Clin. Lab. 2020;66:XXX-XXX

ORIGINAL ARTICLE

Novel Inflammatory-Nutritional Biomarkers as Predictors of Histological Activity in Crohn's Disease

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SUMMARY

Background: **There has increasingly been an interest in histological remission as a therapeutic endpoint in inflammatory bowel disease. The aim of this study was to evaluate the utility of a variety of inflammatory - nutritional markers for predicting histological disease activity in patients diagnosed with Crohn's disease.**
Methods: **Patients with Crohn's disease that had requisite endoscopic, pathological, and laboratory data were retrospectively enrolled in the study. Relevant clinical, laboratory, endoscopic, and pathological data were abstracted. The neutrophil:lymphocyte ratio (NLR), lymphocyte:monocyte ratio (LMR), platelet:lymphocyte ratio (PLR), red blood cell distribution width (RDW), modified Glasgow Prognostic score (mGPS), Prognostic Nutritional Index (PNI), Geriatric Nutritional Risk index (GNRI), CRP/Albumin ratio (CAR), Iron:Ferritin ratio (Fe:F) and the Systemic immune inflammation index (SII) were calculated. The cohort was stratified by presence of histological disease on colonoscopy, and groups were compared with appropriate statistical methods.**
Results: **When comparing patients without histological disease to those with disease, there was a statistically significant difference in CAR (2.9 ± 1.5 vs. 4.2 ± 2, p = 0.001), RDW (13.4 ± 1.3 vs. 14.5 ± 1.8, p = 0.008), PNI (52.4 ± 6.2 vs. 47.4 ± 9.3, p = 0.03), and mGPS (0.2 ± 0.4 vs. 0.6 ± 0.7, p = 0.01). For predicting histological activity, ROC analyses indicated an optimal cutoff of 0.3 for CAR (AUC 0.8, PPV 90.5%), 13.5 for RDW (AUC 0.7, PPV 84.1), 86.1 for PNI (AUC 0.7, PPV 86.1) and > 0 for mGPS (AUC 0.6, PPV 85.2%). The NLR, LMR, PLR, GNRI, Fe: F, and SII did not meet statistical significance (p = 0.4, 0.08, 0.2, 0.5, 0.6, and 0.3, respectively).**
Conclusions: **We report on ten biomarkers, many of them never studied in Crohn's disease, which can help in predicting the presence of active histological disease. Larger prospective studies are needed to investigate the utility of these biomarkers alone and in combination.**
(Clin. Lab. 2020;66:xx-xx. DOI: 10.7754/Clin.Lab.2019.190816)

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Manuscript accepted December 18, 2019

KEY WORDS

Crohn's, histological remission, nutritional biomarkers, inflammatory biomarkers

INTRODUCTION

Crohn's disease is a chronic relapsing inflammatory bowel disease with a complex multifactorial etiology involving multiple genetic and environmental factors, alteration and priming of the intestinal flora, and an abnormal immune mediated response [1]. The determina-

tion of disease activity is essential for tailoring therapy as treatment improves morbidity and mortality [2]. The Crohn's Disease Activity Index [3] has been broadly utilized in large clinical trials. However, it has also been widely criticized due to inter-observer variability as well as a variety of subjective variables included in the index such as "abdominal pain", "general well-being" and to a lesser extent, number of stools reported by patient, which is influenced by presence or absence of the ileum [4,5]. A number of other scoring indices such as the Harvey-Bradshaw index have been developed, but suffer from similar disadvantages [4,6]. Patient symptoms do not always correspond with disease activity, and the study populations in question have a significant amount of concomitant irritable bowel syndrome (IBS), functional diarrhea and abdominal pain, anxiety and depression [7]. Furthermore, these questionnaire-based indices are lengthy and time consuming, have limited utility in daily practice, and are instead reserved for clinical studies [8]. Radiological methods to evaluate activity are widely used to assess disease activity, presence of abscesses, strictures and fistulae. These methods include X-ray based studies for assessment of small and large bowel, computed tomography (CT) and magnetic resonance imaging (MRI) [4] but are again limited by cost, ionizing radiation, as well as variable utility in picking up histological or endoscopic disease activity. Multiple endoscopic indices that grade disease activity, such as the Crohn's Disease Endoscopic Index of Severity (CDEIS) [9], have been developed, but obvious limitations include the invasiveness and cost of endoscopy, as well as lack of histological grading and inter-observer variability [10]. In routine clinical practice, the most common biomarkers used in determining disease activity are C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Although widely used, they have significant limitations in their ability to correlate with endoscopic or histological activity in inflammatory bowel disease. One study showed sensitivity and specificity ranges for CRP of 50.5 - 53.3% and 68.7 - 71.3% and ESR of 85.1 - 87.2% and 63.4 - 66.4%, respectively [11]. Other studies have demonstrated similar poor sensitivity and specificity for distinguishing between active and quiescent disease [12]. This may be in part related to genetic variation in CRP haplotypes which have been shown to produce significantly different levels of CRP [13]. Stool markers such as fecal calprotectin have been studied, but are limited in practice by sample processing time, availability, and ability and willingness of patients to collect stool samples [14].

