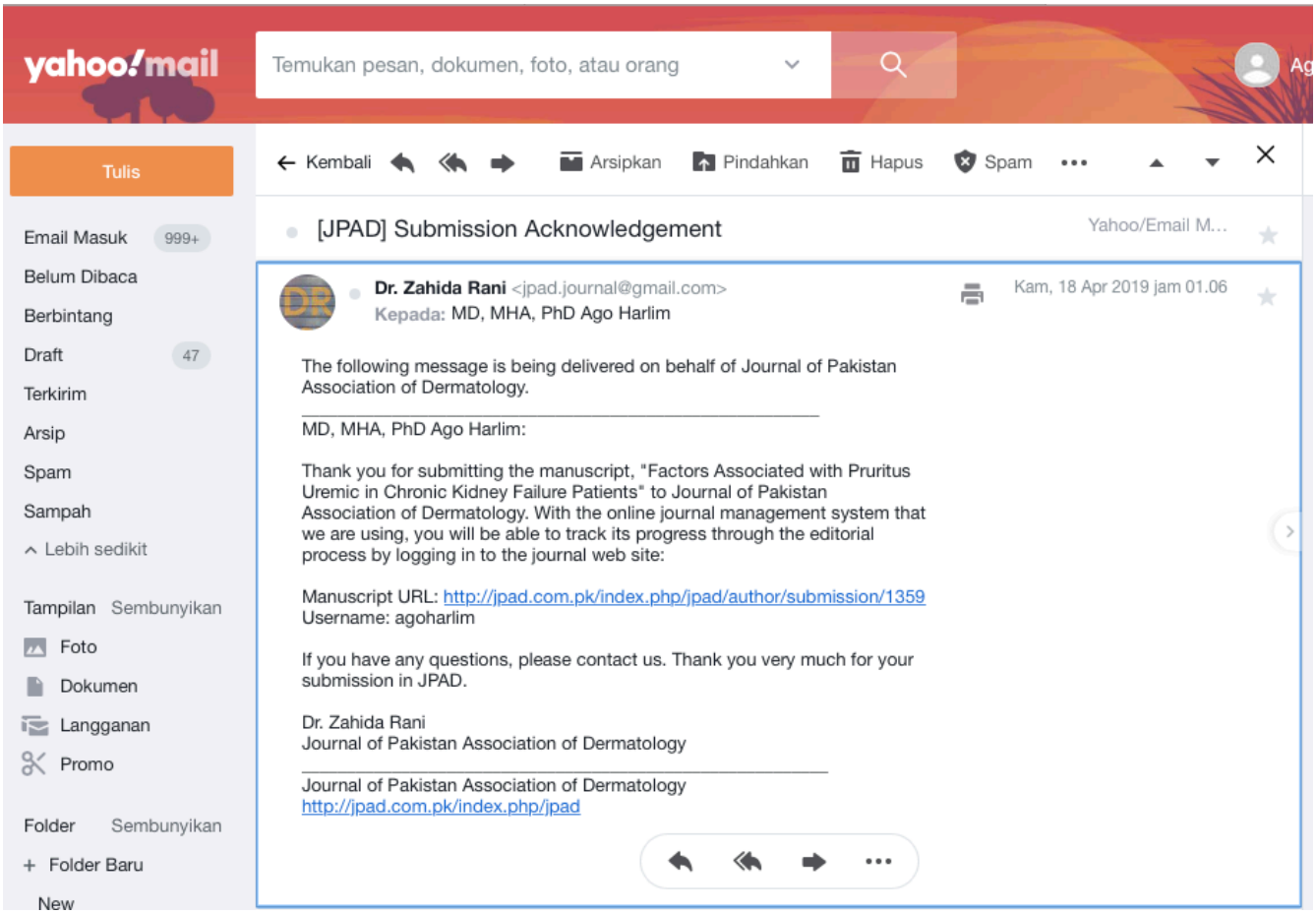
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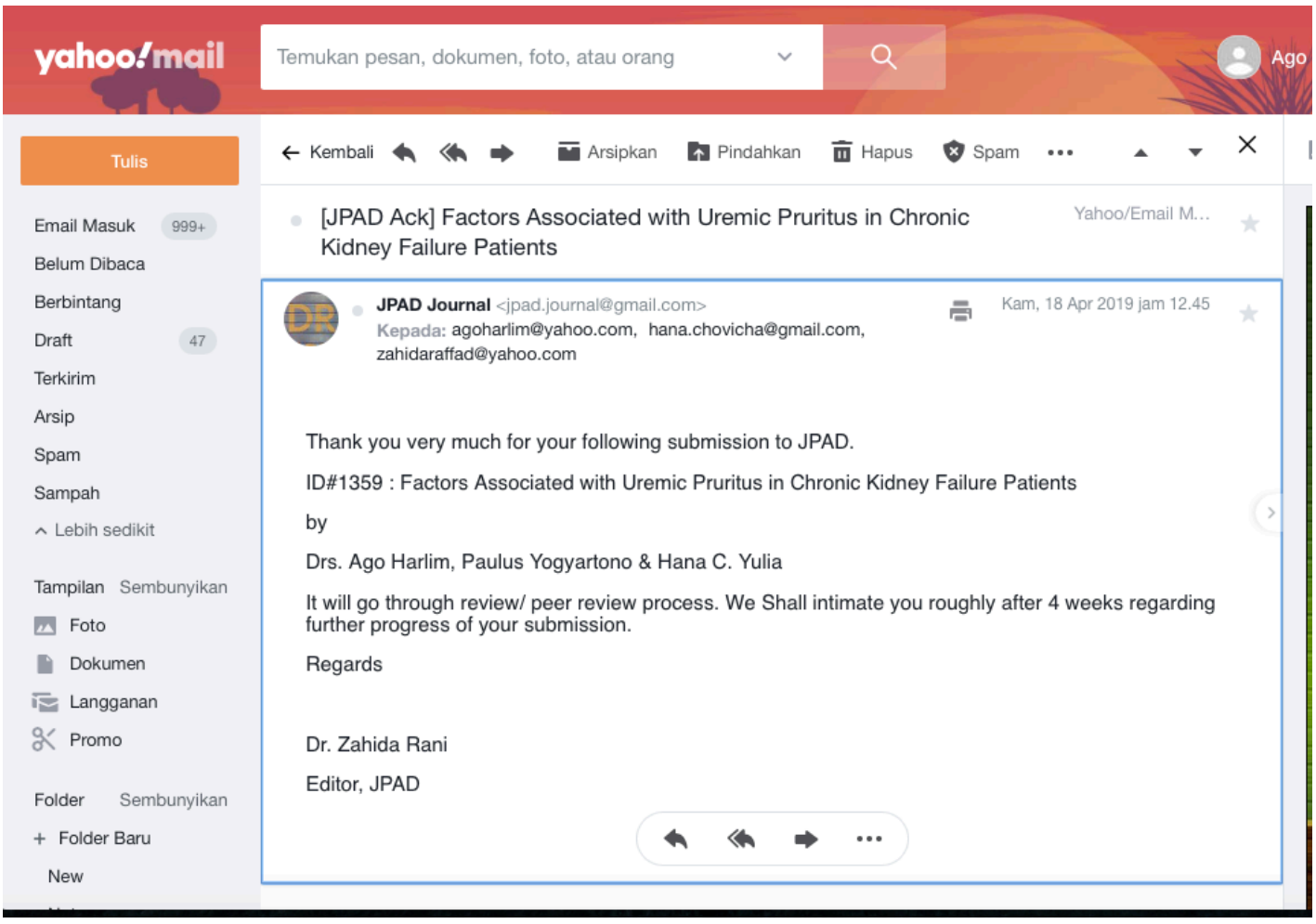
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Drs. Ago Harlim, Paulus Yogyartono & Hana C. Yulia
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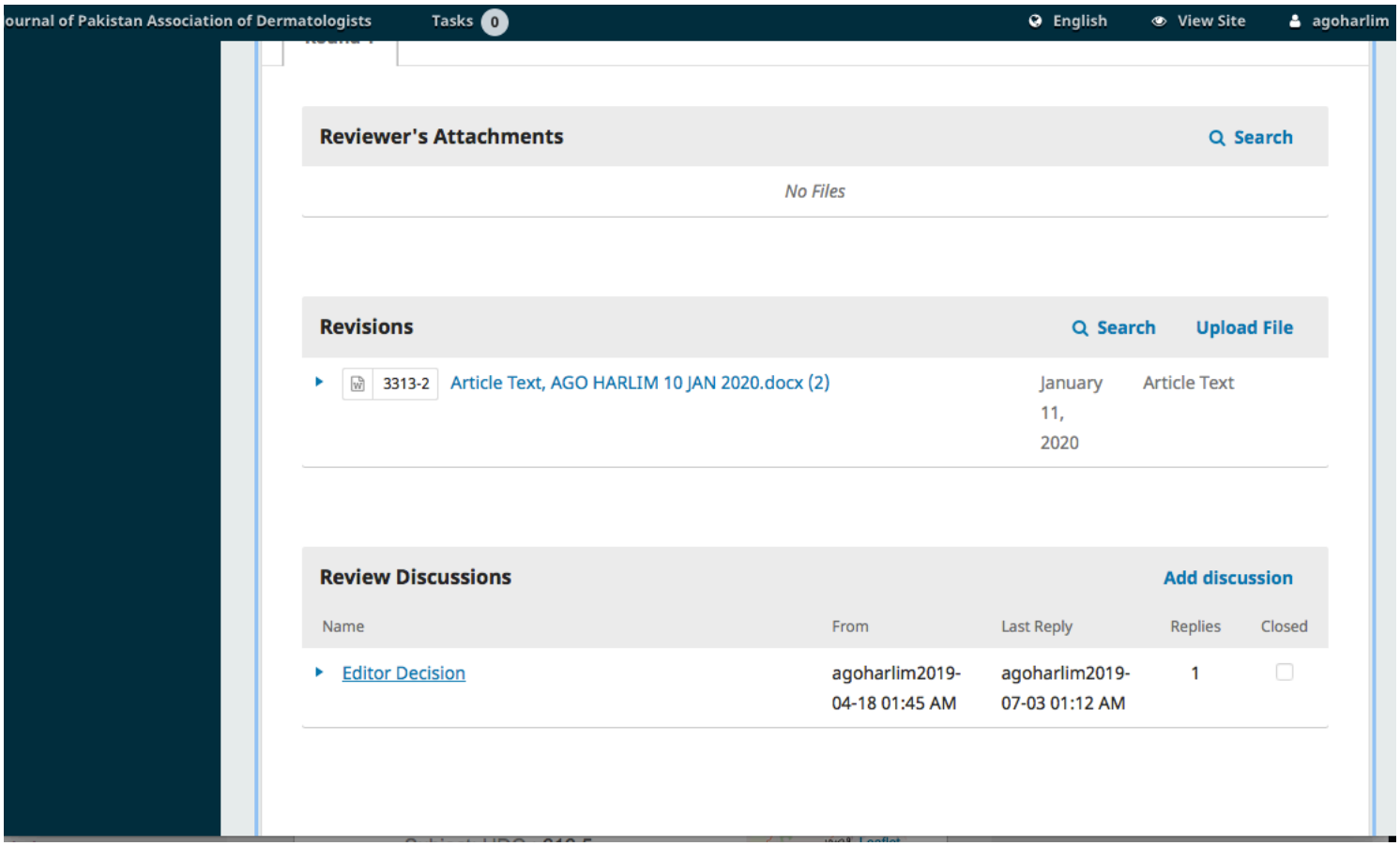
Editor, JPAD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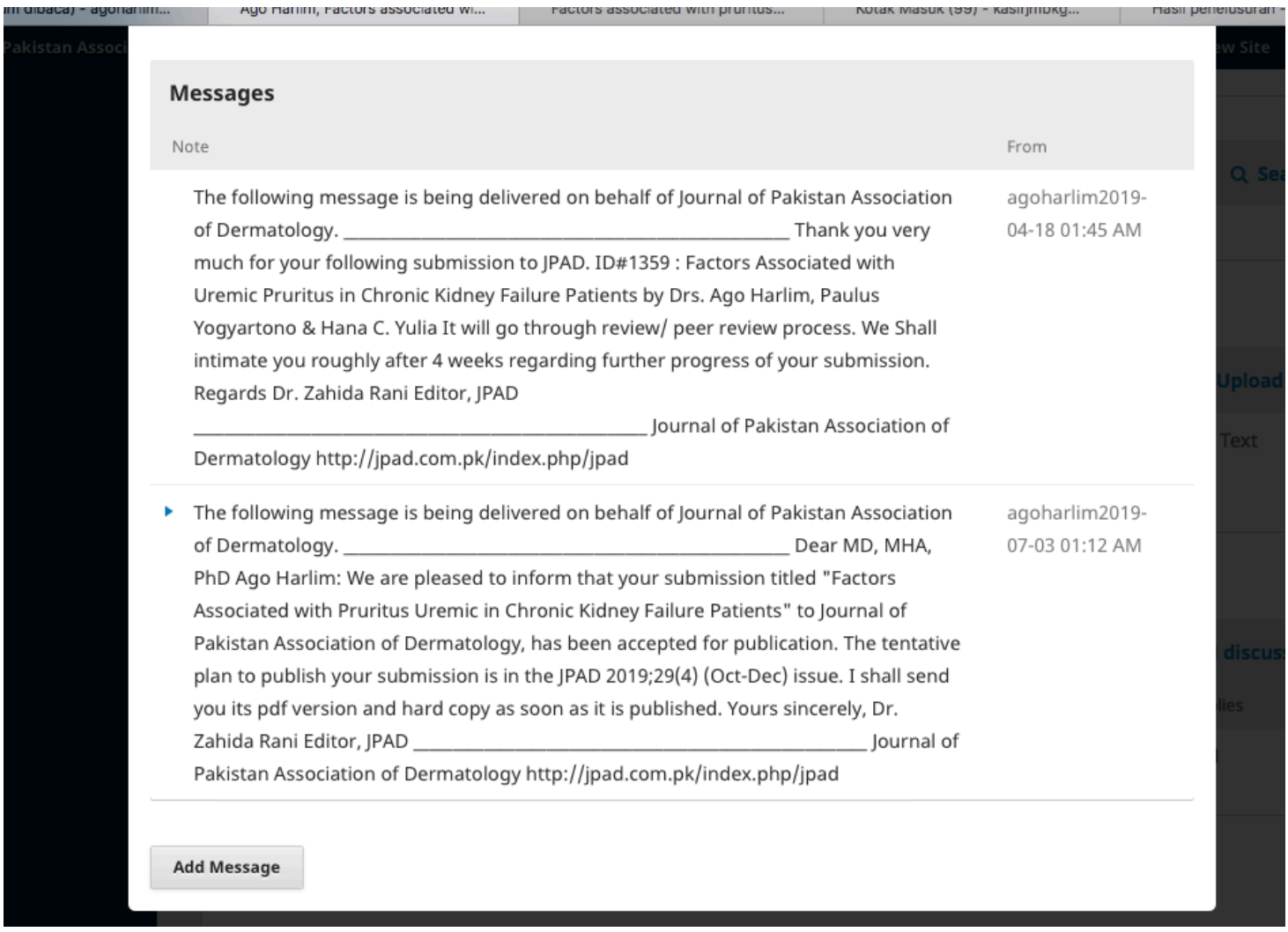
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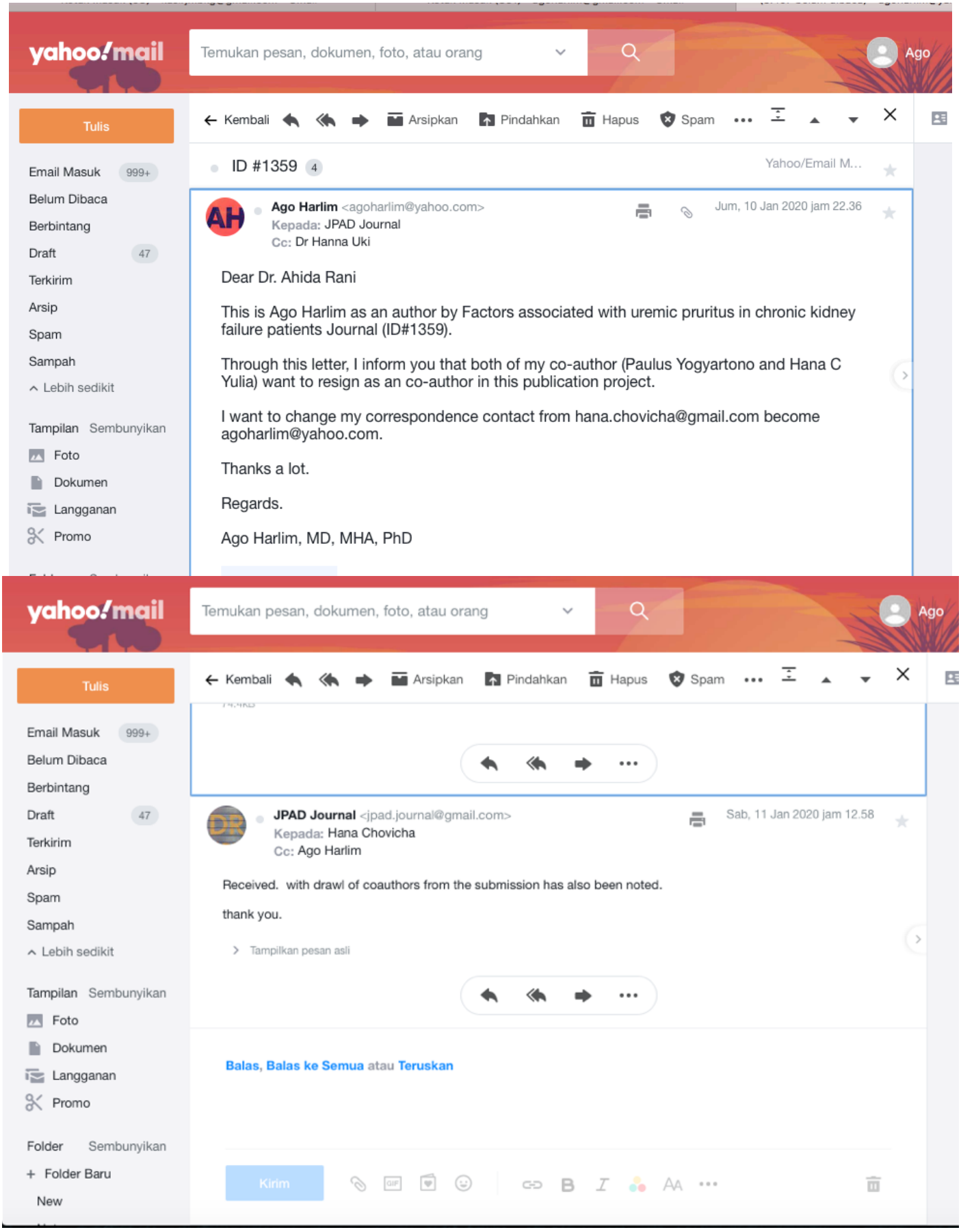
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Kepada: JPAD Journal
