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The Role of Hepcidin Level as a Predictor for Mortality in Cancer Patients with Sepsis

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Abstract

BACKGROUND: Sepsis is the most common cause of death in hospitalized cancer patients. Iron metabolism is one system that is strongly influenced by severe infectious and inflammatory conditions.

AIM: This study aims to determine the difference in survival based on hepcidin levels in surviving and non-surviving cancer patients with sepsis.

METHODS: This study is a cohort study in solid and hematological cancer patients with sepsis aged 18 years and older who were hospitalized from February to June 2022. The criteria for sepsis are the presence of infection accompanied by a Sequential Organ Failure Assessment (SOFA) score of two points or more. A total of 40 samples were included in this study.

RESULTS: We found different survival curves in subjects with high hepcidin levels compared to subjects with low hepcidin levels. The hazard ratio (HR) of hepcidin levels was 7.28 (95% confidence interval (CI) 2.35–22.55), p<0.001. In multivariate analysis, hepcidin levels had an adjusted HR of 7.91 (2.51–24.91), p < 0.001.

CONCLUSIONS: From the results of this study, it can be concluded that cancer patients with sepsis who have high hepcidin levels have lower survival than patients with low hepcidin levels at 28-day follow-up.

Introduction

Sepsis is a systemic inflammatory response with proven infection. Multiple organ dysfunction syndromes (MODSs) are a complication of sepsis which is characterized by physiological and biochemical abnormalities that cause disruption of homeostasis. MODS has a high mortality rate if not immediately identified and treated appropriately. At present, the Sequential Organ Failure Assessment (SOFA) score is used to identify the presence of sepsis. This score assesses disturbances of six organ systems, including respiratory, coagulation, liver, cardiovascular, central nervous system, and renal systems. Each scored from 0 to 4 with an increasing score reflecting worsening organ dysfunction. A high SOFA score is associated with increased mortality [1]. The incidence of sepsis increases with the presence of comorbidities. Cancer is the most common comorbidity in patients with sepsis. Mortality from sepsis is reported to be 30% in hospitalized cancer patients and cancer is an independent predictor of mortality in patients with sepsis [2].

Iron is the main element of hemoglobin. Iron is also an important trace element required in various biological processes, such as oxygen transport, DNA synthesis, and immune function [3]. Iron is also important in the process of oxidation-reduction reactions that induce the formation of reactive oxygen species. Iron in the body is mainly in the form of heme and ferritin whose purpose is to limit their reactivity [4].

Hepcidin is a peptide primarily synthesized in the liver. Hepcidin has a known role in the pathogenesis of anemia of inflammation (AI). Increased levels of hepcidin in inflammatory conditions lead to decreased iron export by macrophages and inhibition of iron absorption in the duodenum. This functional iron deficiency condition causes inflammatory anemia that is often found in critically ill patients [5]. Several studies reported that elevated serum iron and anemia were predictors of mortality in septic patients [6], [7].

Recent studies reported that iron is also required in bacterial pathogenicity. Some bacteria such as Klebsiella pneumoniae and Escherichia coli have the ability to bind iron from transferrin [8]. The host response by increasing hepcidin levels aims to reduce serum iron to limit bacteria binding to iron [9]. However, an increase in intracellular free iron concentration can cause an increase in oxidation activity that produces reactive oxygen species that can trigger cell death, multiple organ damage, and even death [4]. Hepcidin also plays a role in limiting non-transferrin-bound iron (NTBI) so that it can limit the growth of siderophile strains of bacteria [10].

The association between hepcidin levels and prognosis in solid and hematological malignancies with sepsis is still not fully understood. A reliable biomarker is needed to predict survival in cancer patients with sepsis, so studies on hepcidin levels need to be carried out. This study aims to determine the difference in survival based on hepcidin levels at 28-day follow-up in cancer patients with sepsis.

