



Interleukin 6, Ferritin Levels, and Glasgow Prognostic Score in Solid Cancer

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Abstract

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BACKGROUND: Several pro-inflammatory cytokines have been shown to regulate cancer cell growth and contribute to cancer promotion and progression. Interleukin 6 (IL-6) regulates almost all the hallmarks of cancer such as inhibition of apoptosis, proliferation, angiogenesis, and invasiveness and is also known to regulate cell metabolism. The associated increase in serum ferritin is most likely induced by the inflammatory state. In several studies, IL-6 and ferritin have a significant role in the development and clinical outcome in solid cancer and the Glasgow Prognostic Score (GPS) is widely used as a prognostic score in solid cancer. It is currently unclear whether levels of IL-6 and ferritin correlate with GPS in solid cancer patients.

AIM: The aim of this study is to determine the correlation between IL-6 and ferritin levels with the GPS in solid cancer patients.

METHODS: This study was an analytical observational study with a cross-sectional study approach to examine the relationship between IL-6 and ferritin levels with GPS in solid cancer patients. The sampling method was carried out by consecutive sampling. The total number of samples used in the study was 32 solid cancer subjects who had just been diagnosed. IL-6 was examined by kit enzyme-linked immunosorbent assay and ferritin using immunochemiluminescent method at certified laboratory in Manado city, Indonesia. The GPS is based on the results of the patient's C-reactive protein and albumin levels were also examined at certified laboratory in Manado city, Indonesia. Data analysis was done using SPSS version 22.

RESULTS: There were 32 patients with solid cancer who are newly diagnosed and have not undergone chemotherapy. Out of 32 patients, 17 are men (53.13%) and 15 are women (46.87%). The median age of the subject was 52.5 (33–69) years. There was a significant relationship between IL-6 levels and GPS ($p = 0.011$; OR 16.67 95% CI 1.617–171.783). There was no significant relationship between ferritin levels and GPS ($p = 0.148$; OR 5.429 95% CI 0.807–36.506). There was a statistically significant relationship between IL-6 levels and ferritin ($r = 0.554$; $p = 0.001$).

CONCLUSION: There was a significant correlation between IL-6 and GPS and there was a significant correlation between IL-6 and ferritin in solid cancer patients. IL-6 levels can be used to assess the risk of prognosis in solid cancer patients and help provide an idea of what kind of treatment will be given to patients, and can help to determine the plan treatment at the end of the life of cancer patients.

Introduction

Cancer is a complex disease with general characteristics in the form of interference or regulation of cell multiplication mechanisms that cause changes in cell behavior to become uncontrolled and have the ability to invade cellular tissues [1]. Based on data from the Global Cancer Observatory (GLOBOCAN), the incidence of cancer worldwide has increased significantly from 18.1 million cases in 2018 to 19.2 million cases in 2020, and the death rate has also increased from 9.6 million cases in 2018 to 9.9 million cases in 2020. Based on these data, in Indonesia, the number of new cancer cases was 396,914 with a total death 234,511 which the top 10 types of cancer were dominated by solid cancers [2]. Indonesian Basic Health Research (Riskesdas) data in 2019 found that the prevalence of cancer at all ages was 1.8/1000

population, where there has been an increase from Riskesdas 2013 of 1.3/1000 resident [3].

Predicting prognosis is a fundamental component in the management of solid cancer patients for several reasons, such as accurate estimation of prognosis can provide information on which anti-cancer therapy is better to use, help reduce anxiety for both patients and caring families about the uncertainty of cancer prognosis, and can assist in planning care at the end of the patient's life [4]. A wide variety of prognostic tools have been validated but their complexity, subjectivity, and clinical usefulness remain to be considered. Glasgow Prognostic Score (GPS) is a calculation for inflammation-based cancer prognosis obtained from serum C-reactive protein (CRP) and albumin concentrations, which have been reported as a significant prognostic indicator in cancer patients. Elevated serum CRP has been shown to be a prognostic indicator in various neoplasms. In

addition, hypoalbuminemia caused by malnutrition and associated cachexic conditions has been reported to correlate with an unfavorable prognosis of some solid cancers [4], [5].