Cc: Dr Hanna Uki
Jum, 10 Jan 2020 jam 22.36
Dear Dr. Ahida Rani
This is Ago Harlim as an author by Factors associated with uremic pruritus in chronic kidney failure patients Journal (ID#1359).
Through this letter, I inform you that both of my co-author (Paulus Yogyartono and Hana C Yulia) want to resign as an co-author in this publication project.
I want to change my correspondence contact from hana.chovicha@gmail.com become agoharlim@yahoo.com.
Thanks a lot.
Regards.
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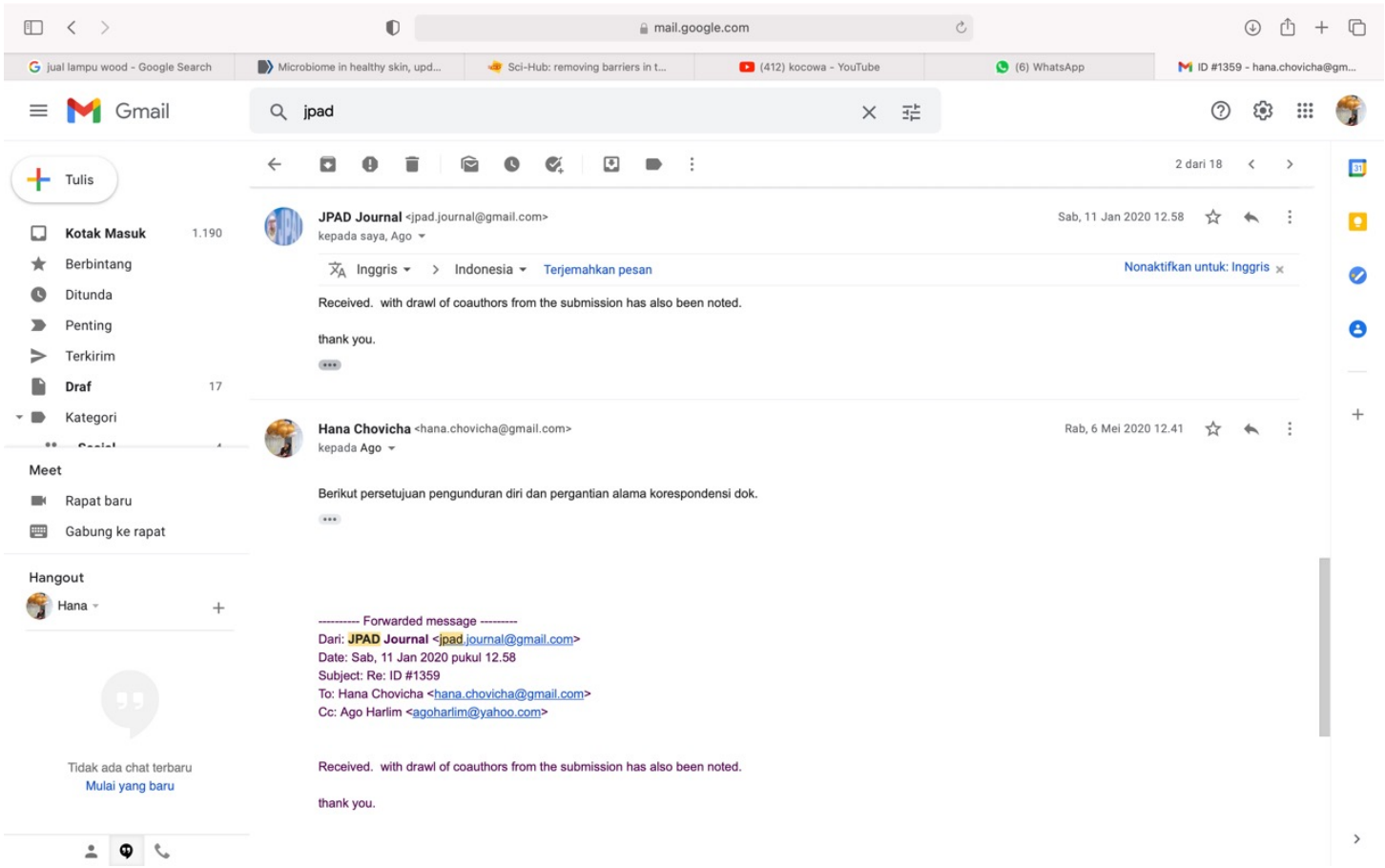