Methods

Study design

This study is an observational study with a prospective cohort design. This study was conducted at Professor I.G.N.G Ngoerah Hospital Denpasar from February 2022 to June 2022. The samples were taken by consecutive sampling from solid and hematological cancer patients with sepsis aged 18 years and older. Patients with thalassemia, liver cirrhosis, gastrointestinal, respiratory, and urogenital bleeding, history of blood transfusion in the previous 3 months, autoimmune hemolytic anemia, iron deficiency anemia, currently receiving oral or intravenous iron treatment, stage 5 chronic kidney disease, and patients with pregnancy were excluded in this study. A total of 40 subjects participated in this study. The criteria for sepsis are the presence of infection accompanied by a Sequential Organ Failure Assessment (SOFA) score of two points or more.

This study has obtained ethical clearance from the Ethics Commission of the Faculty of Medicine, Udayana University.

Data collection

Data collection was carried out after informed consent. Venous blood sampling was performed within 24 h of the patient being admitted to the hospital. Serum hepcidin was examined using the Human Hepc 25 (Hepcidin 25) Enzyme-linked Immunosorbent Assay (ELISA) method (Elabscience E-EL-H5497). Serum hepcidin levels were obtained using ng/mL units.

Data analysis

The data collected were analyzed descriptively. The Shapiro–Wilk test was used to determine the normality of numerical data. To determine the difference in hepcidin levels in surviving and non-surviving sepsis patients, the independent t-test was used on normally distributed data and the Mann–Whitney test on non-normally distributed data. To determine the cutoff of hepcidin levels in predicting mortality, receiver operator characteristic (ROC) analysis was used. Hepcidin levels were defined as high if they were equal to or above the cutoff.

Kaplan–Meier curve was used to obtain median, mean, and overall survival. Cox regression analysis was used to obtain the hazard ratio (HR). Time-independent Cox regression multivariate analysis was used to obtain adjusted HR. All data were analyzed using SPSS for windows version 25.0 program. $p < 0.05$ was used as the limit of statistical significance.

Results

Sample characteristics

A total of 40 subjects were included in this study. The median (minimum-maximum) age of the sample is 50.5 (18–84) years. The most common types of cancer in subjects were non-Hodgkin's lymphoma and acute myeloblastic leukemia (15% each) followed by lung carcinoma at 10%. The most common source of infection was lung infection (pneumonia) at 47.5% followed by urinary tract infection at 35% (Table 1).

Table 1: Characteristics of the sample

Variable	n = 40, n (%)
Age (years), median (minimum–maximum)	50.5 (18–84)
Sex	
Male	22 (55.0)
Female	18 (45.0)
Comorbidity	
Without comorbid	26 (65.0)
With comorbid	14 (35.0)
Type of cancer	
Lymphoma non-Hodgkin	6 (15.0)
Acute myeloblastic leukemia	6 (15.0)
Acute lymphoblastic leukemia	1 (2.5)
Multiple myeloma	3 (7.5)
Chronic myeloid leukemia	1 (2.5)
Cervical cancer	3 (7.5)
Astrocytoma	1 (2.5)
Lung cancer	4 (10.0)
Osteosarcoma	3 (7.5)
Penile carcinoma	1 (2.5)
Nasopharynx carcinoma	2 (5.0)
Renal cells carcinoma	1 (2.5)
Bladder carcinoma	1 (2.5)
Pancreatic carcinoma	3 (7.5)
Colorectal carcinoma	3 (7.5)
Gallbladder carcinoma	1 (2.5)
Source of infection	
Lungs	19 (47.5)
Urinary tract	14 (35.0)
Skin and integument	6 (15,0)
Bile duct	1 (2.5)
Sepsis severity	
Septic shock	9 (22.5)
Sepsis	31 (77.5)
SOFA score, median (minimum–maximum)	8 (4–18)
Hepcidin (ng/mL), median (minimum–maximum)	6.1 (1.43–193.28)

SOFA: Sequential organ failure assessment.

