

**Evaluation of differential leucocytes ratio
as a predictor for disease activity in
patients with ulcerative colitis**

Thesis

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Medicine*

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□ في المرضى الذين يعانون من التهاب القولون التقرحي

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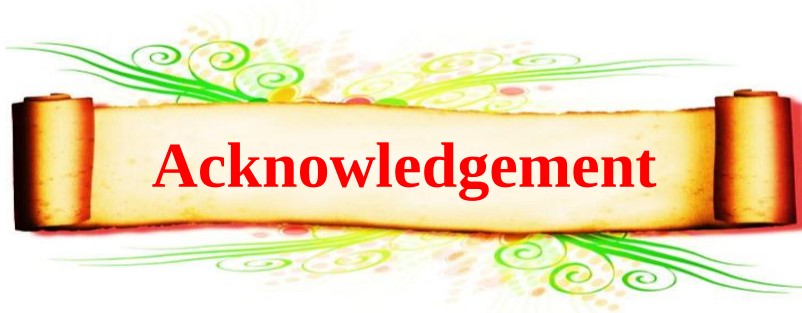
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List of Abbreviations

6-MP	: 6- Mercaptopurin
ACCA	: Anti-chitobioside antibodies
ALCA	: Anti-laminaribioside antibodies
ALT	: Alanine aminotransferase
AMCA	: Anti-mannobioside antibodies
Anti-OmpC	: Anti-Outer membrane protein C
ASA	: Aminosalicylic acid
ASCA	: Anti-Saccharomyces cerevisiae antibodies
ASGE	: American Society for Gastrointestinal Endoscopy
AST	: Aspartate aminotransferase
BE	: Barium enema
Cal	: Calprotectin
CD	: Crohn's disease
CDEIS	: Crohn's disease endoscopic index of severity
CHD1	: Chromodomain helicase deoxyribonucleic acid binding protein 1
CMV	: Cytomegalovirus
CRC	: Colorectal carcinoma
CRP	: C-reactive protein
CSA	: Cyclosporine
CTE	: Computerized tomography enterography
DNA	: Deoxyribonucleic acid
EGD	: Esophago-gastro-duodenoscopy
ELISA	: Enzyme-linked immunosorbent assay
ESR	: Erythrocyte sedimentation rate
FC	: Fecal calprotectin
FDA	: Food and Drug Administration
HBsAg	: Hepatitis B surface antigen
HIV	: Human immunodeficiency virus
HLA	: Human Leukocyte antigen
HLA-DQA1	: Major histocompatibility complex, class II, DQ alpha 1
IBD	: Inflammatory bowel disease
IBS	: Irritable bowel syndrome
IC	: Indeterminate colitis
IG	: Immunoglobulin
IL	: Interleukin
IL1R2	: Interleukin 1 receptor 2
IL7R	: Interleukin 7 receptor

List of Abbreviations

INR	: International normalized ratio
IPAA	: Ileal pouch and anastomosis
IV	: Intra Venous
LAMB1	: Laminin subunit beta 1
LCN2	: Lipocalin-2
Lf	: Lactoferrin
LSD	: The least significant difference
LMR	: Lymphocyte-to-Monocyte ratio
MHC	: Major Histocompatibility complex
MRC	: Magnetic resonance cholangiography
MRE	: Magnetic resonance enterography
MTX	: Methotrexate
NLR	: Neutrophil-to-Lymphocyte ratio
NOD	: Nucleotide-binding oligomerization domain
NPV	: Negative predictive value
NSAID	: Non-steroidal anti inflammatory drug
PAB	: Pancreatic antibodies
p-ANCA	: perinuclear Anti- neutrophil cytoplasmic antibodies
p-ASCA	: Perinuclear Anti-Saccharomyces cerevisiae antibodies
PMN	: Polymorphonuclear
POCT	: Point of care testing
PPV	: Positive predictive value
PSC	: Primary sclerosing cholangitis
ROC	: Receiver operating characteristic
PT	: Prothrombin time
PTT	: Partial thromboplastin time
SC	: Subcutaneous
SD	: Standard deviation
sST2	: Soluble suppression of tumorigenicity 2
TG	: Thioguanine
Th	: T-helper
TNF	: Tumor necrosis factor
TNFRSF 15	: Tumor necrosis factor receptor superfamily 15
TPN	: Total parenteral nutrition
UC	: Ulcerative colitis
WBCs	: White blood cells

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Abstract

Background: Blood neutrophil-to-lymphocyte (N/L) ratio and lymphocyte-to-monocyte (L/M) ratio are indicators of the overall inflammatory status of the body, and an alteration in N/L ratio may be found in ulcerative colitis (UC) patients. The aim of this study was to investigate the utility of N/L & L/M ratios as a simple and readily available predictor for clinical disease activity in UC.