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Dear Dr. Ahida Rani

This is Ago Harlim as an author by Factors associated with uremic pruritus in chronic kidney failure patients Journal (ID#1359).

Through this letter, I inform you that both of my co-author (Paulus Yogyartono and Hana C Yulia) want to resign as an co-author in this publication project.

I want to change my correspondence contact from hana.chovicha@gmail.com become agoharlim@yahoo.com.

Thanks a lot.

Regards.

Ago Harlim, MD, MHA, PhD

GUIDELINE FOR REVIEW OF ORIGINAL RESEARCH ARTICLES FOR JPAD

Title of Manuscript: Factors associated with uremic pruritus in chronic kidney failure patients

Manuscript Reg. No____ Reviewer's Name _____ Date_____

Description of the part of manuscript	Yes	No	Remarks
TITLE • Reflects objectives of the study	✓		
• Does not contain any abbreviations	✓		
• Relevant to the specialty	✓		
ABSTRACT • Size of abstract (250)	✓		
• Summary of Introduction / Back ground	✓		
• Material and Methods	✓		
• Results	✓		
• Conclusion	✓		
• Keyword (3-5)	✓		
INTRODUCTION • Relevant start	✓		
• Subject of paper made clear	✓		
• Importance of study made clear	✓		
• Reasons for the study / rationale clarified	✓		
• International literature of past 05 years recorded		✓	
• National literature reviewed and reviewed and recorded		✓	
AIMS AND OBJECTIVES OF THE STUDY			
• Are clearly stated in measurable terms		✓	
• Are addressed in the study		✓	
Material and Methods • Sampling technique correct			
• Sample selection criteria reliable • Inclusion criteria reliable • Exclusion criteria reliable • Control within the study or literature given			
• Important variable measurement criteria specified			
• Criteria to measure outcome relevant			

• Investigation / procedure / technique clearly given	✓		
• Ethical permissions (IRB) informed consent mentioned			
Results and analysis of results • Presentation of results clear		✓	
• Data satisfies objectives of the study	✓		
• All subjects / variable in the study accounted for	✓		
• Results reported the drops out (if present)	✓		Tables are not precise. confusing.
• Results presented with figures & graphs	✓		
• Appropriate statistical tests applied	✓		Results & discussion should be presented separately.
• Data analysis correctly interpreted			
• Level of significance (preferred less than 0.1%)			
Discussion • Important findings and results discussed	✓		
• Results of the study compared with others in literature	✓		
• Strengths mentioned			
• Weakness mentioned			
Conclusion			
• Conclusion justified by the results / findings			
• Conclusion relevant to the aims & objectives			
References			
• Adequate number of references quoted	✓		
• References in Vancouver style		✓	
• All references authenticated			
• Recent (last 5 years) references mentioned		✓	
Conflict of interest disclosure		✓	
Funding sources acknowledge		✓	
Written english			
• Spelling	✓	✓	Grammatical & spelling
• Grammar	✓	✓	mistakes need correction

REPORT

Accepted with major revision ☑

Accepted with minor revision ☐

Rejected ☐

Revision Required

Journal of Pakistan Association of Dermatologists. 2019; **29(4)**: 1*-1* .

Original Article

Factors associated with uremic pruritus in chronic kidney failure patients

Ago Harlim, Paulus Yogyartono*, Hana C. Yulia

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Abstract

Background Uremic pruritus is one of the most bothersome symptoms in patients with chronic renal failure. Interestingly, pruritus is typically not seen in acute renal failure. ~~The expanding number of alleged pathogenesis factors bears testimony to the elusiveness the causes but its pathogenesis remains unclear.~~ The aim of this study is to evaluate the frequency and intensity of uremic pruritus in hemodialysis patients, and to correlate its presence with several ~~pustule~~ possible etiology factors ~~parameters.~~

Methods This study was a cross sectional study in Dr. Kariadi Hospital Semarang on 33 patients ~~in~~ under hemodialysis ~~room~~ from June until November 2005. Each patient would ~~take~~ provide 6 cc of blood before hemodialysis for ~~examination for~~ blood urea, parathyroid hormone, calcium ~~blood levels~~, phosphate ~~blood levels~~, magnesium ~~blood levels~~, vitamin A ~~levels~~, and interleukin 2, ~~after that~~ patient ~~would~~ were be ~~got~~ interview with examination ~~of~~ other diseases that can cause itching.

Results Uremic pruritus was found in 75.8% of the patients, ~~and the highest frequency in the third degree reached 40%~~. Uremic pruritus ~~doesn't have~~ had no correlation with ~~uremic~~ urea level, secondary hyperparathyroidism, elevation of divalent cations level such as calcium, phosphor, magnesium as well as to hypervitaminosis A, interleukin-2 or a group of those variables. On the other hand, uremic pruritus correlates to accompanying diseases, and the level of education. ~~On further analysis, degree of~~ intensity of uremic pruritus ~~does not correlate to those factors, but~~ correlates to the time occurrence of itch and hemodyalisis period.

Conclusion Multi factorial facets could be involved in the pathogenesis of uremic pruritus. Further experiments are needed to reveal the pathogenesis of uremic pruritus.

Key words
Pruritus uremic, chronic kidney disease, acute kidney disease.

Introduction

Pruritus is an unpleasant skin sensitivity, which causes a desire to scratch. Uremic pruritus is a pruritus that often occurs in CRF with high urea levels.[1,2] According to the other literature, prevalence of CRF patients who increase uremic pruritus between 50-90%.[1,3,4]

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Pruritus is a problem that often occurs in patients with chronic kidney failure (CRF). The results of the study abroad, the prevalence of uremic pruritus in patients with CRF who performed hemodialysis around 50-90% and 65% of patients complained of persistent pruritus.[5,6] Symptoms of uremic pruritus in the form of paroxysmal pruritus are itching with sudden onset, very itchy, often waking the patient, and stopping suddenly after being scratched. Symptoms like this can be found in other diseases such as atopic dermatitis, numularis dermatitis, herpetiform dermatitis,

excoriation neurotic, eosinophilic folliculitis, subacute prurigo, prurigo nodularis and paroxysmal pruritus.[6]

In people with uremic skin it will appear dry, atrophy, yellowish in color, occur in about 67-93% of patients and do not recover from topical moisturizers.[7]

Many studies have been conducted to assess the clinical characteristics and causes of uremic pruritus but the exact cause and mechanism of pruritus in chronic renal failure is still very little understood.[2,3] Several factors thought to play a role in the pathogenesis of uremic pruritus include dry skin, sweat and sebaceous gland atrophy, secondary hyperparathyroidism, cutaneous mast cell proliferation, increased plasma histamine, hyperkalemia, hyperphosphatemia, hypermagnesemia, aluminum overload, Fe deficiency anemia, hypervitaminosis vitamin A, peripheral neuropathy, opioid peptides, pruritic cytokines such as interleukin (IL)-2, inflammatory markers, dialysis efficacy, but in other studies controversial results were obtained. The effect of urea on pruritus has not been studied.[3-6,9,10]

According to Yosipovitch et al., the criteria for uremic pruritus are complaints of itching in people with chronic renal failure, at least 3 episodes in the last 2 weeks, at least 3 episodes in the last 2 weeks, with complaints several times a day, at least a few minutes and disturbing patients, while the itching in uremic pruritus based on visual analog.[1]

In patients with CRF, uremia syndrome occurs where biochemical and chemical disorders occur. Skin disorders often found in the form of pallor/ paleness, ecchymosis, hematoma, pruritus, uremic frost.[11] There can also be xerosis, swelling, atrophy, and pigment abnormalities such as yellowish color due to the retention of urochrome and carotene. Brownish hyperpigmentation due to increased production of melanin due to the low dialysis of beta melanocyte stimulating hormone.[3]

Some etiopathogenesis factors of uremic pruritus are secondary hyperparathyroidism, increased concentration of calcium, magnesium and phosphate on the skin, hypervitaminosis A. Hyperparathyroidism can cause an increase in phosphate and calcium which play a role in soft tissue calcification. Magnesium is involved in modulating nerve conduction and histamine release from mast cells. Magnesium will be excreted in the kidneys so that abnormalities in the kidneys caused hypermagnesium. Hypervitaminosis A caused dry skin.[3,4,6-10,12].

Methods

This study was a cross sectional study with a population of patients with CRF who got hemodialysis in Dr. Kariadi Hospital Semarang from June until November 2005. A total of 33 patients were enrolled, with independent variables are uremia, secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia, hypermagnesemia, hypervitaminosis A, and Interleukin-2. The dependent variable is uremic pruritus. Each patient would take 6cc of blood before hemodialysis for examination blood urea, parathyroid hormone, blood calcium levels, blood phosphate levels, blood magnesium levels, vitamin A levels, interleukin 2 and examination of other diseases that can cause itching, for example blood sugar checks and liver tests.

The inclusion criteria for this study were that patients with hemodialysis with membrane were recycled at Dr. Kariadi Hospital Semarang, willing to be included in the study by signing a statement letter willing to be examined and answer the existing questionnaire, not receiving

CAPD therapy, not receiving pruritus therapy for the last month and not receiving corticosteroid therapy for last month. While the exclusion criteria for patients who have systemic diseases that can cause pruritus but are not associated with kidney disease.

Blood urea levels in mg/dl were taken before hemodialysis. Secondary hyperparathyroidism examination was performed at the IDD Lab in Dr. Kariadi Hospital with an ELISA ELX 800 microplate reader with a wavelength of 490 nm. It was said that secondary hyperparathyroidism when thyroid levels were 8.3-68.0 pg / dl.[13] It is said hyperphosphatemia if it exceeds normal levels 2.6-4.0 mg/dl. It is said that hypercalcemia exceeds 8.8-10.8 mg/dl. Hypermagnesemia if magnesium levels are 1.9-2.5 mg/dl.[14] Hypervitaminosis A if it exceeds the limit of 20-100 µg/dl.[15]

The accompanying disease is internal disease associated with CRF which can cause itching such as DM, and liver disease (cholestasis, primary biliary cirrhosis, extra hepatic billiard obstruction based on a history of diseases such as steatorrhea, dark urine, history of itchy, icteric eyes. Examination will performed by researchers and cross checks by other doctors.

Student T test was used to analyze data with normal distribution, while Mann Whitney Test was used for data with abnormal distribution to see the relationship between blood urea level and IL-2 with uremic pruritus. Chi Square test is used to see the relationship between parathyroid hormone levels, blood calcium levels, blood phosphate levels, blood magnesium levels, vitamin A levels and the incidence of comorbidities with uremic pruritus.

Results and Discussion

Table 1 Frequency Distribution of CRF Sufferers Who Experience Pruritus Uremic

Pruritus Uremic	*n*	*%*
Yes	25	75,8
No	8	24,2
Total	33	100,0

Table 2 Pruritus Uremic Based on Degree of Severity

Severity Degree	*n*	*%*
1st Degree	4	16
2nd Degree	6	24
3rd Degree	10	40
4th Degree	5	20
Total	25	100,0

The number of GGK participants in this study was 35 people, but in the end 2 study respondents dropped out due to unconsciousness and death, resulting in a total sample of 33 people consisting of 27 men and 8 women. With the youngest age is 19 years and the oldest is 73 years.

There was no significant relationship between urea levels and uremic pruritus could explain why the uremic syndrome occurs only in CRF but is not found in ARF. The chronic condition of high urea levels causes the manifestation of uremic syndrome. Patients who have hemodialysis urea levels will quickly decrease but also will quickly rise again so that patients have to do hemodialysis regularly. This instability of chronic urea causes uremic pruritus.

