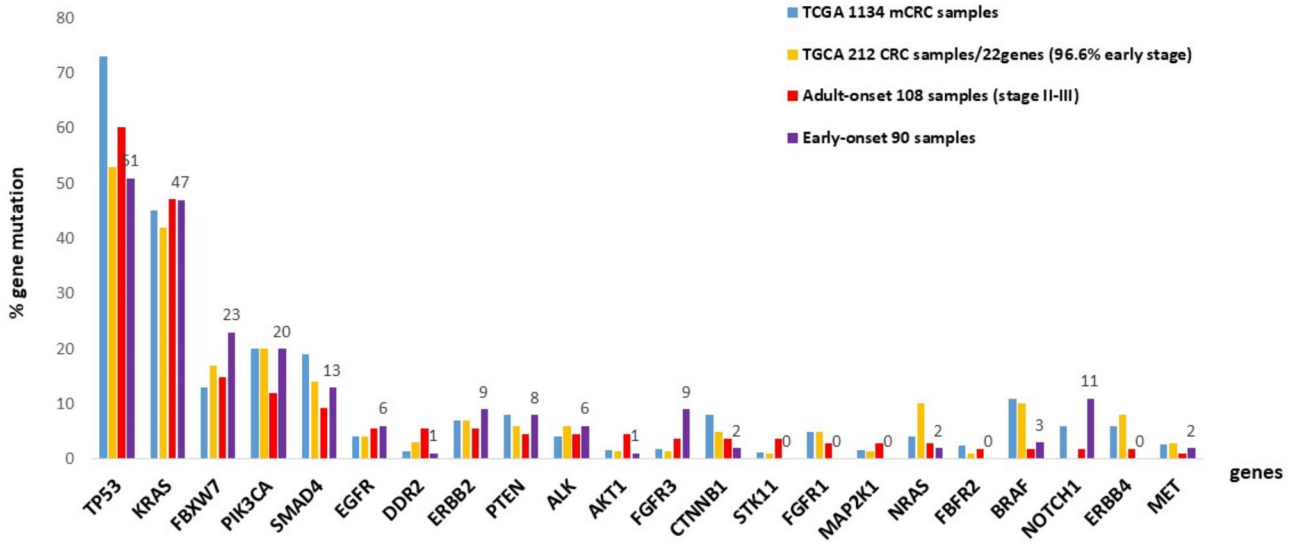

Fig. 2 Gene mutation frequencies from TCGA, adult-onset stage II-III colon cancer patients, and early-onset CRC patients

the genomic landscape of early-onset CRC, specifically focusing on pediatric (PED, 9–19 years) and young adult (YA, 20–39 years) patients, compared to adult (AD, > 60 years) CRC using a targeted NGS assay in 500 cancer-related genes. In young adult CRC, the most frequent alterations were observed in *TP53* (77%), *APC* (50%), *KRAS* (40%), *FAT1* (27%) and *SMAD4* (23%).

Similar to our study, mutations in *APC* (66%), *TP53* (51%), and *KRAS* (47%) were the most common gene mutations in early-onset group. The mutation frequency in *FAT 1 (26%)* and *SMAD4* (13%) in our study also had a similar to that reported by Busino and colleagues. Interestingly, our study demonstrated a high frequency of *ARID1A* and *KMT2B* mutations (31% each) mutations which represents the fourth and fifth most commonly mutated genes, while Busino reported only 20% in both genes.

The AT-rich interaction domain 1 A gene (ARID1A) is commonly mutated in many types of cancer and is classified as a tumor suppressor gene. Deleterious variations of *ARID1A* have been recognized to be correlated with tumorigenesis and with a poor prognosis of CRC. The rate of *ARID1A* variation in CRC cases is diverse in different studies, ranging from 3.6 to 66.7% and is

Table 2 Gene mutation frequencies between the early-onset and adult-onset CRC cases