Recently, there have been a plethora of studies investigating the use of various biomarkers that are thought to reflect inflammatory and nutritional status of the patients and help in prognosticating patients in a variety of disease states. However, they have largely not been studied in Crohn's disease. The aim of this study was to evaluate the utility of a variety of novel inflammatory - nutritional markers such as the neutrophil:lymphocyte ratio (NLR), lymphocyte:monocyte ratio (LMR), platelet:lymphocyte ratio (PLR), red blood cell distribution width (RDW), modified Glasgow Prognostic score (mGPS), Prognostic Nutritional Index (PNI), Geriatric Nutritional Risk index (GNRI), the CRP/Albumin ratio (CAR) the Iron:Ferritin ratio (Fe:F) and the Systemic immune inflammation index (SII) for predicting histological disease activity in patients diagnosed with Crohn's disease.

MATERIALS AND METHODS

Patients

The charts of 306 consecutive patients from the inflammatory bowel disease databank at the University of Florida at Jacksonville from July 2014 to July 2016 were reviewed. Ninety-one patients with Crohn's disease were identified, and 74 patients with Crohn's disease had requisite endoscopic, pathological, and laboratory data and were retrospectively enrolled in the study.

Inclusion criteria

Inclusion criteria included a diagnosis of Crohn's disease, age > 18 years of age, colonoscopy and histopathological review of specimens performed at our institutions, lack of active infection or malignancy, and requisite labs done within two weeks of endoscopy. Patients with ulcerative colitis were excluded.

Endoscopic and histological diagnosis

Endoscopic and histological findings were obtained from endoscopy and pathology reports, respectively. The determination of histologically active disease was defined as acute colitis as determined by expert pathological examination of colonic biopsies that were fixed in 10% formalin, embedded in paraffin wax, which had 5-mm sections stained with hematoxylin and eosin for histology.

Study variables and outcomes

Relevant demographic, clinical and laboratory variables within two weeks of endoscopy were abstracted from the electronic medical record. The equations for the biomarkers are presented in Table 1. The main study outcome and the subsequent predictive ability of these biomarkers are determining histologically active versus inactive disease.

Biomarker selection

In choosing biomarkers for this study, we sought to include blood-derived markers that could be easily calculated, and that have been well validated in the literature for a variety of inflammatory conditions. The NLR is one of the best validated peripheral blood-derived inflammatory markers. It has been used in various diseases and in a wide variety of cancers, totaling over 80,000 patients [15]. It has also been used extensively in non-cancerous conditions including prognosticating patients with COPD [16], acute myocardial infarction

[17], liver cirrhosis [18], brainstem hemorrhage [19], and many others. The LMR is another well studied inflammatory biomarker that has been studied in multiple cancers and in over 20,000 patients [15]. It has also been studied in diseases ranging from acute ischemic stroke [20] to glaucoma [21]. Similarly, the PLR has been used extensively in prognosticating both cancerous conditions [22,23] and non-cancerous conditions such as cardiovascular disease [24], lupus [25], and psoriasis [26]. The CAR has been found to be a useful prognostic marker in patients with septic shock [27] as well as cancers such as renal cell cancer [28] and hepatocellular cancer [29]. Onodera's PNI was first described in assessing patients' risk for postoperative complications and mortality in gastrointestinal tract surgery [30]. It has since been used extensively to prognosticate patients in cancers, particularly gastric cancer [31], esophageal cancer [32], colorectal cancer [33], and lung cancer [34]. The mGPS is one of the best validated inflammation-based prognostic scores for patients with cancer and has been validated in numerous studies and in over 12,000 patients [35]. The SII has been predominantly used in cancers [36], but has also been used to predict outcomes in patients with osteoporosis [37], dementia [38], and vasculitis [39].