In a previous study conducted by Massry S et al. in the 1968 New England Med Journal stating secondary hyperparathyroidism was the cause of uremic pruritus and in the same year as Hampers CL, Katz AI et al.[16] but in the last literature the itching loss in patients who have had parathyroidectomy is temporary.[17] This result is consistent with this study where no significant association was found between secondary parathyroid and uremic pruritus.

Tabel 3 Relationship Between High Low Ureum, Secondary Parathyroid, Calcium Levels, Phosphatemia Levels, Magnesemia Levels, Vitamin A Levels, Interleukin-2 Levels, and other disease caused itchy with Urinary Pruritus Events

Ureum Level Group	*Pruritus Uremic*				*p*
	Yes		*No*		
	n	%	n	%	
High	12	48,0	5	62,5	0,688
Very High	13	52,0	3	37,5	
	25	100,0	8	100,0	
Secondary parathyroid Level Group	Pruritus Uremic				
	Yes		No		
	n	%	n	%	
Yes	15	60,0	5	62,5	1,000
No	10	40,0	3	37,5	
	25	100,0	8	100,0	
Calcium Level Group	Pruritus Uremic				
	Yes		No		
	n	%	n	%	
High	0	0	1	12,5	0,242
Normal	25	100,0	7	87,5	
	25	100,0	8	100,0	
Phosphate Level Group	Pruritus Uremic				
	Yes		No		
	n	%	n	%	
High	9	36,0	3	37,5	1,000
Normal	16	64,0	5	62,5	
	25	100,0	8	100,0	
Magnesium Level Group	Pruritus Uremic				
	Yes		No		
	N	%	n	%	
High	2	8,0	1	12,5	1,000
Normal	23	92,0	7	87,5	
	25	100,0	8	100,0	
Vitamin A Level Group	Pruritus Uremic				
	Yes		No		
	n	%	n	%	
Normal	18	72,0	6	75,0	1,000
High	7	28,0	2	25,0	
	25	100,0	8	100,0	
Interleukin 2 Level Group	Pruritus Uremic				
	Moderate		Severe		
	n	%	n	%	
Moderate	12	48,0	5	62,5	0,688
Severe	13	52,0	3	37,5	
	25	100,0	8	100,0	
Other Diseases That Can Cause Itching	Pruritus Uremic				
	Yes		No		
	n	%	n	%	
Yes	12	48,0	0	0	0,03
No	13	52,0	8	100,0	
	25	100,0	8	100,0	

In this study, divalent ions were examined, namely blood calcium, phosphate and magnesium levels which found no significant association with uremic pruritus. This is consistent with a study conducted by Hiroshige K et al in 1995, Virga G et al. in 1998, Merkus MO et al. in 1999.[4] Congers of 2003 nephrology stated that no evidence found to suggest an association between uremic pruritus and hyperphosphatemia, hypercalcemia and hypermagnesemia.[4] It is said that divalent ions can modulate nerves and histamine release by cell mast.[4] In pruritus uremic we can found many mast cell in skin, it can happened maybe because increasing parathyroid level plasma in secondary hyperparathyroidism. Otherwise this change can happened cause skin respond against skin damage due to itching.[18,19] In recent research states there is no association between histamine count and uremic pruritus. So this still statement requires further research.[4]

In this study there was no significant association with Hypervitaminosis A with uremic pruritus. This can be proven where vitamin A level in the epidermis in CRF with dry skin does not differ significantly in the skin of patients with CRF without dry skin. This statement show dry skin occurs is not due to hypervitaminosis A, but there are abnormalities in corneocyte maturity caused by uremia.[3,18,19]

The theory that states role of IL-2 with uremic pruritus is not proven in this study. There was no significant difference in IL-2 levels in CRF patients who had uremic pruritus with those without uremic pruritus. This can occur because uremic pruritus can occur not only by IL-2 cytokines. IL2 is not only produced by Th1 but also by other T cells, whereas T lymphocytes produce other cytokines such as IL-1, IL-2, IL-6, IL-10, IL-12, IL-14, IL-17, GM-CSF, TNF-α, IFN-β, INF- γ, TGF-α-β.[20]

There was a significant relationship between uremic pruritus and other diseases that can cause itching. In this case, including other diseases are skin diseases, systemic diseases, or idiopathic diseases. It can be understood that the cause of itching in other diseases through impulses is the same as itching in general.[9] Where nerve endings are free to interact with mast cells, and activated cell masts will release triptase which activates receptors at the end of C nerve fibers so that itching will be transmitted to the central nervous system. The release of neuropeptide as a neurogenic inflammatory mediator will involve proteinase-activated receptors type 2 (PAR2) in sensory nerves. PAR 2 will be broken down by triptase from mast cells and neutrophils that results in histamine release. PAR-2 secretes Cacitonis gene-related peptide (CGRP) and substance P (neurokinin 1) from the fibers of C. Caffero and the P substance will cause itching.[9]

From the results of this study, the most complaints were the itching that was felt continuously day and night, while in the second place itching at night. It can be caused by no more work at night so that itching is felt more and psychogenic factors. In his spare time the patient tends to think of his kidney disease, contemplate the things he has done or other things that are psychogenic. This can be connected also with a decrease in blood cortisone levels at night according to circadian rhythms,[20] making it more difficult to withstand stress. While itching during the day can be caused due to the severity of the complaints, which in subsequent analyzes are significantly related to the degree of pruritus.

There are several factors that are not examined during this examination, such as sebaceous gland atrophy and sweat, plasma histamine levels, cutaneous mast proliferation of iron deficiency anemia, peripheral neuropathy, opioid peptide, inflammatory markers, dialysis

methods, daily activity factors and pruritus therapy. As we know dry skin can cause itching, but in this study there was no association between itchy dry skin and hyperuremia. Histamine plasma and aluminum tests were not carried out due to limited examination facilities, while examination of cutaneous mast cells and sebaceous cell atrophy and sweat required a skin biopsy that is not possible. Examination of Fe in the blood to see iron deficiency anemia is inaccurate because sufficient levels of Fe can cause iron deficiency.

Conclusion

Pruritus prevalence in CRF patients in Dr. Kariadi Hospital was 75.8%, with the highest severity at 3rd degree CRF (40%). There was no relationship between blood urea levels, secondary hyperparathyroidism, increasing levels of diavalent cations such as calcium, phosphate, magnesium and hypervitaminosis A. This is consistent with previous studies where the possibility of this is influenced by many factors.

There was no significant association between Interleukin-2 and uremic pruritus where there was an opinion about association between Interleukin-2 and uremic pruritus. This can be caused by the need for the collaboration other cytokines produced by T cells and other pro inflammation to cause uremic pruritus.

Pruritus was significantly associated with complicating factors that accompany CRF, which are other diseases that can cause itching. Although in further studies there was no significant association between uremic pruritus and these two factors, it was significantly associated with the time of occurrence of itching and the duration of hemodialysis.

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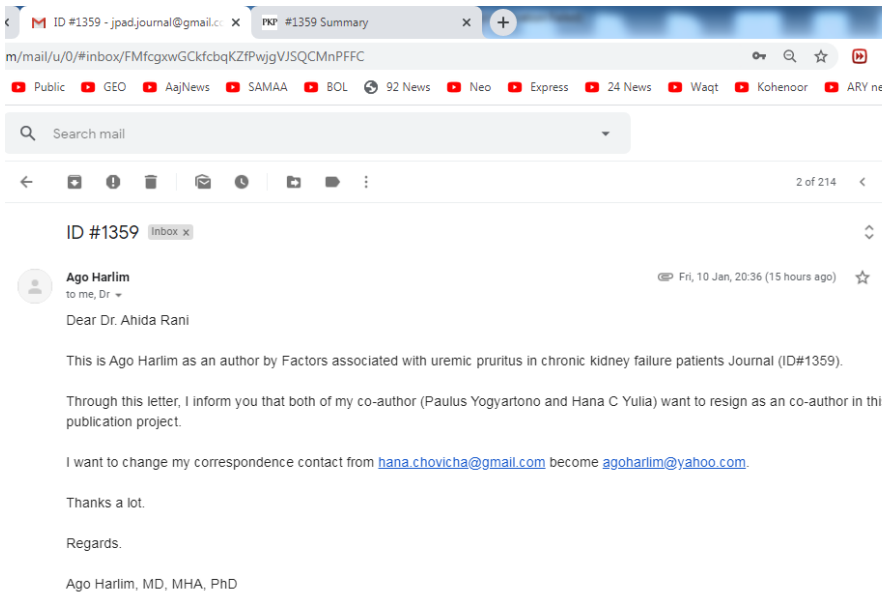

Abstract

Background Uremic pruritus is one of the most distressing symptoms in patients with chronic renal failure. Interestingly, pruritus is not typically found in acute renal failure. Etiology and pathogenesis of uremic pruritus remain unclear. Several studies have demonstrated controversial results. Our study evaluated the frequency and intensity of uremic pruritus in patients with chronic renal failure (CRF) on hemodialysis including its associated factors. The aim of our study was to determine etiology and pathogenesis of uremic pruritus.

Method The study was a cross-sectional study conducted at Dr. Kariadi Hospital in Semarang city involving 33 hemodialysis patients between June and November 2005. About 6 cc of blood volume was withdrawn from each patient before the patient undergoing hemodialysis. Laboratory findings including blood urea, parathyroid hormone, calcium, phosphate, magnesium, vitamin A, and interleukin 2 levels were evaluated. Patient were be interviewed and examined if they had other diseases that may also cause pruritus.

Results Uremic pruritus was found in 75.8% of the patients. Uremic pruritus had no correlation with urea level, secondary hyperparathyroidism elevated divalent cations levels such as calcium, phosphate, magnesium levels as well as with hypervitaminosis A, interleukin-2 level or any group of those variables. On the other hand, uremic pruritus correlated to concomitant diseases. The intensity of uremic pruritus was related to the duration of hemodialysis.

Conclusion Multifactorial facets could be involved in the pathogenesis of uremic pruritus. Further experiments are required to reveal greater details regarding the pathogenesis of uremic pruritus.