Interleukin 6 (IL-6) is a pleiotropic cytokine with various functions where IL-6 will bind to IL-6 receptors, activated Janus kinase (JAK), and further phosphorylate signal transducers and activators of transcription (STAT). The phosphorylated STAT gene migrates into the nucleus and activated target genes such as vascular endothelial growth factor which increases tumor aggressiveness. Inhibiting or eliminating STAT will increase apoptosis and chemotherapy sensitivity and can reduce the process of angiogenesis. The IL-6 cytokine is involved in proliferation and differentiation of various malignant tumor cells such as multiple myeloma, endometrial cancer, lung cancer, colorectal cancer, renal cell carcinoma, cervical cancer, breast cancer, and ovarian carcinoma [6], [7], [8].

Ferritin is differentially overexpressed in tissues of several malignancies, such as in hepatocellular carcinoma, Hodgkin's lymphoma, breast cancer, and pancreatic cancer. Recent studies showed that ferritin-rich tumor-associated macrophages (TAMs) provide further insight into the molecular phenotype of TAMs and allow speculation about the significant function of ferritin in cancer biology. Cancer-associated elevations in serum ferritin are most likely induced by an inflammatory state and not by liver damage or changes in body iron stores. The increase in serum ferritin is largely due to local release of ferritin within the cancer site [9]. Based on the description above, IL-6 and ferritin had a significant role in the development and clinical outcome in solid cancer and GPS was widely used as a prognostic score in solid cancer. It is currently unclear whether levels of IL-6 and ferritin correlate with GPS in solid cancer patient.

Methods

This study was an analytical observational study with a cross-sectional design. This research was conducted at the internal medicine ward of Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia, from July 2021 to February 2022. The study was approved by the local ethics committee with the number: No.070/EC/KEPK-KANDOU/V/2021.

Population and sampling

The population included in this study were all newly diagnosed solid cancer patient at Prof. Hospital, Dr. R.D. Kandou Manado, Indonesia, who met the inclusion and exclusion criteria. Inclusion criteria were patients with solid cancer who are newly diagnosed and have not undergone chemotherapy, aged more than 18 years old, the Karnofsky score is ≥ 70 , and were

willing to participate in the study. Exclusion criteria include history of transfusion in the past 3 months, the presence of hepatitis B and/or C, diabetes mellitus, severe infection or sepsis, autoimmune diseases, and moderate-to-severe anemia. The sampling method was carried out by consecutive sampling.

IL-6 examination

Five milliliter of blood was drawn from the peripheral vein and measurements were taken using the enzyme-linked immunosorbent assay kit (Elecys, cat. No 05109442190 from Roche Diagnostics International Ltd., Rotkreuz, Switzerland). The reference cutoff value of IL-6 values in the study of Lippitz and Harris was 6.95 pg/mL. IL-6 levels were categorized as high if IL-6 levels were >6.95 pg/mL [10].

Ferritin examination

Five milliliter of blood was drawn from the peripheral vein and measurements were taken using the immunochemiluminescent method. The ferritin cutoff recommendation used in research on inflammation and cancer is 200 ng/mL in men and 150 ng/mL in women. Ferritin levels are categorized as high when ferritin levels are >200 ng/mL in men and >150 ng/mL in women [11], [12].

GPS

The GPS is based on the results of the patient's CRP and albumin levels. Five milliliter of blood was drawn from the peripheral vein and measurements the CRP and albumin levels. The GPS value is 0, if the CRP level is 10 mg/L and albumin is 3.5 g/dL, the GPS value is 1 if CRP level is >10 mg/L or albumin is <3.5 g/dL and the GPS value is 2 if CRP level is >10 mg/L and albumin <3.5 g/dL is found [5]. The GPS value is categorized as high GPS if the GPS value is 1 and 2.

Data analysis

The data obtained were analyzed using SPSS 22nd version (SPSS Inc., Chicago,) with a 95% confidence interval (CI). Normality test was conducted using Shapiro–Wilk test. Analysis to determine the correlation IL-6 and ferritin with GPS was using Fisher Exact Test. Analysis to determine the correlation between IL-6 and ferritin was using the Spearman Test (with significantly $p < 0.05$).

