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Peer Review Articles

PDF

Solutions to improve the efficient learning of political theory subjects for students at Tay Nguyen University

Pham Phuong Anh, Nguyen Minh Hai, Truong Van Thuy, Nguyen Thien Tin

791-807

DOI : 10.53730/ijhs.v6nS5.8758

PDF

Variation of histopathological features in colonic mucosal biopsy with clinical diagnosis of suspicious inflammatory bowel disease in Dr. Soetomo General Academic Hospital, Surabaya period 2015 - 2019

Ariadna Anggi Pasang, Alphania Rahniayu, **Anny** Setijo Rahaju

808-818

DOI : 10.53730/ijhs.v6nS5.8759

PDF

A comparative study in acute pancreatitis to find out the effectiveness of early addition of ulinastatin to current standard care in Indian subjects

Jenit P. Gandhi, Rakesh Jasani, Honeypalsinh H. Maharaul, Kunjan P. Shah, Pratik Shaparia

819-832

DOI : 10.53730/ijhs.v6nS5.8763

PDF

Denoising and contrast enhancement of normal eye images and slit lamp images of cataract using optimized deep learning model

Binju Saju, Rajesh R

833-852

DOI : 10.53730/ijhs.v6nS5.8764

PDF

Role of non operative management of extradural hematoma and reasons for conversion in patients admitted in tertiary care hospital in Bihar

Sumeet Kumar, Siddharth Kumar Singh, Santosh Kumar Nayan, Samarendra Kumar Singh

853-862

DOI : 10.53730/ijhs.v6nS5.8770

PDF

Impact of pregnancy induced hypertension upon maternal risk during second and third trimester

A follow-up study

Zainab Yaseen Majeed, Nuha Adel Ibrahim

863-871

DOI : 10.53730/ijhs.v6nS5.8837

PDF

The protective role of almond and thyme in carbonated beverage-induced osteoporosis in male albino rats

Mustafa Adnan Zeyadi, Fares K. Khalifa

880-890

DOI : 10.53730/ijhs.v6nS5.8776

PDF

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Variation of histopathological features in colonic mucosal biopsy with clinical diagnosis of suspicious inflammatory bowel disease in Dr. Soetomo General Academic Hospital, Surabaya period 2015 - 2019

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Abstract---Inflammatory bowel diseases (IBDs) are chronic inflammatory diseases that often relapse and divided into two types, Crohn's disease (CD) and ulcerative colitis (UC). Histopathological findings in colonic mucosal biopsy with clinical diagnosis suspicious IBD can vary and overlap. Therefore, criteria and guidelines have been created to improve the diagnostic accuracy. This descriptive observational study was performed retrospectively with cross sectional approach. 122 samples of colonic mucosal biopsies with clinical diagnosis of suspicious IBD were retrieved from histopathological archives in the Anatomical Pathology Laboratorium of Dr. Soetomo Hospital, Surabaya during period 1st January 2015 - 31st December 2019. The most common histopathological feature found in colonic mucosal biopsies with clinical diagnosis of suspicious IBD was crypt distortion (97/79.50% samples), and the least was irregularity of surface epithelium (30/24.59% samples). 10 of 122 samples was concordant with the final diagnosis of IBD. Knowledges regarding the variations of histopathological features in colonic mucosal biopsy specimens with clinical diagnosis of suspicious IBD, can improve the diagnostic accuracy.

Keywords---IBD, colonic biopsy histopathological, suspicious inflammatory.

Introduction

Colitis is an inflammation in colonic mucosa that can occur either acutely or chronically, which caused by infection, inflammation, ischemic, drugs, or other idiopathic diseases (Nielson & Seidelin, 2012; Puspitarini & Prijambodo, 2022). Inflammatory bowel diseases are the most common of chronic colitis that often relapse, can involve any segment of gastrointestinal tract and divided into two types, CD and UC (Villanacci et al., 2021; Fatimah et al., 2021). The incidence of IBD in Asia has increased significantly in the last two decades, ranged between 4.2 and 3.1 per 100,000 population (Ng et al., 2016; Simadibrata & Adiwinata, 2017).