Ferritin, an acute phase reactant, has been regarded as an inflammatory biomarker and the Fe:F ratio has been used as a prognosticator in multiple disease states including breast cancer [40] and NAFLD [41]. The GNRI has been used as a prognostic marker in a wide scope of disease entities such as heart failure [42], end stage renal disease [43], coronary artery disease [44], and various cancers such as esophageal cancer [45] and small cell lung cancer [46].

Statistical analysis

The association between variables in the subgroups was evaluated by the *t*-test for normally distributed continuous variables, Mann-Whitney test for non-normally distributed data, and by Fisher's exact test or Chi-square test for categorical variables. All analysis were performed using SPSS. All values are presented as mean ± SEM (or percentage where appropriate); statistical significance was determined at $p \leq 0.05$. Receiver operating curves (ROC) for each variable were constructed to assess each biomarker's ability in diagnosing histological disease, and accuracy was determined by measuring area under the curve (AUC). The optimal cutoff value for each biomarker was determined by calculating Youden's Index. The point of maximum sensitivity and specificity, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each test were calculated. Further subgroup analyses were also performed to evaluate for any differences in the biomarkers in patients who had ever received biologics and in patients that had active gastrointestinal symptoms, defined as the presence of abdominal pain, diarrhea or gastrointestinal bleeding.

This study was approved by the University of Florida-Jacksonville Institutional Review Board (IRB-03) at our institution and this work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

Demographics

The mean age was 46.1 ± 15 years and 67.6% were female. The mean BMI was 29.3 ± 8, 45.9% were on biologics, 8.1% had prior surgery related to Crohn's disease, 52.7% had a history of a stricture/fistula, and 12.2% had a history of IBD-associated arthropathy. When stratified by histology, 73% of patients had active histological disease on biopsy (Table 2).

Biomarkers

The biomarkers were calculated as detailed in Table 1, and the results are reproduced in Table 3. When comparing patients without histological disease to those with disease, there was a statistically significant difference in the CAR (2.9 ± 1.5 vs. 4.2 ± 2, p = 0.001), RDW (13.4 ± 1.3 vs. 14.5 ± 1.8, p = 0.008), PNI (52.4 ± 6.2 vs. 47.4 ± 9.3, p = 0.03) and mGPS (0.2 ± 0.4 vs. 0.6 ± 0.7, p = 0.01) between the groups. The difference in the NLR, LMR, PLR, GNRI, Fe:F, and SII between groups did not meet statistical significance (p = 0.4, 0.08, 0.2, 0.5, 0.6, and 0.3, respectively).

When the cohort was split into symptomatic (abdominal pain or diarrhea) and asymptomatic groups there was no statistically significant difference in any of the measured biomarkers between the two groups (data not shown). Similarly, when stratified into patients that had ever received biologics and that had not, there was no statistical difference in any of the measured biomarkers between groups (data not shown).

ROC curves

For predicting histological activity, receiver operating characteristic **(**ROC) analyses (Table 4) indicated that the biomarkers that were best able to determine active histological disease were the CAR at a cutoff of 0.3 (AUC 0.8, 95% CI 0.7 - 0.9, p = 0.0001) with a PPV of 90.5; the RDW at a cutoff of 13.5 (AUC 0.7, 95% CI 0.6 - 0.8, p = 0.004) with a PPV of 84.1%; and the PNI at a cutoff of 48 (AUC 0.7, 95% CI 0.5 - 0.8, p = 0.01) with a PPV of 86.1 (see Figure 1).