Keyword: Pruritus uremic, Chronic Kidney Disease, Acute Kidney Disease

Introduction

Pruritus is an unpleasant skin sensation that induces a desire to scratch, which often occurs in patients with chronic renal failure (CRF).[1,2,3] Uremic pruritus is itching that has been frequently observed in patients with CRF who have high levels of urea.[1,2,4] According to some literatures, the prevalence of patients with CRF who had uremic pruritus may reach 90%.[5]

Pruritus is a common problem in patients with CRF. Other studies have reported that the prevalence of uremic pruritus in CRF patients on hemodialysis is approximately 50% to 90%. Moreover, 65% of the patients complain about persistent pruritus.[1,6-10] Symptoms of uremic pruritus include paroxysmal pruritus, which is a sudden onset of excruciating itching that often wake the patients up from itching in their sleep and it relieves immediately after scratching. Such symptom can be found in other diseases such as atopic dermatitis, nummular dermatitis, dermatitis herpetiformis, neurotic excoriation, eosinophilic folliculitis, subacute prurigo, prurigo nodularis and pruritus uremic.[10]

The skin of uremic patients would appear dry, atrophic and yellowish that occurs in approximately 67-93% cases and the skin condition does not respond to topical moisturizer treatments. [11]

A lot of studies have been performed to evaluate clinical characteristics and etiology of uremic pruritus; however, the certain cause and mechanism of CRF-associated pruritus is still poorly understood. [2,8,12,13]

Some factors are considered to have roles in the pathogenesis of uremic pruritus including dry skin, sebaceous and sweat gland atrophy, secondary hyperparathyroidism, hyperphosphatemia, hypermagnesemia, aluminum overload, iron deficiency anemia, hypervitaminosis A, peripheral neuropathy, opioid peptides, pruritus cytokines such as interleukin (IL)-2, inflammatory markers, and dialysis efficacy.[4,5,14,15] Hyperparathyroidism may cause increased levels of phosphate and calcium, which may have roles in soft-tissue calcification.[16] Hypervitaminosis A may cause dry skin, which will evoke pruritus.[11]However, other studies have demonstrated controversial results. The effect of urea on pruritus has not been extensively studied. [10,16,17] Magnesium is involved in modulated nerve conduction and histamine release from mast cells. It is excreted by the kidneys and therefore, any problem in the kidneys may cause hypermagnesemia.[19,20]

According to Yosipovitch et al, the criteria of uremic pruritus are complaints of itching in CRF patients that occur for at least 3 episodes within the last 2 weeks. The complaints come several times daily for at least several minutes and disturbing the patients; while the severity of itching in uremic pruritus is usually evaluated using visual analog scale. [1]

In patients with CRF, uremic syndrome occurs, in which biochemical and systemic dysfunction take place.[21] Common skin disorders include pallor, ecchymosis, hematoma, pruritus and uremic frost.[19] Xerosis, swelling, atrophy, and pigmentation disorder such as yellowish discoloration due to retained urochrome pigment and high levels of carotene in blood.[6,11] Brownish hyperpigmentation can be found due to increased melanine production resulting from poor dialysis of beta-melanocyte-stimulating hormone (beta-MSH). [6]

Method

The study was a cross-sectional study with a population of CRF patients who underwent hemodialysis at Dr. Kariadi Semarang Hospital in 2005. The study was conducted between June and November 2005. The sample size was 33 patients. The independent

variables were uremia, secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia, hypermagnesemia, hypervitaminosis A and interleukin-2; while the dependent variable was uremic pruritus and the confounding variables were presence or absence of concomitant diseases of CRF that might also cause itching such as skin disease, systemic disease associated with CRF and idiopathic pruritus. Skin disease appeared as a lesion on itching skin. Systemic diseases, which were internal diseases associated with CRF that might cause itching included diabetes mellitus (DM), liver diseases (cholestasis, primary biliary cirrhosis, extrahepatic biliary tract obstruction, acute hepatitis). Laboratory tests such as gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), serum glutamic pyruvate transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT) and blood glucose evaluations were performed whenever there was any suspicion of the systemic diseases. The evaluation was performed when the patients underwent hemodialysis by the investigator and the results were cross-checked by another examiner or doctor. The patients were assessed and categorized into 2 scales, i.e. patients with concomitant diseases and those without concomitant diseases.

In order to obtain data, 6 cc of blood sample was withdrawn prior to the hemodialysis. The patients were then interviewed. History taking and physical examination were performed. The blood samples were assessed for serum levels of urea, parathyroid hormone, calcium, phosphate, magnesium, vitamin A and interleukin-2 as well as for other tests to detect other diseases that might cause itching such as random blood glucose test and liver function tests.

Inclusion criteria of our study were patients who underwent hemodialysis using recycled dialysis membrane at Dr. Kariadi Semarang Hospital. They were willing to participate in our study and had signed the informed consent form that they were agreed to be examined and to answer the questionnaire. The patients did not receive CAPD (Continuous Ambulatory Peritoneal Dialysis) treatment. They also did not receive treatment for pruritus and corticosteroid within the last one month. While the exclusion criteria were patients who had systemic diseases that might cause pruritus, but the diseases were not associated with kidney diseases.

Blood urea level was presented in mg/dL and the blood samples were withdrawn prior to the hemodialysis. Evaluations on secondary hyperparathyroidism and IL-2 were performed using ELISA; while assessments to evaluate hypercalcemia, hyperphosphatemia and hypermagnesemia were carried out using Spectrophotometer 4010. Hypervitaminosis A was assessed using HPLC (High Performance Liquid Chromatography).

To analyze data on correlation between independent variables and uremic pruritus that had normal distribution, a student T-test was used; while for data with abnormal distribution such as IL-2, the Mann-Whitney test was used. ANOVA test was used to evaluate the difference between independent variables and the severity of uremic pruritus except for IL-2 by using Kruskall Wallis test. Chi-square test was used to evaluate the correlation between the levels of parathyroid hormone, blood urea, calcium, phosphate, magnesium, vitamin A as well as the presence/absence of concomitant diseases and the incidence of uremic pruritus.

Results

There were 35 subjects of CRF patients who participated in the study; however, ultimately 2 subjects were dropped out since the subjects were unconscious and died; therefore, the total sample size was 33 subjects including 25 men and 8 women. The youngest age was 19 years and the oldest was 73 years.

Table 1. Frequency distribution of CRF patients experiencing uremic pruritus

Uremic pruritus	n	%

Present	25	75.8
Absent	8	24.2
Total	33	100.0

The severity of uremic pruritus was divided into 4 categories, which were: 1st degree: itching without scratch mark; 2nd degree: itching with scratch mark, but without excoriation; 3rd degree: continuous itching with scratch mark or excoriation; 4th degree: 2nd and 3rd degree and the itching caused the subject became extremely anxious. [7]

Based on the degree of severity, there were 10 subjects (40%) with 3rd degree; while there were 5 subjects (20%) with 4th degree. The frequency distribution of subjects with uremic pruritus based on the degree of severity can be seen in table 2.

Table 2. Frequency distribution of subjects with uremic pruritus based on the degree of severity

Severity	n	%
1st degree	4	16
2nd degree	6	24
3rd degree	10	40
4th degree	5	20
Total	25	100.0

Most subjects reported that the itching was experienced on the back (51.5%); while others said that the itching was found on the abdomen (6.1%), feet (6.1%), face, shoulder, buttock, which were experienced by a subject, respectively. The results were consistent with those of other studies, i.e. the itching mostly was experienced on the back reaching to 70% of cases.[1,12] The second most frequent body location for pruritus was abdomen, which was found in 46% of cases. The back is more difficult to reach for scratching; therefore, the patients probably felt the itch to be more intense. About 33.3% of subjects with pruritus admitted that they often experience both daytime and night-time itching; while nine subjects (27.3%) experienced only night-time itching. There were four subjects (12.1%) who confessed experiencing the itch after hemodialysis procedure and there was only one subject (3%) who had the itch in the morning.

The result of our study showed that continuous daytime and night-time pruritus was the commonest finding and nocturnal pruritus was the second most. It probably occurred since at night-time, there subjects were at rest and had no further tasks; therefore, the itching was felt more intense and there was probably also psychogenic factors that might exist.[22,23] There was a significant correlation between the severity of uremic pruritus and the onset of itching complaint (P= 0.005) as can be seen in table 3.

Table 3. Correlation between the severity of uremic pruritus and the onset of itching complaint

Onset of pruritus	Severity				*P*
	Only complaint		Complaint + skin disorder		
	n	%	n	%	
Night-time	1	25.0	8	38.1	0.005
Daytime and night-time	0	0	11	52.4	
Hemodialysis	3	75.0	1	4.8	

Daytime	0	0	1	4.8	
Total	4	100.0	21	100.0	

Table 4. Mean difference of independent variables in patients with uremic and non-uremic pruritus

Independent variables	Mean ± SD in patients with UP complaints	Mean ± SD in patients without UP complaints	*P*
Age (years)*	49 ± 12.2	49 ± 7.1	0.500
Duration of illness (months)	26 ± 33.9	18 ± 20.6	0.399
Numbers of hemodialysis (times)	84 ± 86.4	63 ± 100.9	0.205
Ureum level	170 ± 54.7	155 ± 38.2	0.688
PTH level	174 ± 209.7	208 ± 156.3	0.679
Calcium level	8.55 ± 0.79	9.05 ± 1.32	0.226
Phosphate level	3.85 ± 0.88	3.84 ± 1.18	0.875
Magnesium level	2.17 ± 0.22	2.30 ± 0.47	0.378
Vitamin A level	76.87 ± 34.00	77.30 ± 41.84	0.977
IL-2* level	0.2797 ± 0.225	0.1967 ± 0.191	0.366

Notes : * = were evaluated using Mann-Whitney test; UP = uremic pruritus

Results of analysis showed that the mean values of those independent variables were not significantly different between patients with and without uremic pruritus complaints. The mean difference of independent variables in table 4 was also tested whether there was a mean difference based on the severity of uremic pruritus. For the sake of the statistical test, we used categorization based on the four degree (the before-mentioned category). Two independent variables, which were age and the level of interleukin 2 in table 4 had abnormal distribution and therefore, they were analyzed using non-parametric method, i.e. by using Kruskal Wallis test. While the other independent variables were evaluated using the one-way ANOVA. Of all independent variables that had been analyzed, we found that only the number of hemodialysis had significant difference with the severity of uremic pruritus (P =0.32). Complete results can be seen on table 5. The Kruskal Wallis test showed that both age and interleukin 2 levels had no significant correlation with the severity of uremic pruritus (Table 6).

Table 5. Differences of independent variables based on the severity of uremic pruritus using ANOVA test

Variables	Calculated F	*P*
Ln duration of illness	0.575	0.638
Ln duration of hemodialysis	3.552	0.032
Ln urea level	0.134	0.939
Ln parathyroid hormone level	0.260	0.854
Ln calcium level	0.916	0.450
Ln phosphate level	0.919	0.449
Ln magnesium level	0.349	0.790
Vitamin A level	2.470	0.090

Table 6. Differences of independent variable IL-2 based on the severity of uremic pruritus

	Interleukin 2 level	Patients' age (yr)
Chi-Square	.670	4.860
df	3	3
Asymp. Sig.	.880	.182

a. Kruskal Wallis Test

b. Grouping Variable: severity of uremic pruritus

Based on the results of ANOVA analysis, we found that the mean numbers of hemodialysis was significantly different from the severity of uremic pruritus (P =0.032). The mean number of hemodialysis in patients with 1st degree uremic pruritus was 100.5 times; while in the 2nd degree, the mean value decreased to only 24.3 times. In patients with the 3rd degree, the mean number of hemodialysis was the highest, i.e. 135.7 times. However, the mean decreased again to 39 times of hemodialysis in patients with 4th degree. The mean number of hemodialysis for each degree of severity of uremic pruritus can be seen in table 7.

Table 7. Mean number of hemodialysis for each degree of severity of uremic pruritus

	N	Mean	Std. Deviation	Std. Error	95% Confidence interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
1st degree	4	100.50	111.60	55.80	-77.08	278.08	10	260
2nd degree	6	24.33	31.72	12.95	-8.96	57.62	3	87
3rd degree	10	135.70	89.10	28.18	71.96	199.44	5	244
4th degree	5	39.00	39.18	17.52	-9.65	87.65	6	98
Total	25	84.00	86.43	17.29	48.32	119.68	3	260

In further analysis, the investigator performed the post hoc test to evaluate mean difference of the number of hemodialysis for each degree of severity for uremic pruritus. Results of post hoc test LSD showed a significant difference of mean numbers of hemodialysis between patients with 4th degree and 3rd degree (P = 0,03). The mean difference between the 3rd and 4th degree was 96.7 times hemodialysis. Complete results of post hoc test LSD analysis can be seen in table 8.