The criteria and guidelines have been created to improve the diagnostic accuracy of IBD when the colonic biopsy was used as the initial surveillance in patients with the chief complaint of diarrhea. Histopathological diagnosis of IBD established based on combination of microscopic findings and clinical history which include patient's age, symptoms, duration of symptoms, and colonoscopy results (Lang-Schwarz et al., 2021).

Chronic colitis, in this case is IBD, determined histopatologically from presence of chronicity features, as follows: crypt distortion, crypt atrophy, chronic inflammation, basal lymphoplasmacytosis, granulomas, and paneth cell metaplasia (Feakins, 2013). The histopathological features in biopsy samples can vary and overlap. Therefore, the completes of clinical information and examination history are important to make the correct diagnosis and plan the effective therapeutic options (Villanacci et al., 2021; Kalishah et al., 2022).

Crohn's disease and ulcerative colitis differ from each other in aspects of epidemiology, clinical presentation, endoscopy, and histopathology features as well as the complication and management. The correct pathological approach and adequate biopsy samples can also contribute to classify the CD and UC (Villanacci et al., 2021).

At this time, studies about variation of histopathological features in colonic mucosal biopsy with clinical diagnosis of IBD are still limited. This study describes variation of histopathological features in colonic mucosal biopsy specimen with clinical diagnosis of IBD.

Materials and Methods

This research descriptive observational study had been performed with a cross sectional approach, using histopathological archives from colonic mucosal biopsy specimen with clinical diagnosis suspicious of IBD in the Anatomical Pathology Laboratory of Dr. Soetomo Hospital Surabaya during the period from 1st January 2015 - 31st December 2019, which had endoscopy results and had not received the previous IBD therapies. The slides were reviewed by two pathologists to

evaluate histopathological features of IBD (basal lymphoplasmacytosis, crypt distortion, transmucosal lymphoplasmacytic, crypt atrophy, mucin depletion, irregularity of surface epithelium), and presented as frequency distribution in table. This study had been approved by the Committee of Health Research Ethic at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (0915/LOE/301.4.2/V/2021).

Results and Discussions

There were 122 samples of colonic mucosal biopsy with clinical diagnosis of suspicious IBD. Most samples in this study were aged between 51 – 60 years with mean age was 43.23 years. Most samples were male (76 samples, 62.29%).

Based on the slide review, we found the variation of histopatological features in colonic mucosal biopsy, as follows: crypt distortion (97/122 samples, 79.50%), lymphoid aggregates (87/122 samples, 71.31%), transmucosal lymphoplasmacytic (45/122 samples, 36.88%), crypt atrophy (37/122 samples, 30.32%), mucin depletion (36 samples, 29.50%), basal lymphoplasmacytosis (32/122 samples, 26.22%), and irregularity of mucosal surface epithelium (30/122 samples, 24.59%) (Table 1). The variation of histopathological features in colonic mucosa biopsy with clinical diagnosis of IBD, is depicted in Figure 1. We did not find granuloma feature in this study samples. We also could not assess the Paneth cells metaplasia in this study due to lack of information about where the location of biopsy samples was taken, whether from the left or right side of colon.

There were 2/122 samples (1.63%) each for amebic colitis, eosinophilic colitis, and amyloidosis (Figure 2A, B, C). Congo-red stain was performed for definitive diagnosis of amyloidosis (Figure 2D). There was 1/122 sample (0.81%) with histopathological features of chronic colitis with mild dysplasia (Figure 2E). There were 13/122 samples (10.65%) with interpretation of non-specific colitis because from the microscopic features, only obtained the lymphoid aggregates and erosion of the surface epithelium, but there are no chronicity features. There were 7/122 samples (5.73%) with non-diagnostic because from the microscopic feature, there was no muscularis mucosae.

Based on the medical record from Internal Medicine Department, there were 10/122 (8.19%) samples that had final diagnosis with IBD, 9 samples with UC and 1 sample with CD. All the samples showed the chronicity features that supported to IBD diganosis (Table 2).