Genes	% Mutation frequency in early-onset ($n=90$)	% Mutation frequency in adult-onset cases ($n=108$)	*P*-value
TP53	51.1	60.2	0.26
KRAS	46.7	47.2	1.00
FBXW7	23.3	14.8	0.18
PIK3CA	20.0	12.1	0.18
SMAD4	13.3	9.3	0.50
NOTCH1	11.1	1.9	0.016*
FGFR3	8.9	3.7	0.22
ERBB2	8.9	5.6	0.53
PTEN	7.8	4.6	0.53
ALK	5.6	4.6	1.00
BRAF	3.3	1.9	0.84
NRAS	2.2	2.8	1.00
MET	2.2	0.9	0.26

Table 3 Prevalence of *KRAS* mutations

	Number ($n=90$)	%
KRAS		
Wild-type	48	53.3
Mutant	42	46.7
G12 mutation	35	38.9
G12A	1	
G12C	3	
G12D	24	
G12R	1	
G12S	1	
G12V	5	
G13 mutation	3	3.3
G13D	2	
G13V	1	
A146 mutation	4	4.4
A146T	4	

associated with medullary histology, *BRAF V600E* mutation, and microsatellite instability tumors. The variation of the ARID1A variation was associated with the cooccurrence variation of *TP53* and some other genes (i.e., *APC, FBXW7, PIK3CA and KRAS*) and the regulation of signaling pathways (i.e., Akt signaling and WNT signaling) [23]. This might be explaining the high rate of *ARID1A* mutation in our study.

When comparing early-onset and adult-onset CRC, Lieu CH et al. [21] reported that gene alteration rates in the younger and older microsatellite stable cohorts were largely similar for the majority of genes analyzed. However, alterations in *TP53* and *CTNNB1* were more common in the early-onset group, while variants *APC, KRAS, BRAF,PIK3CA* and *FAM123B* were more frequent in the older-onset group. Our study also demonstrated a similar rate of gene mutations between early-onset and adult-onset CRC, including *TP53, KRAS, NRAS*, and *BRAF*. However, our study identified *NOTCH1* (11% vs. 2%), *FBXW7* (23% vs. 15%), *PIK3CA* (20% vs. 12%), and *FGFR3* (9% vs. 4%) were commonly found in early-onset CRC compared to adult-onset CRC.

Some studies indicate that *KRAS* mutation is more common among patients with early- onset CRC [21], while other studies suggest that the incidence of *KRAS* mutations is lower among the younger population [19]. More recent studies demonstrated similar rates of *KRAS* mutations among patients with early-onset and adult-onset CRC [22]. Despite a similar prevalence of *KRAS* mutations regardless of the age of diagnosis, our study demonstrated that *KRAS G12* mutations were more frequent (almost 40%) in early-onset patients.

NOTCH1 (neurogenic locus notch homolog protein 1) is one of the four genes (*NOTCH1-4*) encoded for the transmembrane glycoprotein involved in the epithelial-mesenchymal transition (EMT) in cancer cells [24]. Notch1 signaling activation was associated with consensus molecular subtype (CMS) 4 [25]. As CMS4 was known to confer a higher probability of distant metastasis, increased resistance to treatment, and poorer survival, an enrichment of *NOTCH1* mutations in cases of