Results

This study recruited a total of 32 patients solid cancer who are newly diagnosed and have not

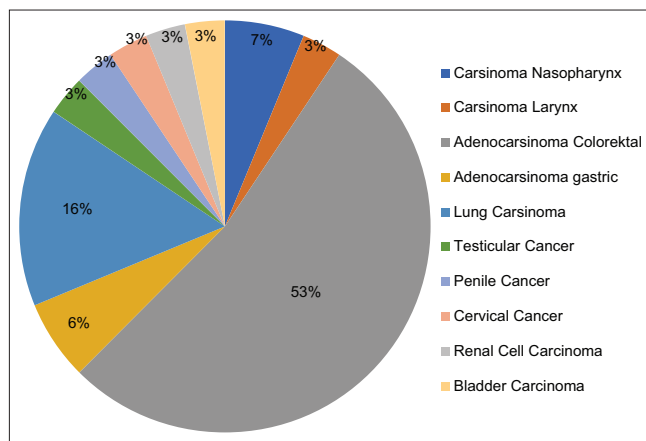


Figure 1: Distribution by type of cancer

undergone chemotherapy. Out of the total 32 patients, 17 are men (53.13%) and 15 are women (46.87%). A total of 17 (53.13%) patients were diagnosed with colorectal adenocarcinoma (Figure 1). The median age was 52.5 (33–69) years. The median of IL-6 was 10.59 pg/mL (1.50–507.10 pg/mL). The median of ferritin was 266.09 ng/mL (8.90–2187.20 pg/mL). The baseline characteristics of the patients are shown in Table 1.

Table 1: Basic characteristics of the study population

Characteristics	N	Min	Max	Median
Age (year)	32	33	69	52.50
Karnofsky	32	70	90	80.00
IL-6 (pg/mL)	32	1.50	507.10	10.59
Ferritin (ng/mL)	32	8.90	2187.20	266.09
CRP (mg/L)	32	0.40	277.70	27.70
Albumin (g/dL)	32	1.70	4.00	3.30

N: Number of sample, Min: Minimum, Max: Maximum, IL-6: Interleukin-6, CRP: C-Reactive protein.

A total of 26 (81.3%) patients had high GPS and 6 (18.8%) patients had a normal GPS. A Fisher's exact test was conducted to assess the correlation between IL-6 and GPS. The result showed a significant correlation between IL-6 with GPS. The results of the calculation of risk estimates in this study show that solid cancer patients with high IL-6 are at risk of 16 times to get high GPS values ($p = 0.011$; OR: 16.67; 95% CI: 1.671–171.783) (Table 2).

Table 2: Correlation between variables

		GPS		p*	OR	95% CI
		High	Normal			
IL-6	High (>6.95 pg/mL)	20 (76.9%)	1 (16.7%)	0.011	16.67	1.617–171.83
	Normal (≤6.95 pg/mL)	6 (23.1%)	5 (83.3%)			
Ferritin	High (>200 ng/mL in men and >150 ng/mL in women)	19 (73.1%)	2 (33.3%)	0.148	5.429	0.807–36.506
	Normal (≤200 ng/mL in men and ≤150 ng/mL in women)	7 (26.9%)	4 (66.7%)			

IL-6: Interleukin-6, GPS: Glasgow Prognostic Score, *: Fisher's exact test; OR: Odds ratio, CI: Confidence interval.

We also used a Fisher exact test to assess the correlation between ferritin and GPS. The result showed no significant correlation between ferritin with GPS. However, the results of the calculation of risk estimation in this study showed that solid cancer patients with high ferritin are at risk of 5 times to get a high GPS value ($p = 0.148$; OR 5.429 95% CI 0.807–36.506) (Table 2).

The normality test of the data with the Shapiro–Wilk test obtained an abnormal data

Table 3: Correlation between IL-6 and ferritin in solid cancer patients

Variable correlation	N	Correlation coefficient	p*
IL-6 with ferritin	32	0.554	0.001

IL-6: Interleukin-6, N: Number of sample, *: Spearman test.

distribution; therefore, the Spearman test was carried out for further analysis to determine whether there is a relationship between IL-6 levels and ferritin levels. The result showed a statistically significant correlation between IL-6 with ferritin in solid cancer patients ($p = 0.001$; $r = 0.544$) (Table 3). The correlation coefficient showed that IL-6 has a moderate and unidirectional relationship with ferritin levels, where increasing IL-6 level also caused an increase in ferritin levels (Figure 2).