DISCUSSION

Over the past several years there has been increased interest in utilizing easily obtained biomarkers calculated from routine bloodwork for prognosticating outcomes in a wide variety of disease entities. However, there has been limited research in using these for inflammatory bowel disease (IBD). This study is the first time mGPS, GNRI, Fe:F, SII, CAR, and PNI have ever been studied

Table 1. Variables and formulas.

Variable	Calculation
Lymphocyte: Monocyte Ratio (LMR)	Absolute Lymphocyte Count/Absolute Monocyte Count
Neutrophil: Lymphocyte Ratio (NLR)	Absolute Neutrophil Count/Absolute Lymphocyte Count
Platelet: Lymphocyte Ratio (PLR)	Platelet Count/Absolute Lymphocyte Count
Geriatric Nutritional Risk Index (GNRI)	1.489 x serum albumin (g/L) + (41.7 x present weight (kg)/ideal body weight(kg))
Onodera's Prognostic Nutrition Index (PNI)	10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm^3)
Lorenzo's Ideal Body Weight (IBW)	Men = (height (cm) - 100) - ((height (cm) - 150)/4); Women = (height (cm) - 100) - ((height (cm) - 150)/2)
Modified Glasgow Prognostic Score (mGPS)	CRP < 1.0 mg/dL = mGPS 0 irrespective of albumin level; CRP level > 1.0 mg/dL and albumin ≥ 3.5 g/dL = mGPS1; CRP level > 1.0 mg/dL and albumin < 3.5 g/dL = mGPS2
Iron:Ferritin Ratio (Fe:F)	Iron (µg/dl)/Ferritin (ng/mL)
CRP:Albumin Ratio (CAR)	CRP (mg/dl)/Albumin (g/dL)
Systemic Immune Inflammation Index (SII)	Platelet count x (neutrophil count/lymphocyte count)

Table 2. General demographics.

Variables	All	Histologically inactive (n = 20)	Histologically active (n = 54)	p-value
Age (years)	46.1 ± 15	50.4 ± 15	44.5 ± 15	0.1 *
Age at diagnosis (years)	33.0 ± 14	32.8 ± 12	33.1 ± 15	0.9 *
BMI	29.3 ± 8	26.8 ± 7	30.2 ± 8	0.1 *
Gender				0.01 †
Male	32.4%	10%	40.7%	
Female	67.6%	90%	59.3%	
History of Stricture/Fistula	52.7%	40%	57.4%	0.005 †
Prior surgery for Crohn's	8.1%	10%	7.4%	0.5 †
History of treatment with biologics	45.9%	35%	50%	0.2 †
History of IBD-Associated Arthropathy	12.2%	10%	13%	0.5 †

*** - p-value indicates results from Student's *t*-test.**
† - p-value indicates results from chi-square analysis for categorical variables.

in IBD and the first time the LMR and PLR have been studied for predicting histological activity in Crohn's disease. The results of this study demonstrate that Crohn's patients with evidence of histological inflammation on biopsy had elevated RDW, CAR, mGPS, and a lower PNI compared to patients without histological inflammation, and ROC analysis showed that these biomarkers could be useful in predicting histological disease.

CAR has never been studied in IBD. An increased CRP level represents the increased inflammatory response in IBD, and a low albumin level is representative of malnutrition and a heightened systemic immune response, whereby the production of albumin by hepatocytes is suppressed by pro-inflammatory cytokines such as TNF-a, IL-1, and IL-6 [47].

The use of RDW in IBD has been investigated in a few studies [48-51]. In one study, a higher RDW was an independent predictor of disease activity in patients with Crohn's disease without anemia, surpassing even CRP and ESR [49]. RDW is a measure of anisocytosis, the variability in size of circulating erythrocytes. The rela-

Table 3. Biomarkers: histological activity.