Table 1
Variation of histopathological features in colonic mucosa biopsy with clinical diagnosis of IBD

Variation of histopathological features	Number of cases from 122 samples	Percentages
Crypt distortion	97	79.50%
Lymphoid aggregates	87	71.31%
Transmucosal lymphoplasmacytic	45	36.88%

Crypy atrophy	37	30.32%
Mucin depletion	36	29.50%
Basal lymphoplasmacytosis	32	26.22%
Irregularity of surface epithelium	30	24.59%

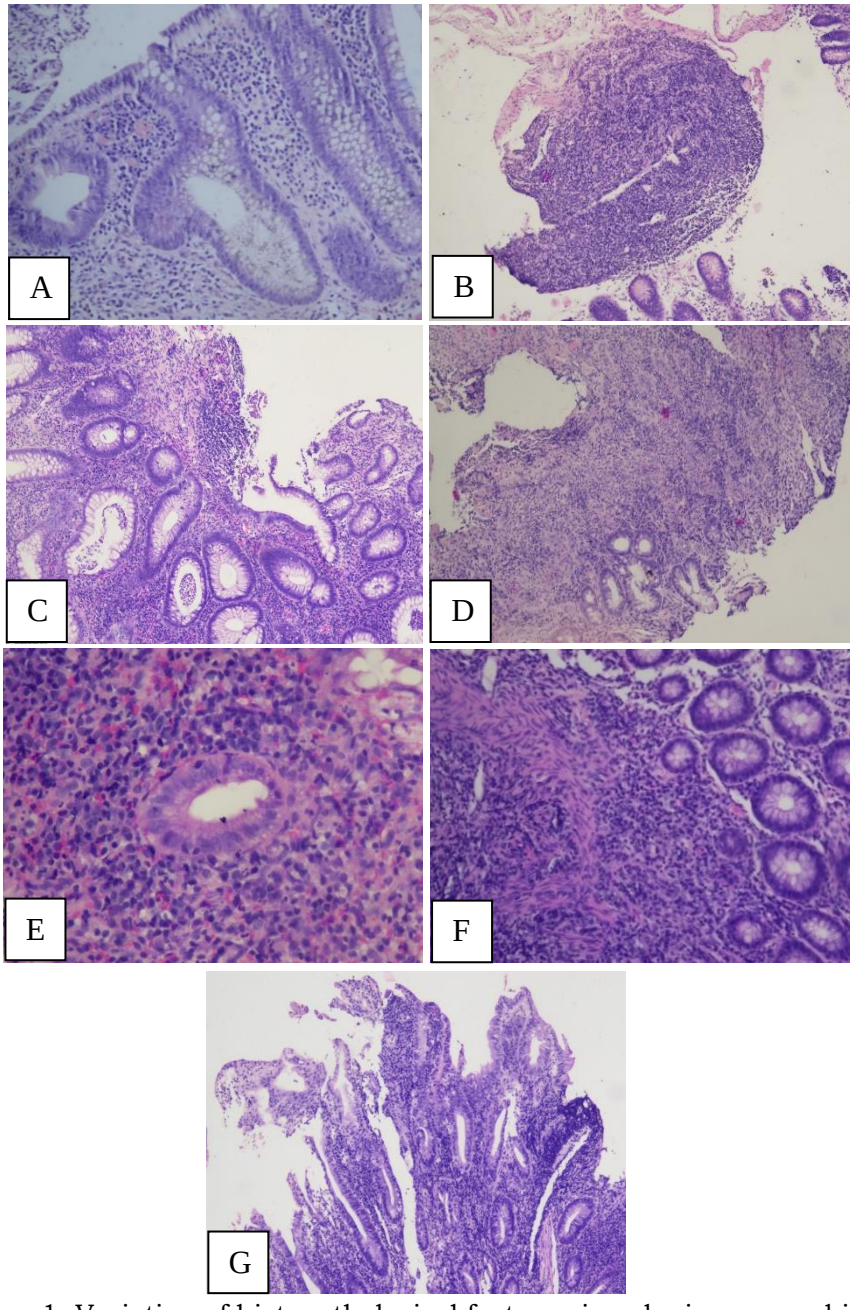

Figure 1. Variation of histopathological features in colonic mucosa biopsy with clinical diagnosis of IBD. (A) Crypt distortion (HE, 200x). (B) Lymphoid aggregates (HE, 100x). (C) Transmucosal lymphoplasmacytic (HE, 100x). (D) Crypt atrophy (HE, 100x). (E) Mucin depletion (HE, 100x). (F) Basal lymphoplasmacytosis (HE, 200x). (G) Irregularity of surface epithelium (arrow) (HE, 400x).