Table 8. Post hoc test: mean difference of the number of hemodialysis based on the severity of uremic pruritus

(I) the severity of uremic pruritus	(J) the severity of uremic pruritus	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence interval	
					Lower Bound	Upper Bound
1st degree	2nd degree	76.17	48.79	.133	-25.30	177.64
	3rd degree	-35.20	44.72	.440	-128.20	57.80
	4th degree	61.50	50.71	.239	-43.95	166.95
2nd degree	1st degree	-76.17	48.79	.133	-177.64	25.30
	3rd degree	-111.37*	39.03	.010	-192.54	-30.19

	4th degree	-14.67	45.77	.752	-109.85	80.52
3rd degree	1th degree	35.20	44.72	.440	-57.80	128.20
	2nd degree	111.37*	39.03	.010	30.19	192.54
	4th degree	96.70*	41.40	.030	10.60	182.80
4th degree	1st degree	-61.50	50.71	.239	-166.95	43.95
	2nd degree	14.67	45.77	.752	-80.52	109.85
	3rd degree	-96.70*	41.40	.030	-182.80	-10.60

*. The mean difference was considered significant at the .05 level.

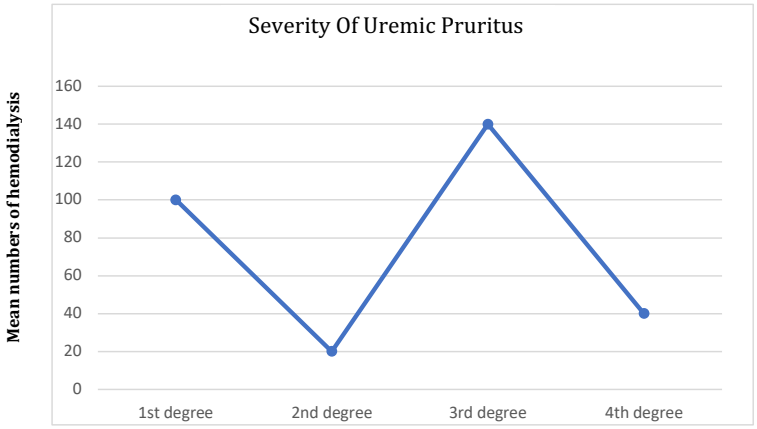

Figure 1. Graph of mean numbers of hemodialysis based on the severity of uremic pruritus in CRF patients

On the graph, there is a tendency of increased severity of uremic pruritus with increased mean numbers of hemodialysis, which is between the mean value of 24.3 and the 39 times of hemodialysis and such tendency can also be seen when the mean value is more than 100.5 times hemodialysis. It can be demonstrated based on the results of post-hoc test analysis, which showed significant results between the 2nd and the 3rd degree as well as between the 3rd and the 4th degree.

On the history of hemodialysis procedure, i.e. between the mean value of 39 and 100.5 times hemodialysis, there was reduced severity of uremic pruritus complaint. It can be explained as there is an adaptation factor for the itching sensation. Another possibility is that the kidney function can still be maintained though using hemodialysis instrument; therefore, the pruritogenic substances can be excreted although the substances may not be fully removed. On further stage, i.e. more than 100.5 times hemodialysis, there was a tendency of greater uremic pruritus severity as the itching exacerbated in consistent with the severity of CRF, which had become more severe.

Affected / dependent variables in our study were categorical data; therefore, some of laboratory results in table 4 should also be categorized. The result of categorization can be seen in table 9.

Table 9. Frequency distribution of some factors affecting uremic pruritus

Affecting factors	Categories	n	%
Urea level (n = 33)	High	17	51.5
	Low	16	48.5
Parathyroid hormone (n = 33)	With secondary hyperparathyroidism	20	60.6
	Without secondary hyperparathyroidism	13	39.4
Calcium level (n = 33)	Hypercalcemia	1	3.0
	No hypercalcemia	32	97.0
Phosphate level (n = 33)	Hyperphosphatemia	12	36.4
	No hyperphosphatemia	21	63.6
Magnesium level (n = 33)	Hypermagnesemia	3	9.1
	No hypermagnesemia	30	90.9
Vitamin A level (n = 33)	Hypervitaminosis A	9	27.3
	No hypervitaminosis A	24	72.7
Interleukin 2 (n = 33)	High	16	48.5
	Moderate	17	51.5
Concomitant disease	Present	12	48.0
	Absent	13	52.0

Results of 2 x 2 cross tabulation showed that there was no correlation between urea level and the incidence of uremic pruritus (table 10). Moreover, an analysis was also performed to find any correlation between the high or low urea level and severity of uremic pruritus. The severity of uremic pruritus was categorized into two groups including those with complaints alone ant those with complaints accompanied by skin disorders. The results of 2 x 2 cross tabulation also did not show any significant correlation between the severity of uremic pruritus and urea level (P = 1.000), which can be seen in table 18.

Table 10. Correlation between the high or low urea level and the incidence of uremic pruritus

Urea level	Uremic Pruritus				
	Present		Absent		
	n	%	N	%	*P*
High	12	48.0	5	62.5	0.688
Very high	13	52.0	3	37.5	
	25	100.0	8	100.0	

Meanwhile, results of 2 x 2 cross tabulation between the incidence of uremic pruritus and the presence or absence of hyperparathyroidism can be seen in table 11. Results in the table 11 also shows that there was no significant correlation between the incidence of uremic pruritus and hyperparathyroidism (P = 1.000)

Table 11. Correlation between secondary hyperparathyroidism and the incidence of uremic pruritus

Secondary	Uremic Pruritus

hyperparathyroidism	Present		Absent		
	N	%	N	%	*P*
Present	15	60.0	5	62.5	1.000
Absent	10	40.0	3	37.5	
	25	100.0	8	100.0	

Commented [A1]:

Results in table 12 shows that there was no significant correlation between the incidence of uremic pruritus and hypercalcemia ($P = 0.242$)

Table 12. Correlation between hypercalcemia and the incidence of uremic pruritus

Calcium Level	Uremic Pruritus				
	Present		Absent		
	N	%	N	%	*P*
Hypercalcemia	0	0	1	12.5	0.242
No hypercalcemia	25	100.0	7	87.5	
	25	100.0	8	100.0	

Results in table 13 shows that there was no significant correlation between the incidence of uremic pruritus and hyperphosphatemia (P = 1.000)

Table 13. Correlation between hyperphosphatemia and the incidence of uremic pruritus

Phosphate level	Uremic Pruritus				
	Present		Absent		
	N	%	N	%	*P*
Hyperphosphatemia	9	36.0	3	37.5	1.000
No hyperphosphatemia	16	64.0	5	62.5	
	25	100.0	8	100.0	

Results in table 14 shows that there was no significant correlation between the incidence of uremic pruritus and hypermagnesemia (P = 1.000)

Table 14. Correlation between the presence or absence of hypermagnesemia and uremic pruritus

Magnesium level	Uremic pruritus				
	Present		Absent		
	N	%	N	%	*P*
Hypermagnesemia	2	8.0	1	12.5	1.000
No hypermagnesemia	23	92.0	7	87.5	
	25	100.0	8	100.0	

Results of Fisher's Exact test showed $P = 1.000$, which means that there was no significant correlation between the incidence of uremic pruritus and hypervitaminosis A. The correlation between hypervitaminosis A and the incidence of uremic pruritus can be seen in table 15.

Table 15. Correlation between hypervitaminosis A and the incidence of uremic pruritus

Vitamin A level	Uremic pruritus				
	Present		Absent		
	n	%	n	%	*P*
Normal	18	72.0	6	75.0	1.000
Above normal	7	28.0	2	25.0	
	25	100.0	8	100.0	

Meanwhile, there was also no correlation between uremic pruritus and interleukin 2 ($P = 0.688$) as seen in table 16.

Table 16. Correlation between interleukin 2 and the incidence of uremic pruritus

Interleukin-2 level	Uremic pruritus				
	Present		Absent		
	n	%	n	%	*P*
Moderate	12	48.0	5	62.5	0.688
High	13	52.0	3	37.5	
	25	100.0	8	100.0	

The variables of concomitant diseases in CRF patients were defined as other diseases that might cause itching including skin, systemic or idiopathic diseases. Laboratory tests were necessary for those with a suspicion of the concomitant diseases. The evaluation for detecting the concomitant diseases in CRF patients was performed using cross-checking method by another doctor, which provided a very good result, i.e. a kappa value of 1.00. The 2 x 2 cross tabulation in table 17 shows that there was a significant correlation ($P = 0.03$) between other diseases causing pruritus and the incidence of uremic pruritus.

Table 17. Correlation between other diseases that may cause itching and uremic pruritus

Other diseases that may cause itching	Uremic Pruritus				
	Present		Absent		
	n	%	n	%	*P*
Present	12	48.0	0	0	0.03
Absent	13	52.0	8	100.0	
	25	100.0	8	100.0	

To evaluate the correlation between the levels of urea, parathyroid hormone, phosphate, magnesium, vitamin A, interleukin 2 as well as other concomitant diseases and the severity of uremic pruritus, therefore, the severity of uremic pruritus was divided into 2 categories, i.e. the group with itching symptom alone and the other with itching symptom and skin disorder. Afterward, 2 x 2 tabulation was carried out. After the chi-square test was performed, we found that there was no significant correlation between the levels of urea, parathyroid hormone, phosphate, magnesium, vitamin A, interleukin 2 as well as concomitant disease and the severity of uremic pruritus (Table 18). The correlation between calcium level and the severity of uremic pruritus could not be evaluated since all CRF patients with uremic pruritus did not have hypercalcemia.

Table 18. Correlation between the levels of urea, parathyroid hormone, phosphate, magnesium, vitamin A, interleukin 2 as well as concomitant disease and the severity of uremic pruritus

Severity of Uremic Pruritus	
Urea level	*P* : 1.000
Parathyroid hormone level	P : 1.000
Phosphate level	P : 0.602
Magnesium level	P : 0.300
Vitamin A level	P : 0.593
Interleukin 2 level	P : 1.000
Other diseases that cause itching	P : 0.593

Note : were tested using Chi square test

Discussion

Uremic pruritus is a sensation that evokes the desire to scratch, which often occurs in patients with chronic renal failure undergoing hemodialysis. Uremic pruritus is often a major problem for patients with end-stage renal disease and it affects as many as 90% of HD patients.[5] Many studies have been done to evaluate the clinical characteristics and etiology of uremic pruritus, however, the certain etiology and mechanism of pruritus in chronic renal failure has been poorly understood.

The patient's age in our study had no significant correlation with uremic pruritus (P = 0.500) as seen on table 4. Other studies have suggested that the complaints of uremic pruritus are rarely found in children undergoing hemodialysis. Schwab M, Mikus G, Mettang T in 1999 reported that out of 199 children undergoing hemodialysis, there were only 9.1% who had complaints of pruritus with mild intensity or mild pruritus severity.[12] The study did not explain why it rarely occurred in children, but it mentioned that the pathogenesis of uremic pruritus in children still needs further studies. Another study has indicated that in elderly people, there is a greater tendency that T helper cells may have differentiation into Th1 compared to children. Increased Th1 will produce greater interleukin 2, which will cause itching.[12] Our study did not include children as our subjects were generally older adults (Table 4). This may explain why the age did not have any significant correlation with uremic pruritus. There was no significant correlation between urea level and uremic pruritus and it may explain why uremic syndrome only occurs in CRF but it is not found in patients with acute renal failure (ARF). Chronic condition of high urea level induces the manifestation of uremic syndrome.

In patients undergoing hemodialysis who had high urea level, their blood urea level will rapidly decrease after the hemodialysis and it will increase quickly within sometime after the hemodialysis; therefore, the patients must have regular hemodialysis treatment. Unstable blood urea level has a tendency of high level and becomes chronic, which may occur with an assistance using hemodialysis instrument and it supports the CRF patients' survival. Therefore, it should be emphasized that temporary high blood urea level can not be determined as a reference of developing uremic pruritus. In contrast, unstable and persistent high urea level may induce further problems including uremic pruritus. This notion is supported by evidences found in our study, i.e. there was a significant difference found between the severity of uremic pruritus and the mean numbers of hemodialysis (P = 0.032, ANOVA test Table 5) and such correlation was not found for blood urea level (P = 1.000. Table 18).