Variable	Mean ± SD	Histologically inactive (n = 20)	Histologically active (n = 54)	p-value *
RDW	14.2 ± 1.7	13.4 ± 1.3	14.5 ± 1.8	0.008
NLR	3.4 ± 3.8	3 ± 2.9	3.6 ± 4.2	0.4
PLR	197.9 ± 220	151.1 ± 84	216.8 ± 254	0.2
LMR	4.1 ± 3.3	5.2 ± 5.0	3.7 ± 2.1	0.08
PNI	48.7 ± 8.8	52.4 ± 6.2	47.4 ± 9.3	0.03
GNRI	98.6 ± 13.5	100 ± 15.1	98.1 ± 13	0.5
mGPS	0.5 ± 0.7	0.2 ± 0.4	0.6 ± 0.7	0.01
Fe:F	1.3 ± 1.8	1.2 ±1.3	1.7 ±2.9	0.6
CAR	3.9 ± 2	2.9 ± 1.5	4.2 ± 2	0.001
SII	1,042 ± 600	819 ± 450	1,133 ± 580	0.3

Univariate analysis comparing the values of the biomarkers in patients with histologically inactive disease compared to histologically active disease.
RDW - Red Blood Cell distribution width, NLR - Neutrophil to lymphocyte ratio, PLR - Platelet to lymphocyte ratio, LMR - Lymphocyte to monocyte ratio, PNI - Prognostic nutritional index, GNRI - Geriatric nutritional risk index, mGPS - modified Glasgow prognostic score, Fe:F - Iron to ferritin ratio, CAR - C-Reactive Protein to Albumin ratio, SII - Systemic immune inflammation index.
*** - p-values in this table indicate results from Student's *t*-test.**

Table 4. Receiver Operating Characteristic (ROC) curves.

	AUC	Cutoff	Sensitivity (%)	Specificity (%)	PPV	NPV	p-value
RDW	0.7	13.5	69.8	65.0	84.1	44.8	0.004
NLR	0.6	1.5	87.2	31.6	75.9	50.0	0.4
PLR	0.6	85.9	93.6	31.6	77.2	66.7	0.2
LMR	0.5	5.5	89.4	31.6	76.4	54.6	0.6
PNI	0.7	48.0	58.5	73.7	86.1	38.9	0.01
GNRI	0.6	110.4	62.6	65.0	82.5	39.4	0.3
mGPS	0.6	> 0	46.9	77.8	85.2	35.0	0.02
Fe:F	0.6	1.2	72.7	46.2	82.0	33.3	0.5
CAR	0.8	0.3	79.2	76.5	90.5	56.6	0.0001
SII	0.6	0.2	59.6	63.2	80.0	38.7	0.3

ROC Curve analysis of the biomarkers showing the area under the curve (AUC) of each biomarker, as well as optimal cutoff according to Youden's index, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detecting histologically active disease.
RDW - Red Blood Cell distribution width, NLR - Neutrophil to lymphocyte ratio, PLR - Platelet to lymphocyte ratio, LMR - Lymphocyte to monocyte ratio, PNI - Prognostic nutritional index, GNRI - Geriatric nutritional risk index, mGPS - modified Glasgow prognostic score, Fe:F - Iron to ferritin ratio, CAR - C-Reactive Protein to Albumin ratio, SII - Systemic immune inflammation index.

tionship between RDW and disease activity in IBD is not clear, but it is postulated that inflammatory cytokines cause inhibition of erythrocyte maturation and cause anisocytosis by the release of immature red blood cells into the circulation [49]. Onodera's PNI has never been investigated in inflammatory bowel disease. The PNI is a function of low albumin levels, which is a reflection of malnutrition as well as inflammatory cytokine suppression of hepatic albumin production, whereas elevated lymphocyte levels are consistent with the increased inflammatory response in IBD. The mGPS has never been investigated in diagnosing Crohn's or predicting histological activity. In this study, mGPS was higher in the histologically active group ($p = 0.01$) but ROC analysis revealed only a fair predictive ability with an AUC of 0.6 with a PPV of 85.2%.