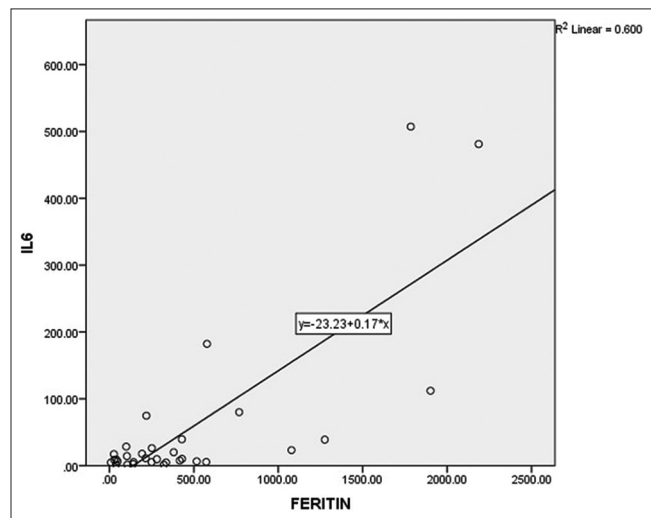


Figure 2: Graph of the correlation between IL-6 and ferritin

Discussion

Our result showed a higher distribution of men compared to women (53%–47%), which was similar to data from a GLOBOCAN 2020 where men have a higher risk of getting cancer than women [2], [13]. The median age in this study was 52.5 years and this is different from the Surveillance, Epidemiology, and End Results data from the National Cancer Institute, where the median age at diagnosis of solid cancer is 66 years [14].

In this study, IL-6 levels in solid cancer patients ranged from 1.5 to 507.10 pg/mL with a mean of 55.11 ± 121.31 pg/mL and a median of 10.59 pg/mL where 21 patients (65.6%) had high IL-6 levels and 11 patients (34.4%) had normal IL-6 levels. This study is in line with the study conducted by Siagian *et al.*, which found elevated levels of IL-6 in patients with lung cancer with a mean of 45.99 pg/mL [15]. A study by Kinoshita *et al.* in colorectal cancer patients showed high levels of IL-6 increased in the colorectal cancer patient population compared to the normal population (35.7 ± 69.0 pg/mL vs. 4.3 ± 1.0 pg/mL; $p = 0.0093$) [16]. A study by Vinocha *et al.* also showed similar results where there was an

increase in IL-6 in patients with lung cancer with cancers of the mouth, lung, gallbladder, and esophagus with a mean IL-6 of 993 pg/mL, 813 pg/mL, 960 pg/mL, and 381 pg/mL. The mechanisms underlying the increase in IL-6 in solid cancer patients include malignancy-related chronic stress, IL-6 secretion and production by tumor-associated macrophages, or IL-6 production by tumor cells themselves [17].

This study found ferritin levels in solid cancer patients ranged from 8.90 to 2187.20 ng/mL with a mean of 474.06 ± 568.52 ng/mL where 21 patients (65.6%) had high ferritin levels and 11 patients (34.4%) had normal ferritin levels. The results are similar to the study by Skoko *et al.* on 46 solid cancer patients, where the ferritin concentration in solid cancer patients ranged from 5.98 to 850.78 g/L with a mean of 174.62 g/L [18]. Park *et al.* also showed the similar result in the Taiwan population with pancreatic cancer showed high ferritin levels with a mean of 608.4 ± 126.3 ng/mL [19]. The increased in ferritin levels in patients with solid cancer was most likely a result of inflammation and ferritin production by the cancer itself [9].

