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Submission date: 20-Feb-2020 01:09PM (UTC+0700)
Submission ID: 1260689465
File name: ignancy_among_gastric_cancer_patient_in_Palembang,_Indonesia.pdf (495.73K)
Word count: 3447
Character count: 17394

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Abstract. Gastric cancer is a malignant gastric mucosal cancer that often began on the side where the gastric layer is inflamed. Previous research has shown that high uric acid levels are associated independently with an increased risk of gastric cancer and it is suspected that there is a correlation between gastric cancer and elevated levels of uric acid levels but is still poorly known in detail. The aim of this study was to analyse the correlation between uric acid levels and stage of malignancy of gastric cancer patients in the oncology department of Mohammad Hoesin Hospital Palembang. This research was an analytic observational study by using a cross-sectional design to test the correlation between uric acid levels and stages of malignancy in gastric cancer. The results obtained was analyzed using Goodman and Kruskal's Gamma correlation test. The Goodman and Kruskal's gamma test results showed a strong correlation (p=0,033; r=0,746) between uric acid levels and which shows a significant correlation with 95% of confidence levels. Every increment in uric acid levels would be followed by an increase in stages of malignancy in gastric cancer.

1. Introduction

Cancer or carcinoma is a term for abnormal cell growth with growth rates exceeding normal and uncontrolled [1]. Gastric cancer is an abnormal growth in gastric, hollow organs in the gastrointestinal tract where food is destroyed. Gastric cancer is a cancer of a malignant gastric mucosa that is often initiated on the side where the gastric layer is inflamed [2].

Gastric cancer is the fifth most common cancer in the world after lung, breast, colorectal, and prostate cancer. Nearly one million new cases (952,000 cases) are estimated to occur in 2012. More than 70% of cases occur in developing countries and half of the total events in the world are found in East Asia (mainly China) [3,4]. The incidence rate of gastric cancer in Indonesia is 3,811 cases [3].

Gastric cancer is also ranked third cause of death from all types of cancer worldwide with the number of deaths of 723,000. The highest mortality rates are estimated to occur in East Asia and the lowest in North America. High mortality rates are also found in Central and Eastern Europe as well as America Central and South [3]. The World Cancer Report estimates that there are 12.4 million new cases and 7.6 million deaths in 2008 [4]. In Southeast Asia, gastric cancer is still ranked fourth on incidence basis and fifth by mortality. This cancer is also one of the five most common cancers found in men and is more vulnerable to older people over 50 years. In addition, the mortality rate in Indonesia is 3,430 cases [3,5,6].

In this study, the independent variables are uric acid levels and the dependent variable is the stage of malignancy of gastric cancer. Previous research has shown that high uric acid levels are indirectly associated with an increased risk of cancer and it is suspected that there is a correlation between gastric cancer with an increase in uric acid levels is still less well known in detail [7,8]. Uric acid is a nitrogen compound produced from the process of purine catabolism both from the diet and from endogenous nucleic acids (DNA). Uric acid is mostly excreted through the kidneys and only a small part through the gastrointestinal tract. Increased uric acid levels are called hyperuricemia which is a trigger factor for gastric cancer [9,10].

Excessive uric acid production is found in patients with malignant gastric cancer because of high purine and purine turnover levels. The association of uric acid and gastric cancer is less known so far. Previous research has shown that hyperuricemia contributes to a system of increase in the size of the cell in the form of high levels of cell turnover which may accelerate the proliferation of cancer cell nuclei that may already exist in gastric cells and cause tumorigenesis in gastric cells suggesting a possible link between purine metabolic abnormalities and gastric cancer [11].

In addition, there are studies suggest that gastric cancer can also cause a decrease in the absorption of proteins, which in turn causes increased purine metabolism in the human body because uric acid is the end product of the catabolism of endogenous proteins in the blood that is in the form of nucleoprotein [7,12]. Nucleoprotein composed of proteins and nucleic acids and nucleic acids comprising nucleotide is a collection of purine base, pyrimidine and solving phosphate. Nucleoprotein cause increased uric acid in the body [13,14].

In addition, gastric cancer may also cause a decreased appetite which further increases the body's compensation for the metabolism of the nucleoproteins present in the body. Decreased appetite is caused by a nucleus of gastric cancer cells that triggers pro-inflammatory production i.e. cytokines such as IL-1-α, IL-1-β, IL-6, IL-8, TNF-alpha, which further trigger the hypothalamus with hyperactivation of anorexigenic neurons and suppresses prophagic neurons. Anorexigenic neurons are neurons that suppress appetite, which in turn mitigates the patient's gastric cancer condition and may increase the stage of malignancy of gastric cancer [15].