The determination of disease activity in inflammatory bowel disease is an essential aspect of management for

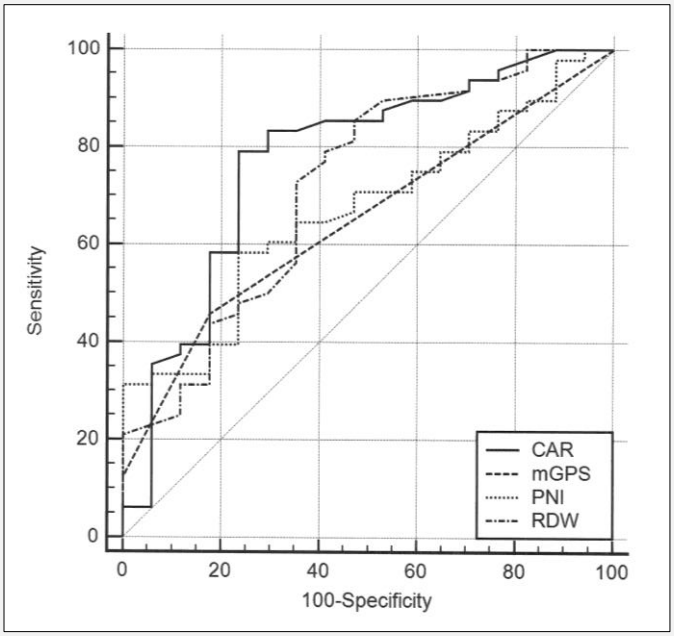

Figure 1. Receiver Operating Characteristic (ROC) curve of significant biomarkers.

In this receiver operating characteristic (ROC) curve, four biomarkers are plotted, with sensitivity against the false positive rate to obtain the area under the curve, which in this case is a measure of how well each biomarker can distinguish patients with histologically active disease. CAR performed the best, with an AUC of 0.8, followed by the PNI and RDW with an AUC of 0.7.
Red Blood Cell distribution width, PNI - Prognostic nutritional index, mGPS - modified Glasgow prognostic score, CAR - C - reactive protein to Albumin ratio.

tailoring therapy, but as of now the gold standard is endoscopic evaluation, which is limited by its direct and societal costs, peri-procedural risks, and patient inconvenience. In the era of biologic therapy, there has been a paradigm shift where deep remission has supplanted clinical remission as a treatment endpoint [52,53]. Deep remission is defined by some as the presence of clinical remission (Crohn's disease activity index < 150) as well as complete mucosal healing on endoscopic evaluation [54]. Mucosal healing is thought to alter the natural course of the disease, decrease need for surgical intervention, and potentially decrease incidence of dysplasia and cancer [53]. However, there has increasingly been an interest in histological remission as a therapeutic endpoint in IBD rather than simply mucosal healing [55,56]. Studies evaluating histological activity in IBD have found that active inflammation on histology predicted clinical relapse on follow-up whereas endoscopic features did not [57]. In addition, histological remission correlated with a reduction in colorectal cancer risk [58], increased likelihood of remaining symptom free [59], and decreased rates of hospitalization and surgery [60]. Furthermore, it has been suggested that IBS-like symptoms which persist in IBD patients may be related to sub-clinical mucosal or histological inflammation, with subsequent increased mucosal barrier permeability and consequent stimulation of the brain-gut axis [61]. For example, some studies have found that the presence of IBS symptoms in patients with IBD with endoscopic remission was significantly higher than controls [62], and in another study, IBD patients who were considered to be in clinical remission but had IBS-type symptoms had elevated levels of calprotectin compared to IBD patients who did not [63]. Therefore, in symptomatic patients, treatment to a goal of histological remission instead of deep remission may be a target for symptomatic relief.

There are several limitations of this study, including its single-center, retrospective design as well as its limited sample size. The strengths of the study include the wide range of biomarkers evaluated, the range of clinical variables collected and assessed as well as the use of histological activity as an endpoint.

CONCLUSION

This is the first study to evaluate the utility of the mGPS, GNRI, Fe:F, SII, CAR, and PNI in IBD, and the first time the LMR and PLR have been studied for predicting histological activity in Crohn's disease. Crohn's patients with evidence of histological inflammation on biopsy had elevated RDW, CAR, mGPS, and a lower PNI compared to patients without histological inflammation. Given our findings as well as the multitude of studies validating these biomarkers in other inflammatory conditions, we believe these biomarkers warrant further investigation for use in IBD in larger prospective studies.

Financial Support:
No financial support was provided for this work.

Disclaimers:
None.

Ethics Statement:
This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the IRB-03 at the University of Florida - Jacksonville under the IRB# 201601465.

Declaration of Interest:
All authors declare no conflicts-of-interest related to this article.

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