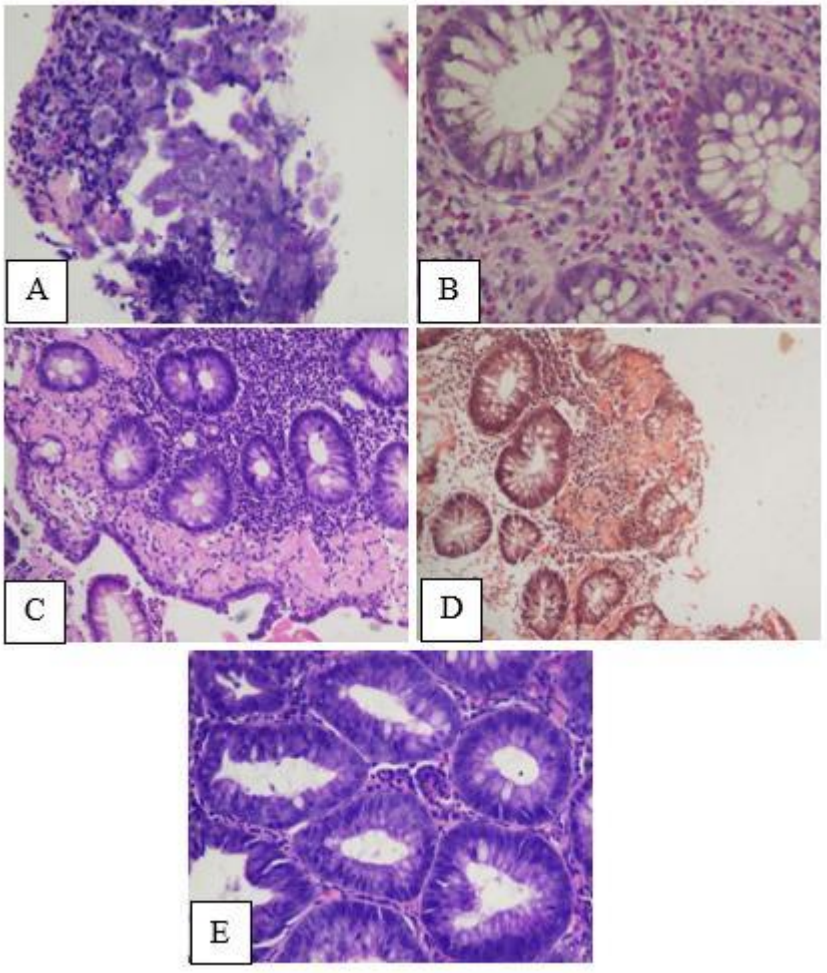

Figure 2. (A) Amebic colitis (HE, 400x). (B) Eosinophilic colitis (HE, 400x). (C) Amyloidosis (HE, 200x). (D) Congo-red is positive in amyloid deposits (Congo-red, 200x). (D) Chronic colitis with mild dysplasia (HE, 400x).

Table 2
Final diagnosis vs morphology finding parameter

Final diagnosis	Morphology finding parameter						
	Trans mucosal lympho plasma cytic	Crypt distort ion	Crypt atro phy	Basal lympho plasma cytosis	Irregula rity of surface epitheliu m	Lym phoid aggre gate	Mucin depletio n
Ulcerative colitis	✓	✓	✓	✓	✓		✓
Ulcerative colitis	✓	✓	✓		✓	✓	

Ulcerative colitis	✓	✓	✓	✓	✓	✓	
Ulcerative colitis	✓	✓	✓	✓	✓	✓	✓
Ulcerative colitis	✓	✓		✓		✓	
Ulcerative colitis	✓	✓	✓	✓	✓	✓	✓
Ulcerative colitis	✓	✓	✓		✓	✓	✓
Ulcerative colitis	✓	✓	✓	✓	✓	✓	
Ulcerative colitis	✓	✓	✓	✓	✓		✓
Crohn's disease	✓	✓	✓	✓		✓	✓