Methods: 40 patients and 20 healthy individuals served as a control group was enrolled in the study. The neutrophil, lymphocytes and monocyte counts were recorded, and the N/L and L/M ratios were calculated from these parameters. The severity of the disease was based on mayo's score of classification.

Results: N/L ratio was found to be higher in patients with active disease ($P < 0.001$). The optimum N/L ratio cut-off value for active UC was 2. L/M ratio was found to be lower in patients with active ulcerative colitis, with optimum cut-off value for active UC was 1.65.

Conclusion: our results demonstrates that N/L is higher in active UC compared with controls and inactive UC and a cut-off value of 2 can be used to identify patients with active UC. Also it shows that L/M ratio is lower in patients with active UC compared with controls and inactive UC and a cut-off value of 1.65 can be used to identify patients with active UC.

Key word: differential leucocytes, ulcerative colitis, *Internal Medicine*

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory bowel disease that causes inflammation and ulcers in the innermost layers of the large intestine (colon) and rectum. Assessment of intestinal inflammation in UC is crucial and still remains a difficult challenge for the clinician. Although endoscopic modalities with biopsy sampling seem to be the most reliable method for estimating disease severity, they are invasive and costly. Apart from endoscopic interventions, disease severity can be assessed using both laboratory studies and non-invasive imaging tests (*Cakal et al., 2009*).

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBCs), acid glycoprotein, platelet count and albumin are in common use but have only modest accuracy in reflecting UC disease activity. Therefore, adjunctive use of additional serum markers that will be more sensitive and specific for determination of disease activity and achieving diagnostic accuracy is strongly needed in daily clinical practice (*Xiang et al., 2008; Yüksel et al., 2009*).

UC patients usually perform white blood cell differentials during routine clinical visits, which have been discussed previously as biomarkers in inflammatory diseases. Neutrophils and peripheral blood mononuclear cells were found to correlate with disease activity and

predict disease severity in some diseases as rheumatoid arthritis, acute coronary syndrome and inflammatory bowel disease (**Lester et al., 2009**). Changes in leukocyte numbers, especially monocytes, were found early in IBD (**Zhou et al., 2009; Mee et al., 1980**). Indeed monocytes, macrophages, and neutrophils are uniquely involved in the pathophysiology of IBD (**Wallace et al., 2014**).

An interest in the need for cost effective biomarkers in IBD has reinvigorated the examination of leukocyte patterns for this purpose, but only a few studies have reported their potential to serve as biomarkers in IBD. Absolute neutrophil and lymphocyte counts and their ratios have been reported to correlate with disease activity in UC. However, the other cell types and ratios were not examined, and the effects of medications and infections on those parameters and their correlation with endoscopic disease activity are unknown (**Celikbilek et al., 2013; Torun et al., 2012**).

Aim of the work

The aim of this work is to evaluate the differential leucocyte ratio as a simple, easy and available predictor for disease activity in patients with ulcerative colitis.

Ulcerative colitis UC

Definition:

Ulcerative colitis (UC) is a chronic relapsing disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95 % of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus (*Kornbluth et al., 1993; Meyers et al., 1989*).

Epidemiology:

Worldwide, UC is more common than Crohn's disease. Both diseases are more common in the industrialized world, particularly North America and Western Europe, although the incidence is increasing in Asia. The overall incidence is reported as 1.2 to 20.3 cases per 100,000 persons per year, with a prevalence of 7.6 to 245 cases per 100,000 per year (*Danese and Fiocchi 2011; Loftus, 2004*).

Etiology:

The exact pathogenesis of UC is unknown, although there are a number of genetic and environmental factors that have been found to increase the risk of the disease. A current hypothesis suggests that primary dysregulation of

the mucosal immune system leads to an excessive immunologic response to normal micro flora (***Strober et al., 2007***). It can be considered as an inappropriate inflammatory response to the gut contents in genetically predisposed individuals (***Abraham and Cho, 2009***).

Environmental

Cigarette smoking has a protective effect against UC, and cessation of cigarette smoking has been associated with an increased risk of developing the disease (***Ng et al., 2013; Mahid et al., 2006; Garcia et al., 2005***). However, given the complications associated with cigarette smoking, patient should be counseled to stop smoking. The role of diet has been evaluated in numerous studies, but no specific diet has been consistently linked to an increased risk of UC (***Ng et al., 2013; Geerling et al., 2000; Hart et al., 2008***).

Women who used nonsteroidal anti-inflammatory drugs for at least 15 days were at an increased risk of developing IBD especially those taking higher doses for a longer time were at the highest risk (***Ananthakrishnan et al., 2012***). Antibiotic exposure, particularly to tetracyclines, is also associated with a higher risk of UC (***Shaw et al., 2011***). Other risk factors may include hormone replacement therapy and oral contraceptives (***Khalili et al., 2012; Cornish et al., 2008; Garcia et al., 2005***)

The presence of Shigella or Shigella-like toxin and Yersinia has been investigated as a possible cause of UC,