Other studies have suggested that the possibility of uric acid in the form of a hypothetical antioxidant may prevent the development of cancer cells but for example there is excess uric acid in the body will cause oxidative stress in the body and disrupt the function of uric acid and cause side effects such as disturbance in ROS (Reactive Oxygen Species) homeostasis and cause progression and development of gastric cancer cells [16,17].

The purine metabolism and the stage of malignancy of gastric cancer correlate with elevated levels of uric acid in the body, malabsorption, decreased appetite and impaired uric acid function, the factor will cause malignancy in gastric cancer to become more serious and the stage of malignancy in gastric cancer will get serious. Due to increased uric acid which eventually interferes with the proliferation of gastric cancer cell nucleus and subsequently the stage of malignancy of gastric cancer in gastric cancer patients will increase following the degree of I-IV [7,8].

2. Methods

This was an observational analytic study using a cross-sectional study design to test the correlation between uric acid levels and malignancy in gastric cancer. The population of this research is all gastric cancer patient in Installation of medical record Mohammad Hoesin Palembang period 2017. Samples in the study conducted by total sampling method. All patient data diagnosed by gastric cancer based on Histopathology examination or based on TNM stadium recorded in the medical record in Installation of medical record Mohammad Hoesin Hospital Palembang.

Patients who had other cancers and did not have complete data were excluded from the study. Samples in this study that met the inclusion criteria and did not meet the exclusion criteria were randomly selected to 33 samples. Independent variables studied were uric acid levels and the variables studied were stage of malignancy of gastric cancer patients. Uric acid levels were determined by Clinical Pathology Laboratory of Mohammad Hoesin Hospital. Normal uric acid levels were 2.5-5 mg/dL in female and 3.5-6 mg/dL in male. If uric acid levels were more than 5 mg/dL (in female) or

more than 6 mg/dL (in male), then it was defined as hyperuricemia. Stage of malignancy was determined by Anatomy Pathology Laboratory of Mohammad Hoesin Hospital.

The data obtained will be analyzed by Goodman and Kruskal's Gammel Correlation Test to know correlation between uric acid levels with different degrees of malignancy in gastric cancer patients. The results are presented in the form of frequency tabulation, graph, and narrative.

3. Results

This research used secondary data that was taking the data of uric acid level and degree of gastric cancer malignancy from medical record of the patient from the oncology department of Mohammad Hoesin Hospital Palembang in 2017. There were 67 samples from the medical record, diagnosed by gastric cancer contained in Mohammad Hoesin Hospital Palembang, and from 67 samples of medical records, there are 33 samples of medical records of patients who meet the minimum sample size and criteria of this study.

3.1. Characteristics of research subject

The results showed the majority (63.6%) of gastric cancer patients were men of the total patient or nearly twice that of women. In this study, the majority (54.54%) of gastric cancer respondents were patients over the age of 50 years (table 1). The lowest age in this study was 10 years and the highest age was 80 years.

Table 1. Characteristics of research subject.

Characteristics	N	%
Sex		
Male	21	63.6
Female	12	36.4
Age		
≤50 years	15	45.5
>50 years	18	54.5

3.2. The correlation between uric acid level and stage of malignancy of gastric cancer

This study showed the majority (51.5%) of gastric cancer patients suffering from hyperuricemia but the percentage was relatively the same (table 2). Table 2 showed that the majority (54.6%) of respondents suffering from gastric cancer were in stage I and II (the early stage). In addition, from this study could be seen that the pattern of patients coming to treatment at a certain stage that was in the early stage many patients and after that become less and more in stage IV. This might be due to stage IV, the patient experiencing symptoms that disturbed the patient causing the patient to be tired or the severity of the patient causing the patient to die without being diagnosed.

Table 2. The correlation between uric acid level and stage of malignancy.

Uric Acid Level	Stage of Malignancy								Total	%	p[a]	r[b]
	Stage I		Stage II		Stage III		Stage IV					
	n	%	n	%	n	%	n	%				
Normouricemia	8	88.9	6	66.7	0	0.0	2	28.6	16	48.5	0.000	0.746
Hyperuricemia	1	11.1	3	33.3	8	100	5	71.4	17	51.5		
Total	9	100	9	100	8	100	7	100	33	100		

[a]Goodman and Kruskal's Gammel Correlation Test, $p<0.05$.
[b]Correlation strength was strong.

In this study, stage of malignancy of most gastric cancers was in stage III that was 100% who had hyperuricemia and stage I data was 88.9% who have normouricemia data. In addition, this study showed that the pattern of decreasing the number of normouricemia from stage I to IV that was from 88.9% to 28.6%. Meanwhile, this study could also be seen there was a pattern of increasing the number of hyperuricemia patients from stage I to IV that was from 11.1% to 71.4%.