Some textbooks or journals of research reports have suggested that the pathogenesis of uremic pruritus is still vague.[7,10-12,24] Many theories have been proposed to explain the causes of uremic pruritus, but further studies have refuted the theories.

An older study, which was conducted by Massry S et al and published in the New England Med Journal in 1968, indicated that secondary hyperparathyroidism is the cause of uremic pruritus and in the same year, Hampers CL, Katz AI et al reported disappearance of uremic pruritus following parathyroidectomy;[12] however, in the last literature, the disappearance of itching in patients who had undergone parathyroidectomy was temporary.[24] It is consistent with results of our study, in which no significant correlation was found between secondary parathyroidism and uremic pruritus. In our study, we evaluated divalent cations, i.e. the blood levels of calcium, phosphate and magnesium and we found no significant correlation of them with uremic pruritus. The results are consistent with results of studies conducted by Hiroshige K et al in 1995, Virga G et al in 1998 and Merkus MO et al in 1999.[7] However, there is a report indicating that there is a correlation between uremic pruritus and hyperphosphatemia, hypercalcemia and hypermagnesemia.[14] It is said that divalent ions may cause nerve modulation and histamine release by mast cells, but recent studies have demonstrated that there is no correlation between the amount of histamine and uremic pruritus; therefore, it still requires further studies. [7,8,25]

Theories about divalent ions that can cause nerve modulation and histamine release by mast cells still need further investigation. A study conducted in hemodialysis patients has demonstrated that the skin mast cells in patients with uremic pruritus is not different from those in control group.[25] The most recent studies have also reported that the concentration of histamine does not correlate with uremic pruritus.[7,8,25]

Most of current literatures have excluded the divalent ions as the cause of uremic pruritus. In the Fitzparick's dermatology in general medicine 9th edition, it is said that the etiology of uremic pruritus may comprise many factors including xerosis, peripheral neuropathy, mast cell hyperplasia, increased serum level of histamine, vitamin A, parathyroid hormone and inflammatory factors.[5] Multifactorial causes may also have role in the pathogenesis of developing uremic pruritus.

In our study, there was no correlation between hypervitaminosis A and uremic pruritus. Some literatures have reported that hypervitaminosis A does have role on the development of uremic pruritus.[6,7,11,26] Nevertheless, the pathogenesis of vitamin A causing pruritus has not been clear. It is assumed that vitamin A, which is fat soluble can not be excreted during dialysis and it causes hypervitaminosis A that may lead to dry and itchy skin.[11] Results of another study conducted by De Kroes S, Smeerk G in 1998 have indicated that there is no evidence that hypervitaminosis A may cause uremic pruritus.[7] Most recent literatures even have not mentioned vitamin A as one of causes for uremic pruritus.[24] Another study has reported that hypervitaminosis A at the epidermis of CRF patients does not have significant difference between CRF patients with and without dry skin. It is said that the dry skin does not occur due to hypervitaminosis A, but it occurs because there is some abnormalities in corneocyte maturity resulting from uremia.[6]

The theory that suggests the role of IL-2 on uremic pruritus has not been confirmed by our study, which did not find any significant difference of IL-2 levels in CRF patients between those with and without uremic pruritus. It may occur since uremic pruritus is not induced only by IL-2 cytokines and IL-2 is produced not only by Th1 but also by other T cells; while T lymphocytes also produce other cytokines such as IL-1, IL-2, IL-6, IL-10, IL-12, IL-14, IL-17, GM-CSF, TNF-α, IFN- β, INF- γ, and TGF-α-β .[27]

Other diseases that cause pruritus such as fungal disease, dermatitis or other skin diseases will exacerbate the existing pruritus. Uremic pruritus is often accompanied with other local skin disease due to weakened immune system. In our study, there was a

significant correlation between uremic pruritus and other diseases that may cause itching. In this case, the other diseases include skin, systemic or idiopathic diseases. It can be easily understood as pruritus in other diseases is developed through the same impulse of itching in general, in which the free nerve endings interact with mast cells and the activated mast cells will release tryptase that will further activate receptors at nerve endings of type C nerve fibers; therefore, the itching sensation will be transmitted to central nervous system.[10,28] Neuropeptide release as neurogenic inflammatory mediator involves type 2 proteinase-activated receptors (PAR2) in sensory nerve. PAR 2 is broken down by tryptase from mast cells and neutrophils resulting in histamine release. PAR 2 produces calcitonin gene-related peptide (CGRP) and P substance (neurokinin 1) from nociceptors of type C nerve fibers.[16] CGRO and P substance will cause pruritus. In other diseases, similar mediator release occurs.

As the definition of pruritus is itching sensation that causes the desire to scratch[7,28] and the sensation occurs due to impulses from the central nerve system (CNS),[20,28,29] therefore, the itching sensation can also be felt as uremic pruritus. In this case, the development of pruritus can also due to the scratching itself as a result of complications accompanying CRF, which stimulates the release of mediators causing pruritus that will obviously induce the itching sensation.

Based on results of our study, most complaints were about persistent itching that had been experienced during daytime and night-time; while the second most were complaints of night-time itching. It may occur since at night-time there was no more work and therefore, the itching sensation became more obvious and psychogenic factors may also have roles.[23] During their leisure time, patients are more likely to think about their kidney disease, considering their previous actions or other psychogenic issues.[22,23] It can be associated with reduced blood cortisol level at night-time, which is consistent with the circadian rhythm and therefore, it is more difficult to manage stress at night-time.[22] Meanwhile, daytime pruritus can be caused due to the severity of the existing complaints, which further analysis showed that it has significant correlation with the severity of pruritus (P =0.005) as seen on table 3.

It is necessary to have further studies on the role of psychogenic factors in the pathogenesis of uremic pruritus. Some studies have reported that depression and stress are often found in patients with terminal CRF as the patients are overwhelmed by their kidney diseases, which they think it is difficult to heal and they realize that their life merely depends on hemodialysis.[30,31] A study conducted by Koo et al has demonstrated that psychological stress in CRF patients on hemodialysis may reach 56.5%.[31]

There were some factors that had not been evaluated in our study such as sebaceous and sweat gland atrophy, plasma histamine level, cutaneous mast cell proliferation, iron deficiency anemia, peripheral neuropathy, opioid peptides, inflammatory markers, dialysis method and factors of daily activities. As we have known, dry skin may cause pruritus; however, in our study, we found no correlation between dry skin and uremic pruritus. Evaluations on plasma histamine and aluminum level were not performed due to our limitation on evaluation facilities; while cutaneous mast cells and sebaceous and sweat gland atrophy were not assessed as it required skin biopsy, which was not possible for our settings. Evaluation of blood iron level to assess iron deficiency anemia is not accurate since adequate iron level could not exclude the occurrence of iron deficiency.

Conclusion

The prevalence of pruritus of CRF patients at Dr. Kariadi Hospital is 75.8% and most patients (40%) have 3rd degree severity.

Results of our study show that both variables assumed as the cause of uremic pruritus and the uremic syndrome, i.e. groups of those variables do not have significant correlation with uremic pruritus and severity of uremic pruritus. It is possible that many factors are still

unknown in the pathogenesis of uremic pruritus. It also possible that the interactions of those factors that actually may cause uremic pruritus. It may also obvious in our study since there was a significant correlation between other diseases causing itching and uremic pruritus. Our study also has demonstrated that uremic pruritus also correlated to the duration of hemodialysis. We need to calculate and investigate further about the role of psychogenic factors on the pathogenesis of uremic pruritus.

We also need to investigate further about the role of cytokines on pathogenesis of uremic pruritus. Little knowledge has been revealed about those mediators, neuropeptides and itching receptors in various diseases; however, it is obvious that the mediators have roles in pathogenesis of pruritus. However, mediators or receptors that have roles in the pathogenesis of uremic pruritus, particularly those which are associated with type C nerve fibers have not been revealed by other investigators. In this case, they may have roles in pathogenesis of uremic pruritus that requires further studies.

Similar with other studies, the investigator assumes that multifactorial causes probably have roles in the pathogenesis of uremic pruritus. Further studies involving many multidisciplinary experts are required to reveal the certain pathogenesis of uremic pruritus.