The GPS is an inflammation-based prognostic score that is often used to assess the prognosis for solid cancer [20]. This study showed that of the 32 samples, 26 (81.3%) had high GPS and 6 (18.8%) have a normal GPS. A study by Brown *et al.* in 38 lung cancer patients and 12 gastrointestinal cancer patients showed 78% of the study sample had a high GPS [21]. Forrest *et al.* also showed that 81% of patients with lung cancer had a high GPS [5]. The GPS using CRP and albumin was described an ongoing systemic inflammatory response with a progressive decrease in nutrition [5], [20]. At present, many studies reveal that high levels of GPS are significantly associated with poor survival outcomes in various cancers [22], [23], [24], [25].

Patients with high IL-6 levels are generally associated with a poorer prognosis and shorter survival, while lower IL-6 levels are associated with a better response to therapy [26]. In this study, high levels of IL-6 were found in 65.6% of the subjects and there was a significant relationship between IL-6 levels and the GPS ($p < 0.05$). A study by Korpacka *et al.* on 97 gastroesophageal cancer patients showed that GPS was positively correlated with an increase in IL-6 with $r = 0.466$ and $p = 0.003.61$ [27]. A study by Yu *et al.* on 164 colorectal cancer patients in Taiwan showed that IL-6 had a significant relationship with high GPS with $p = 0.026$ [28]. Our study also showed that solid cancer patients with high IL-6 had a 16 times risk of having a high GPS. In this study, 95% CI indicated a high probability of IL-6 having a high GPS of 1.671–171.783 times. The wide range of 95%CI values may be due to the diversity of the population used in this study.

In this study, high ferritin levels were found in 73.1% of subjects and there was no significant relationship between ferritin levels and GPS ($p > 0.05$). This result is different from the study conducted by Lee

et al. where in this study, it was found that ferritin levels were a poor prognostic factor in the group with metastatic colorectal cancer ($p = 0.002$) [29]. This study differed from Lee *et al.* study because they were used colorectal cancer research subjects who had metastasized, while this study used solid cancer research subjects regardless of the stage of the disease at the time the diagnosis was made. Lee *et al.* found that ferritin is a potential parameter for cancer progression, which acts as a significant prognostic factor for overall survival and is directly correlated with survival time in patients with advanced lung cancer. Ferritin is better used to predict prognosis in patients with advanced cancer who have relapsed or refractory than in newly diagnosed early-stage cancer [29]. High ferritin levels cannot be used to assess the risk of prognosis in solid cancer patients, especially at an early stage when the diagnosis was made [30].

In cancer-associated inflammatory conditions, IL-6 affects erythropoiesis to varying degrees [31]. In this study, there was a correlation significance between IL-6 and ferritin. The correlation coefficient in this study showed that IL-6 levels had a moderate and unidirectional relationship with ferritin levels, where increasing IL-6 levels were also followed by increasing ferritin levels. This study showed the same results as the study conducted by Hohaus *et al.* where the study examined the relationship between IL-6 with parameters of iron metabolism and acute-phase reactants and found a significant relationship between IL-6 and ferritin ($p = 0.016$) [32]. Similar results were also found in a study conducted by Bao *et al.*, where in this study, a significant relationship was found between IL-6 and ferritin ($r = 0.363$, $p = 0.003$) [33]. Interleukin-6 can cause impaired proliferation of erythroid progenitors and their effect on erythropoietin and alter iron metabolism by modulating liver gene expression and hepcidin synthesis which is ultimately responsible for the occurrence of functional iron deficiency, where iron stores can be normal or increased in the bone marrow, there is an increase ferritin and TIBC and serum iron levels can be normal or decreased [31].

The limitation of this study is that the examination of IL-6 and ferritin levels was carried out in newly diagnosed patients regardless of the stage at the time of diagnosis. For a more accurate correlation between IL-6 and ferritin with GPS before therapy, it is possible to separate patients in the early and advanced stages.

Conclusion

There was a significant correlation between IL-6 and GPS and there was a significant correlation between IL-6 and ferritin in solid cancer patients. Therefore, it can conclude that IL-6 levels can be used

to assess the risk of prognosis in solid cancer patients and help to provide information in choosing treatment options for cancer patients and also help to determine the treatment regimen at the end of the life of cancer patients. Further research is needed to assess post-therapy IL-6 levels and the relationship between IL-6 and overall survival in solid cancer patients. More studies are also needed to determine the causal relationship between IL-6 and ferritin in solid cancer patients to support this study.

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