Most cases were 51 – 60 years old, with male predominance (76/62.29% samples). Ulcerative colitis tends to occur in adolescent and young adult, although there is a second incidence peak among middle-aged men. In CD, most patients are diagnosed in second to fourth decades of life, with incidence peak between 20 and 30 years (Odze & Goldblum, 2015). Ulcerative colitis in Asia is usually found between ages of 35 – 45 years, and CD is diagnosed at a younger age than UC (Ng, 2014). However, about 10 -15% of IBD cases can be found at the age of > 60 years. The incidence peak of a bimodal age for IBD, occurs between ages of 50 – 70 years (Val, 2011). The incidence of CD in Asia is generally more common in male, and gender distribution in UC is equal. The lifestyle factors, such as smoking, a high-fat and low-fiber dietary and enviromental sanitation problems, are the several factors that can increase the risk of IBD (Alatab et al., 2020).

Study from Gajendran et al. in 2019 reported that IBD diagnosis shows 2 or 3 from 4 microscopic changes, such as crypt distortion, decreased crypt density, irregularity mucosal surface, and diffuse transmucosal inflammation (Gajendran et al., 2019). A strong indicator for IBD diagnosis is focal or diffuse of basal lymphoplasmacytosis (Geboes & Van Eyken, 2009). Basal lymphoplasmacytosis is one of the earliest of histopathological features of IBD and has a high predictive value compared with other non-IBD colitides (Canavese et al., 2017). Crypt distortion was the most common histopathological finding in this study (97/79.50% samples). Study by Surawicz and Belic reported that crypt distortion is also one of the characteristics of IBD besides basal lymphoplasmacytosis (Surawicz & Belic, 1984). Various studies showed distorted architectural crypt in UC could occur ranging from 57% to 100% cases (Dhakhwa et al., 2016).

Lymphoid aggregates can be one of the histology indicators for IBD, especially CD (Villanacci et al., 2020; Avisiena et al., 2019). Some of studies revealed that lymphoid aggregates also can be seen in normal colon (Assarzadegan et al., 2017). No granuloma was found in all study samples. Study by Turner et al. showed that only 9% from 10,000 patients with CD had non-necrotizing epithelioid granuloma appearance. Colonic biopsy specimens tend to involve only the mucosa, occasinonally part of the muscularis mucosa, but rarely from the underlying submucosa. Therefore, biopsy specimen-based would almost never find granulomas located below the muscularis mucosa (Turner et al., 2014). The metaplasia of Paneth cells could not be assessed in this study because there was no information about where the location of biopsy samples was taken. Paneth cells are normal component located at the base of the crypt in small intestine and proximal colonic mucosa. The Paneth cells in the distal colon are a metaplastic adaptation to chronic mucosa damage (Feakins, 2013).

Diagnostic uncertainty is commonly found for IBD or to distinguish UC and CD. This is caused by many factors, such as therapy, disease severity, and experience of clinicians and pathologists in patient management, that can disrupt the correct diagnosis. Pathologists often did not get the sufficient information about patient's clinical and endoscopy result. The final diagnosis can only be made if the overall supporting clinical information is obtained (Jenkins et al., 1997; Farmer et al., 2000).

The adequate of taking biopsy samples from endoscopic sampling is also can increase the correct diagnosis of IBD. Optimal sampling for newly diagnosed IBD needs at least two biopsy samples in the terminal ileum and in each segment of the colonic sites. The specimens are separated according to the sampling location and provides information, as follows: terminal ileum (bottle 1), ascending and tranverse colon (bottle 2), descending and sigmoid colon (bottle 3), and rectum (bottle 4) (Villanacci et al., 2021).

The term of non-specific colitis refers to inflammation in colon that microscopically does not have characteristic features of any specific form of colitis and usually found in pathology report from colonoscopy biopsy. This term is used for colonic inflammation that does not have specific pathological features from common cause of colitis (Emara et al., 2019). In this study, the samples with the lymphoid aggregate features and erosion on the surface epithelium were included into the non-specific colitis interpretation.