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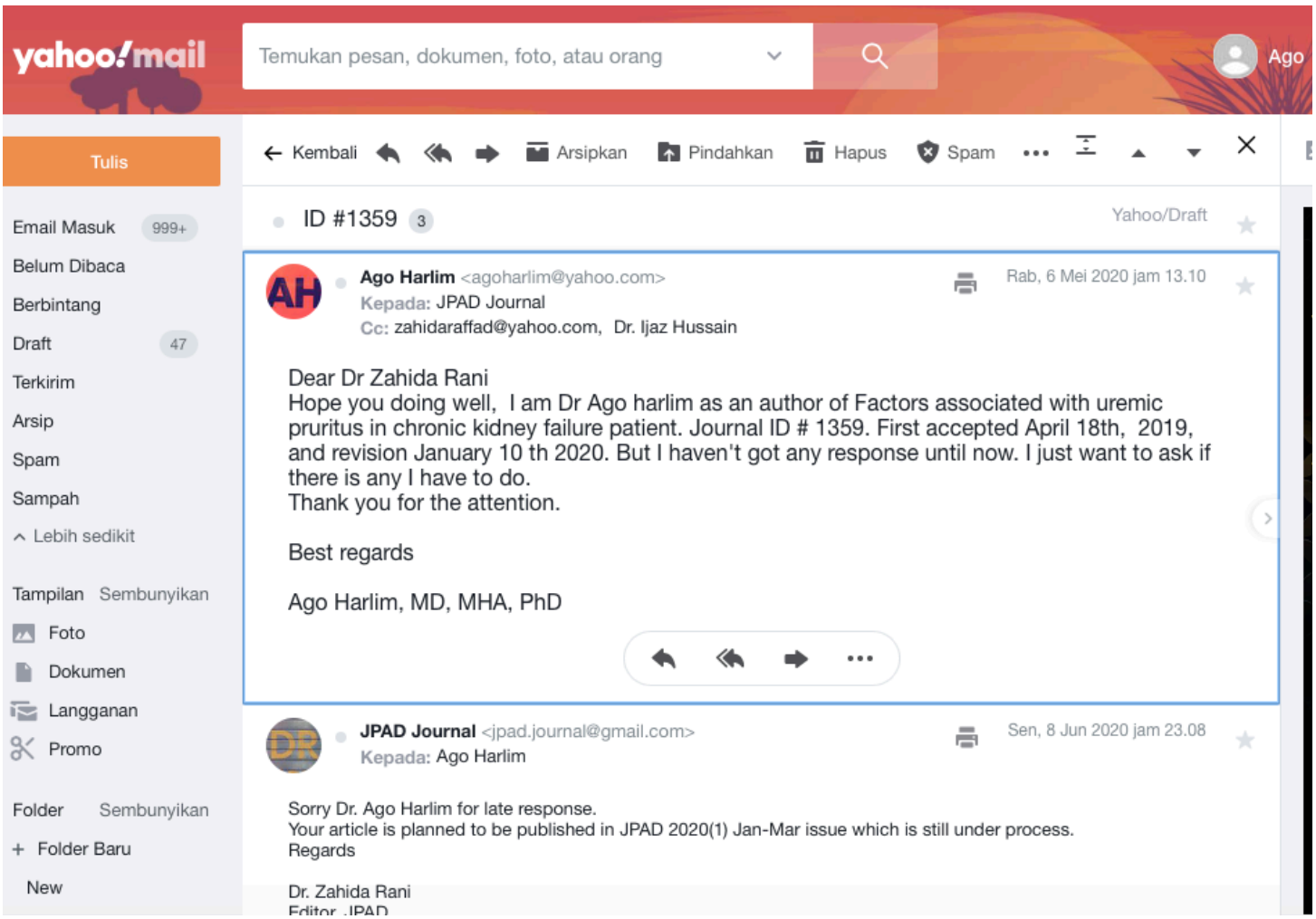
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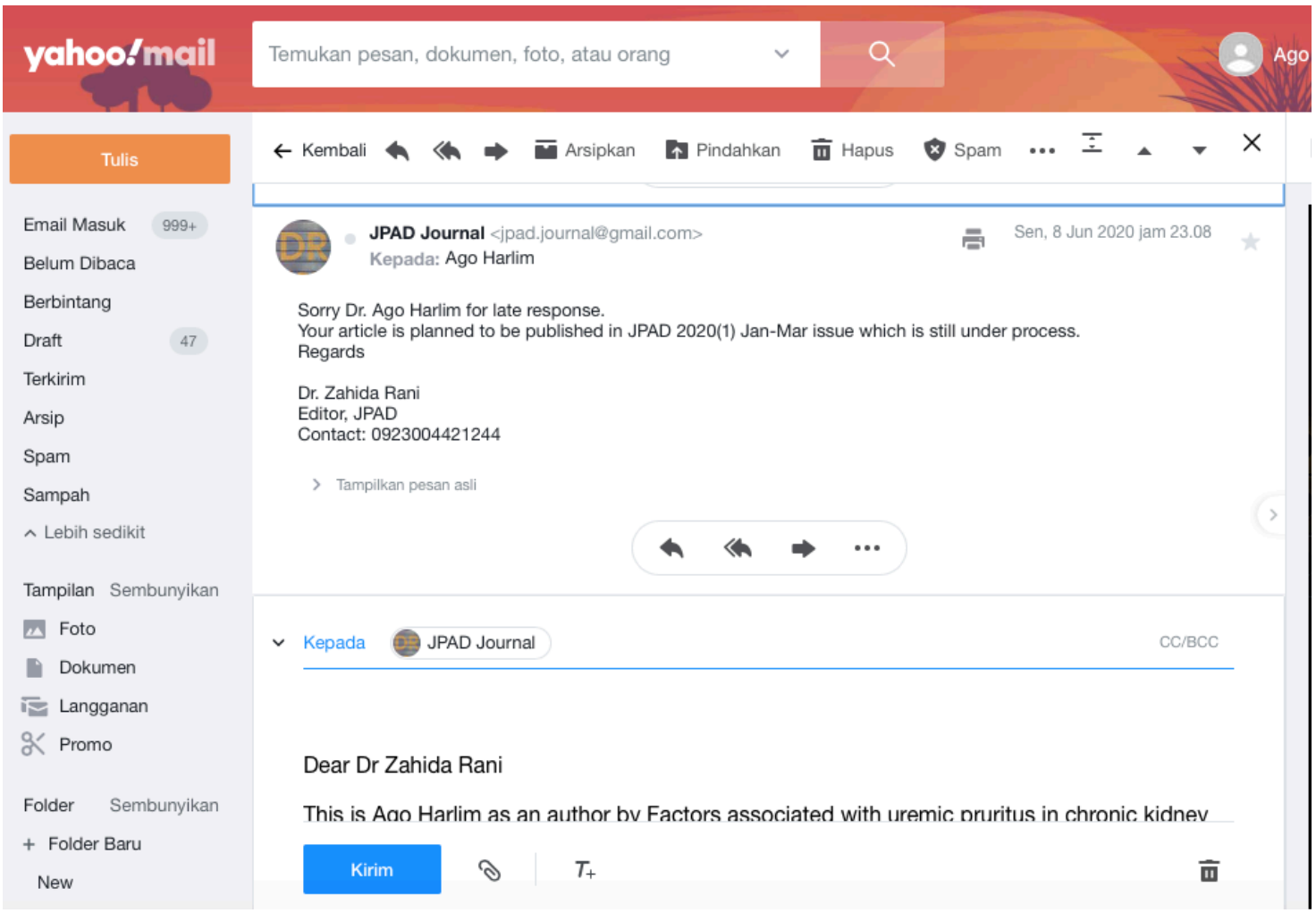
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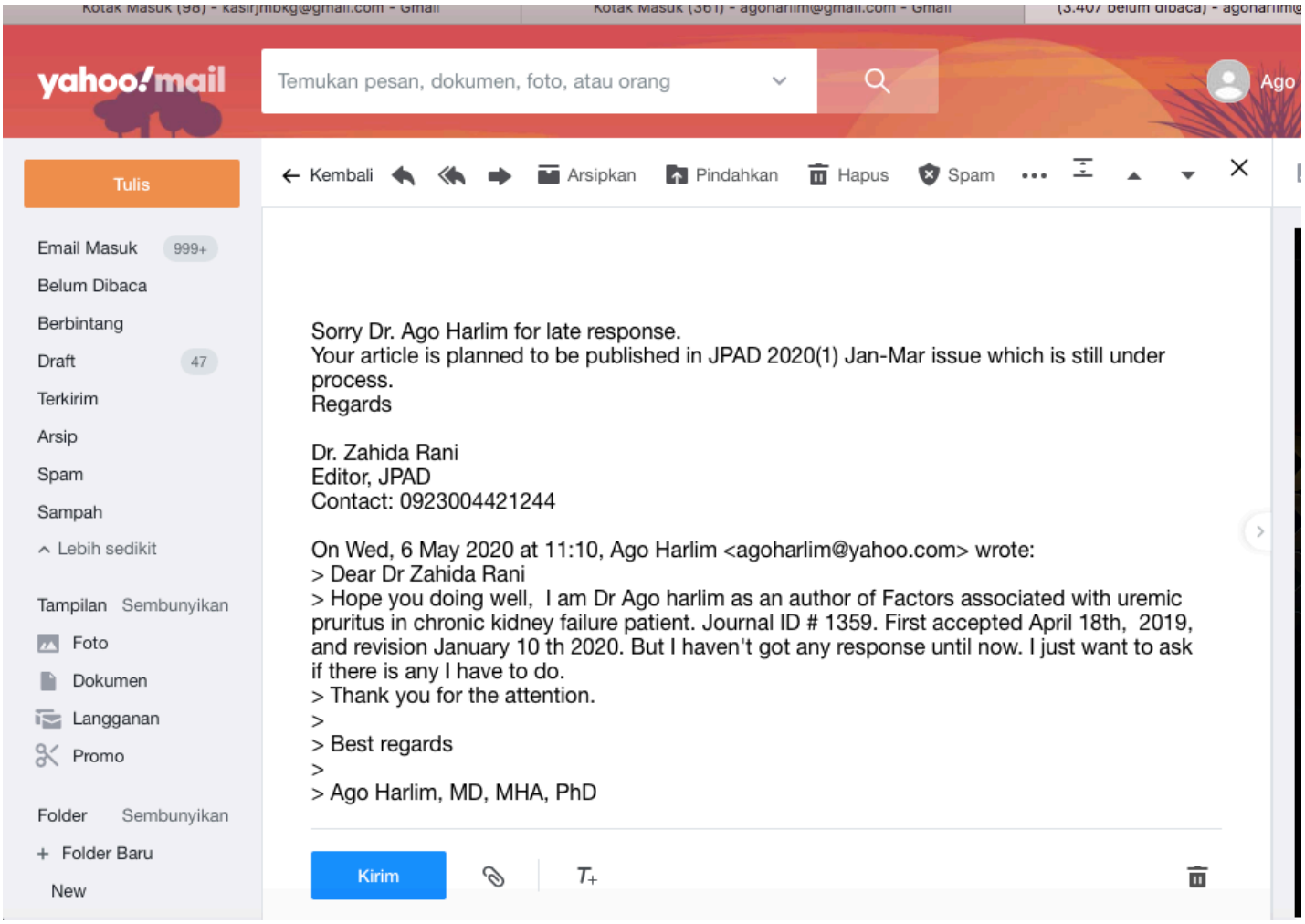
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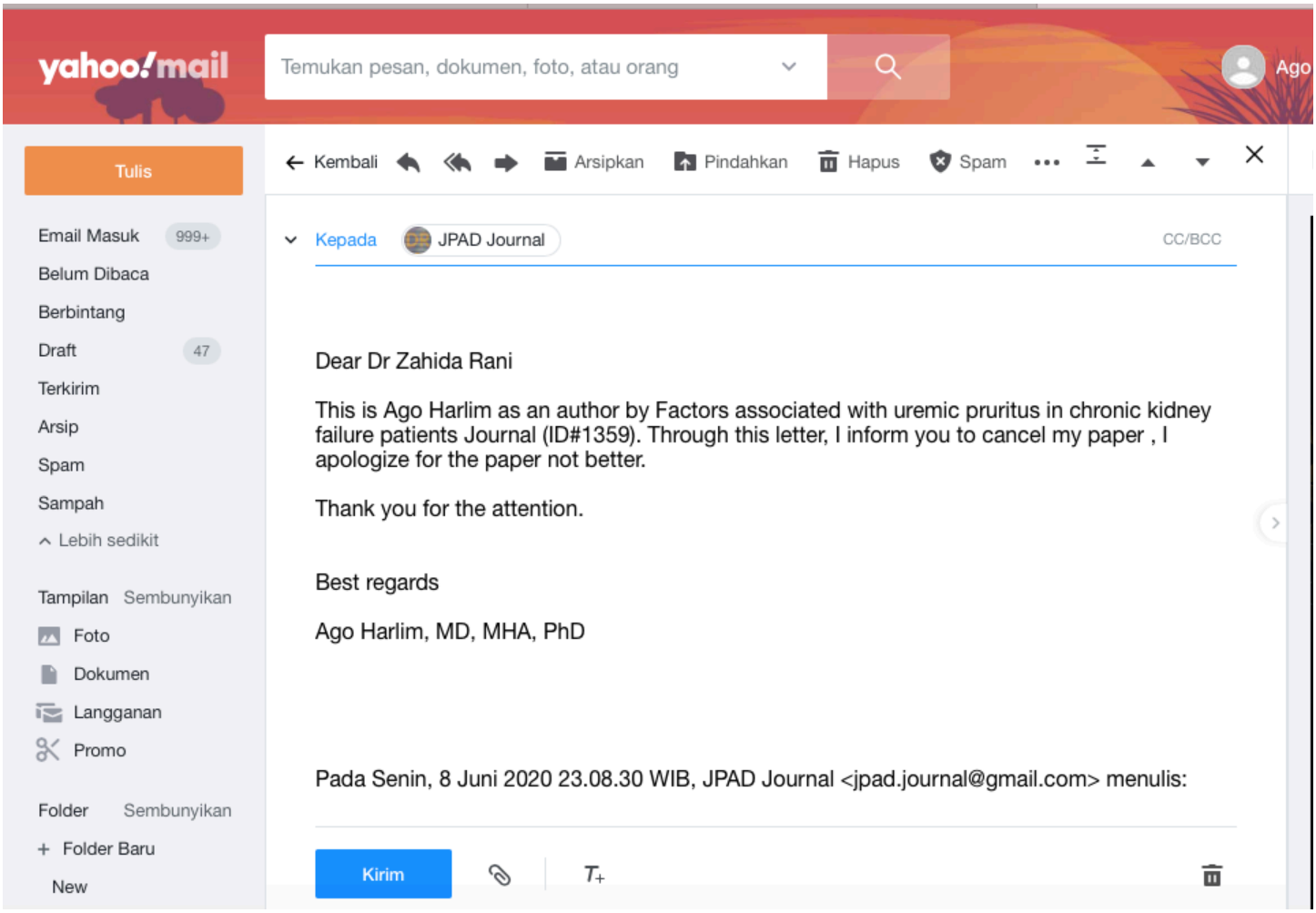
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