In the results of this study, the value of correlation coefficient (r) is 0.746 (positive correlation) which indicates that there is a strong correlation between uric acid levels with stage of malignancy of gastric cancer. The p-value was 0.000 ($p<0.05$) which mean that the correlation relationship was significant at 95% confidence level. That was, any increase in uric acid levels would increase the stage of malignancy.

4. Discussions

The results of this study indicated that more male patients (63.6%) suffer from gastric cancer than female patients. There were several studies suggesting that more gastric cancer patients were male because of the presence of estrogen. This estrogen was an estrogen receptor that can help the dysregulated signals involved in the proliferation, metastasis and deep invasion by gastric cancer cells that can help to prevent gastric cancer and still no research on why men are more likely to develop gastric cancer [3,6,7].

The proportion of patients aged with gastric cancer increased with age and found that most patients suffering from gastric cancer were at age ≥50 years (54.54%). There had been studies suggesting that an older patient would cause DNA cell nucleus damage that might be caused by biological processes or exposure to other risk factors that would lead to gastric cancer [3,7].

In addition, the proportion of uric acid levels in gastric cancer patients showed that there were more patients with hyperuricemia of 51.5%. Hyperuricemia could be seen in patients with gastric cancer might be due to decreased protein absorption that would cause increased purine metabolism in the human body. Uric acid was the end product of endogenous nucleotide catabolism in the blood. In addition, there was another study that suggests that hyperuricemia was a trigger of gastric cancer that would cause increased gastric cell turnover which would lead to increased gastric cell proliferation and caused gastric cancer [7,11].

Meanwhile, the distribution of patients based on the degree of gastric cancer was most commonly obtained 27.3% in stage I and II. The findings in this study are consistent with IARC statistics for 2012, Cancer Research UK 2014 and ASCO 2017 showing that more men suffer from gastric cancer than women. The proportion of patients suffering from gastric cancer increases with age until more patients with gastric cancer are at the age of 50 [3,5,6].

The results showed that there was a strong correlation between uric acid levels and gastric cancer malignancy with p-value of 0.000 and r=0.746. It can be concluded with an increase in uric acid levels will increase the stage of malignancy in patients with gastric cancer. Research by Kolonel et al., 1994 and Wang et al., 2015 showed a significant association between uric acid levels and gastric cancer ($p<0.001$). Kolonel et al.'s study, used a cohort study with a student t-Test to test the hypothesis by measuring uric acid levels in 214 gastric cancer patients. The conclusions from Kolonel et al. showed that the association between uric acid levels and gastric cancer malignancy was still less consistent than complete. Meanwhile, Wang et al.'s research, using P-value ($p= 0.007$) and relative risk value of 1.39 indicates the relationship between uric acid levels and digestive cancer was significant. Conclusions from the results of Wang et al.'s study, states that hyperuricemia increases the risk of developing gastric cancer [18,19].

Other studies have suggested that hyperuricemia contributes to a high-density cell proliferation system that can precipitate the proliferation of cancer cell nuclei. It may already be present in gastric cells and cause tumorigenesis in gastric cells suggesting a possible link between purine metabolic abnormalities and gastric cancer and an increase in the stage of malignancy in gastric cancer. In addition, there is research suggesting that gastric cancer may also cause a decrease in protein absorption, which further leads to increased purine metabolism in the human body because uric acid is the end product of endogenous protein catabolism in the blood in the form of nucleoproteins. Of these two factors can cause the stage of malignancy in gastric cancer patients to become more severe and serious [7,11,12].

The measurement of a large number of samples and the study was based on all common and less specific cancers contributed to the differences in the results of the study because in this study the sample used only 33 samples. In addition to the research Wang et al., and Kolonel et al., did not conduct research on the stage of malignancy of gastric cancer that can cause differences in the results

of research. Meanwhile, studies on the correlation between uric acid levels and other malignancy rates of gastric cancer and the correlation of uric acid levels and prognosis of gastric cancer are still lacking which may lead to less information about the study.

There are some limitations to the research. There are other factors that may affect gout besides gastric cancer that is not studied in this study.

5. Conclusions

It can be concluded that uric acid level has a strong positive correlation with stage of malignancy in gastric cancer patients at Mohammad Hoesin Hospital Palembang. Thus, uric acid levels can be considered to asses stage of malignancy in gastric cancer patient.

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Acknowledgments

Here, We would like to thank Department of Clinical Pathology and Department of Anatomy Pathology of Mohammad Hoesin Hospital Palembang who help data confirmation. We say special thank to dr. Dwi Indira Setyorini, SpPD for your consultation and advice, and I love you like crazy.

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