There were 2 samples each for amoebiasis, eosinophilic colitis, and amyloidosis. Chronic inflammation and crypt architectural changes were also found in amoebiasis cases in this study. Study by Singh et al. revealed that architectural changes and chronic inflammation could also be found in amebic colitis as in IBD, but the architectural changes and inflammation in amebic colitis were only mild or moderate (Singh et al., 2015). Diagnostic histopatologically of eosinophilic colitis is determined by the existence of eosinophil clusters in lamina propria (> 60 eosinophils/ 10 HPFs), eosinophilic cryptitis, crypt abscess, and crypt distortion can be found as well (Bates, 2012; Walker et al., 2019). Amyloidosis is a disease that has the similar pathogenesis with other unrelated diseases, wherein all the insoluble fibrillar proteins converge in the extracellular tissue of various organs and cause the organ dysfunction. Amyloidosis consists of primary and secondary amyloidosis. The secondary amyloidosis is caused by extracellular deposition of fibrils from serum amyloid A (SAA) protein. The secondary amyloidosis can also occur in IBD and shows the uncontrolled and persistent of inflammation activity. Amyloidosis occurs approximately 0.9% in CD and 0.7% in UC. The reason why CD is more prone to have complication of amyloidosis than UC is not known but may be related to degree of systemic inflammation that is higher in CD than UC, especially in association with abscesses and fistulae (Sattianayagam et al., 2009). The serum concentrations in acute phase proteins, C-reative protein dan SAA protein, are also higher in CD than UC (Saverymuttu et al., 1986). In this study, 1 case of amyloidosis was found in patient with a history of SLE.

The histopatological features of chronic colitis with mild dysplasia also obtained in this study. Patients with long-standing IBD have an increased risk for

colorectal cancer. Dyplasia is the best marker for increased risk of malignancy. The identification and grading of dysplasia are the basis for the management of IBD (Villanacci et al., 2021).

Non-diagnostic interpretation was found in 7 samples because from the microscopic feature there was no muscularis mucosae. Ideal mucosa samples that are obtained from colonoscopy consist of mucosa and slight of superficial submucosa (Montgomery et al., 2012). Optimal assessment can be obtained if the biopsy specimens contain of all the full thickness of mucosa and muscularis mucosae (Jenkins et al., 1997). If there is no muscularis mucosae, we also cannot assess the basal lymphoplasmacytosis because it is located between the base of crypt and muscularis mucosae, and basal lymphoplasmacytosis is a strong indicator for IBD diagnosis (Geboes & Van Eyken, 2009).

There were 10/122 samples that had final diagnosis with IBD, 9 samples with UC and 1 sample with CD. The final diagnosis we got from medical record data of Internal Medicine Department. We have performed re-evaluations for all samples that met the inclusion criteria. Samples with final diagnosis IBD (UC or CD) showed the morphology with chronicity features that also supported to IBD diagnosis. Histopathological diagnosis is not the golden-standard modality for diagnosis IBD. The diagnosis is based on the combination of clinical symptoms, endoscopy, laboratory tests, and histopatholgy. After receiving the pathology report that suspicious of IBD, clinicians should correlate the report with patient clinical symptoms and all the supporting examinations, such as laboratory and endoscopy for the final diagnosis. The diagnostic procedure that involves a multidisciplinary approach, aims to rule out any differential diagnoses, such as infection or any other types of colitis (Kellermann & Riis, 2021).

Conclusion

Based on the review of colonic mucosal biopsy specimens with clinical diagnosis of suspicious IBD from 2015 until 2019, the most patients were male, and the largest age group was at the age group of 51 - 60 years. Knowledges regarding the variations of histopathological features in colonic mucosal biopsy specimens with clinical diagnosis of suspicious IBD, can improve the diagnostic accuracy and start an appropriate treatment.

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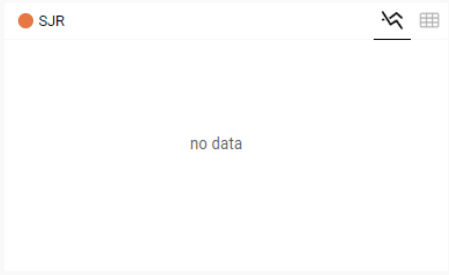