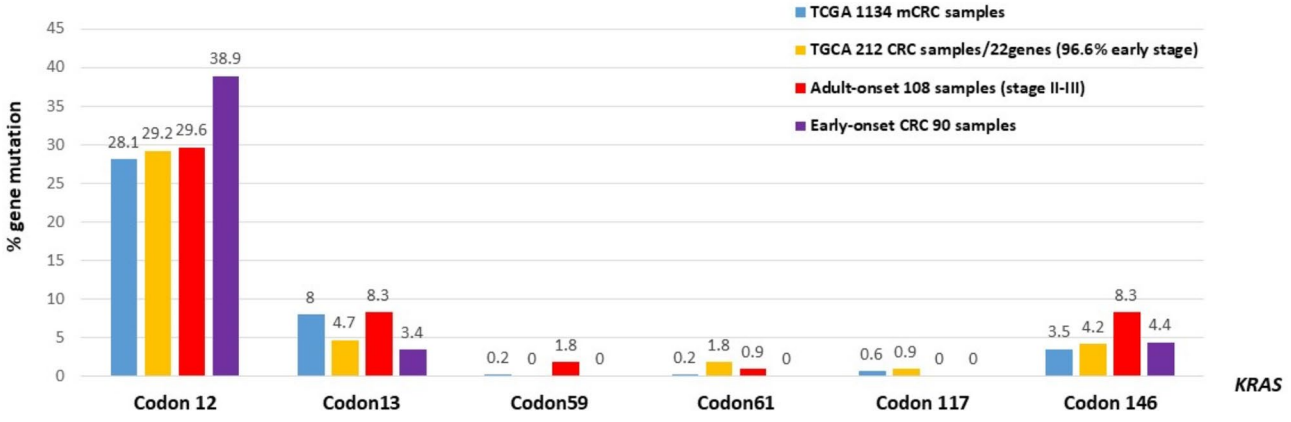

Fig. 3 Prevalence of *KRAS* gene mutations

early-onset may suggest a more aggressive nature of the disease and may explain the onset of cancer at an early age [26].

FBXW7 (F-box and WD repeat domain containing 7) is a tumor suppressor gene that transcribes a component of the E3 ubiquitin ligase complex. Mutations in *FBXW7* result in impaired protein degradation in several cellular pathways, including mitogen-activated protein kinase (MAPK), PI3K-Akt-mTOR, and Notch signaling, which ultimately leads to cancer proliferation [27]. The low expression of FBXW7 increased cell migration and stem-like properties through the accumulation of NOTCH1 in cholangiocarcinoma [28]. Inhibition of *FBXW7* also resulted in activation of the mTOR pathway, resulting in angiogenesis, tumorigenesis, and cancer metastasis [29]. Furthermore, *FBXW7* alterations were reported to be associated with immunotherapy resistance [27]. Our study showed an increased prevalence of the *FBXW7* mutation in the early-onset population (23.3%) which is a similar rate to previously reported studies [11, 30]. These data may suggest the possibility of higher resistance to treatment in younger adults [15, 31, 32].

Despite considerable efforts by multiple groups to investigate genomic mutation landscape of patients compared to adult patients, it has been difficult to find actionable data from these analyzes of somatic mutations that could help to understand the pathogenesis or guide the treatment of patients with early-onset CRC. We suggest that further study in multi-omics analysis including epigenome, transcriptome, proteome, metabolome, and microbiome might be further next step for more understanding in biological mechanism and a deeper exploration of some candidate genes.

It is worth noting that our study has some limitations. First, the limited number of included patients can result in inadequate power to detect statistical significance for associations and differences. Second, data comparison with adult-onset cohort was limited to 22 genes and may miss other clinically significant genomic alterations. Lastly, our study did not consider gene mutations, fusions, and copy number variants outside the genes listed in our sequencing panel. However, our study is one of the few studies that specifically focuses only on early-onset sporadic CRC, which could exclude the potential bias of genomic data in inherited subtypes.

Conclusions

In general, the genomic landscape between early- and older-onset CRC appears similar. However, our study revealed the enrichment of *FBXW7,NOTCH1*, and *FGFR3* mutations in early-onset sporadic CRC patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13745-5.

Supplementary Material 1: Oncoplot of the 22 genes selected from early-onset CRC

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Author contributions

All authors helped to perform the research; B.P. collected the data, analyzed the data and drafted the manuscript; P.S. analyzed the data, reviewed and edited manuscript; E.R. co-supervised the field activities, performed genome sequencing, reviewed and edited manuscript; A.P. co-supervised the field activities, prepared specimens, reviewed and edited manuscript; C.A. collected the data, reviewed and edited manuscript; M.P. co-supervised the field activities, obtained research funding, reviewed and edited manuscript; K.K. designed the study, supervised the study, obtained research funding, collected the data, reviewed and edited the manuscript, and approved the final version.

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Data availability

The data sets generated and/or analyzed during the current study are not publicly available due to confidential patient information and institutional policy, but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was adhered to the Helsinki Declaration and approved by the Siriraj Institutional Review Board of the Siriraj Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand (EC1 No. 515/2561, Si 538/2018). This study is a retrospective study and does not have adverse effects on the rights and health of the participants, so the requirement of informed consent is waived. At the same time, patients' privacy and personal identity information are protected. The preparation of the article was followed in accordance with the STROBE guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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