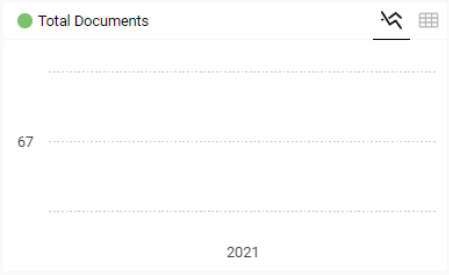

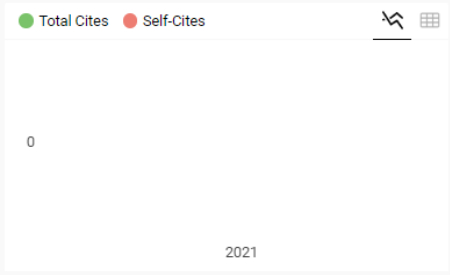

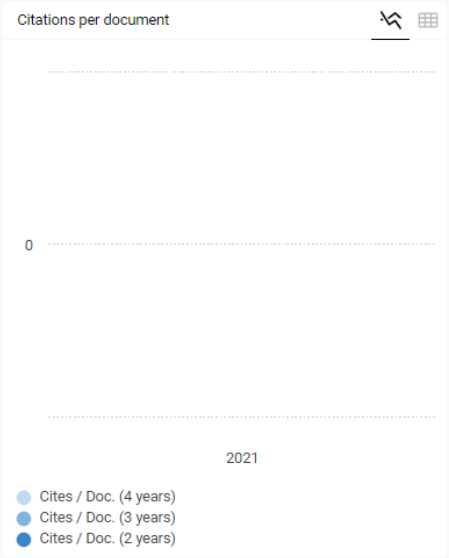

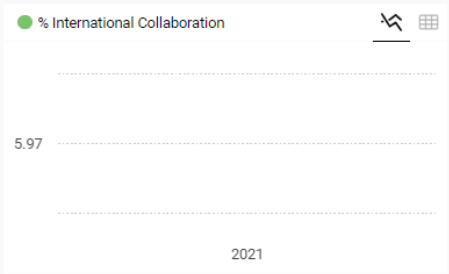

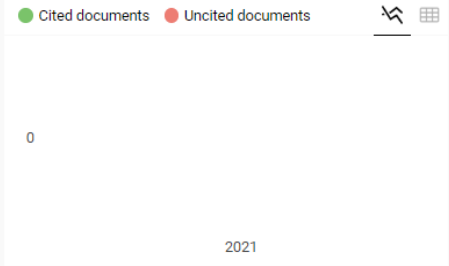

PEMERINTAH PROPINSI JAWA TIMUR
RUMAH SAKIT UMUM DAERAH Dr. SOETOMO
KOMITE ETIK PENELITIAN KESEHATAN
Jl. Mayjen Prof. Dr. Moestopo No. 6-8, Telp. 031-5501071-5501073, Fax. 031-5501164
SURABAYA 60286

SURAT EXEMPTION

(" LETTER OF EXEMPTION ")

Ref. No. : 0915/LOE/301.4.2/V/2022

Judul Protokol Penelitian	:	VARIASI GAMBARAN HISTOPATOLOGI BIOPSI MUKOSA KOLON DENGAN DIAGNOSIS KLINIS CURIGA INFLAMMATORY BOWEL DISEASE (IBD) DI LABORATORIUM PATOLOGI ANATOMIK RSUD DR. SOETOMO, SURABAYA PERIODE 1 JANUARI 2015 SAMPAI DENGAN 31 DESEMBER 2019
Dokumen yang disetujui	:	1425/120/4/V/2022 (versi: 2)
Tanggal terbit	:	29 Mei 2022
Berlaku sampai	:	29 Mei 2023
Peneliti Utama	:	Dr. Anny Setijo Rahaju, dr., Sp.PA (K)
Peneliti Lain	:	1. Alphania Rahniayu, dr., Sp.PA (K) 2. Ariadna Anggi Pasang, dr.
Instalasi/Tempat Penelitian	:	RSUD Dr. Soetomo

Komite Etik Penelitian Kesehatan RSUD Dr Soetomo menyatakan bahwa dokumen diatas sesuai dengan The Office for Human Research Protections (OHRP) dibawah persyaratan the U.S. Department of Health and Human Services (HHS) Regulasi 45 CFR bagian 46 untuk **exempt review**.

RSUD Dr. Soetomo Komite Etik Penelitian Kesehatan SURABAYA

Dr. Dominicus Husada dr., SpA(K)
Ketua Panel 4

Dr. Evelyn Komaratih dr., SpM(K)
Sekretaris Panel 4