Differences in hepcidin levels in surviving and non-surviving cancer patients with sepsis

There were significant differences in SOFA scores and hepcidin levels in surviving and non-surviving cancer patients with sepsis ($p < 0.001$). There was no significant association between age, gender, the presence of comorbidities, and type of cancer with survival in cancer patients with sepsis ($p = 1.000$, 0.348, 0.521, and 0.523, respectively) (Table 2).

Table 2: Differences in hepcidin levels and other variables in surviving and non-surviving cancer patients with sepsis

Variable	Survivors (n = 23), n (%)	Non-survivors (n =17), n (%)	p
Age category (year old)			
≥ 60	6 (26.1)	5 (29.4)	1.000
< 60	17 (73.9)	12 (70.6)	
Sex			
Male	11 (47.8)	11 (64.7)	0.348
Female	12 (52.2)	6 (35.3)	
Comorbidity			
With comorbid	7 (30.4)	7 (41.2)	0.521
Without comorbid	16 (69.6)	10 (58.8)	
Type of cancer			
Malignancy hematology	9 (39.1)	9 (52.9)	0.523
Malignancy solid	14 (60.9)	8 (47.1)	
Sepsis severity			
Septic shock	1 (4,3)	8 (47.1)	0.02*
Sepsis	22 (95.7)	9 (52.9)	
SOFA score, median (minimum–maximum)	5 (4–11)	14 (8–18)	<0.001*
Hepcidin (ng/mL), median (minimum–maximum)	4.51 (1.43–9.04)	21.98 (3.28–193.28)	<0.001*

*Statistically significant. SOFA: Sequential organ failure assessment.

Cutoff of hepcidin levels in predicting mortality

Using ROC curve analysis, we found that the optimal cutoff of hepcidin levels for predicting mortality in cancer patients with sepsis is ≥7.5 ng/mL (Figure 1 and Table 3).

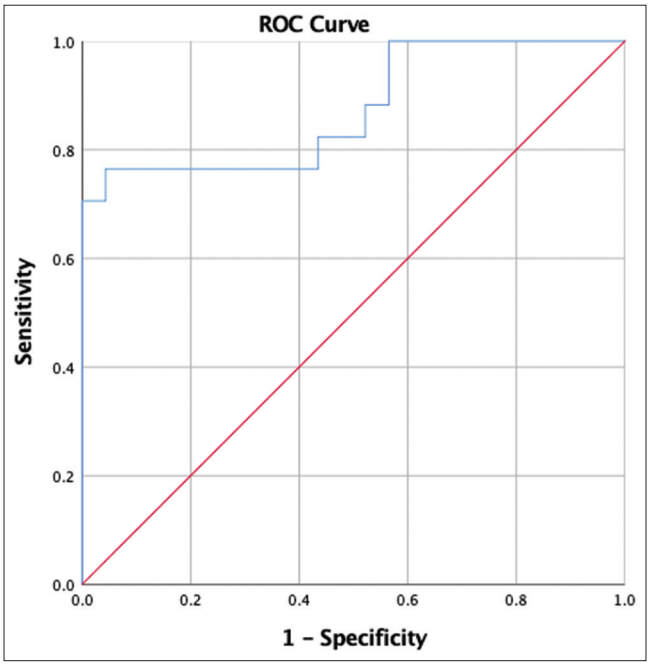

Figure 1: ROC curve for hepcidin levels to predict mortality in cancer patients with sepsis

Table 3: Cutoff values, sensitivity, specificity, and area under the curve of hepcidin levels in predicting mortality in cancer patients with sepsis

Variable	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	p
Hepcidin level (ng/mL)	≥ 7.5	76.5	82.6	0.875	0.757–0.992	0.043*

CI: Confidence interval, AUC: Area under the curve.

Kaplan–Meier curve based on hepcidin levels

There were differences in survival curves based on hepcidin levels. In the group of subjects with high hepcidin levels, the median survival obtained is 8 days, which means that 50% of the subjects died within 8 days of observation (Figure 2 and Table 4). In the group of subjects with low hepcidin levels, median survival was not obtained, because the number of deaths did not reach 50% of cases.

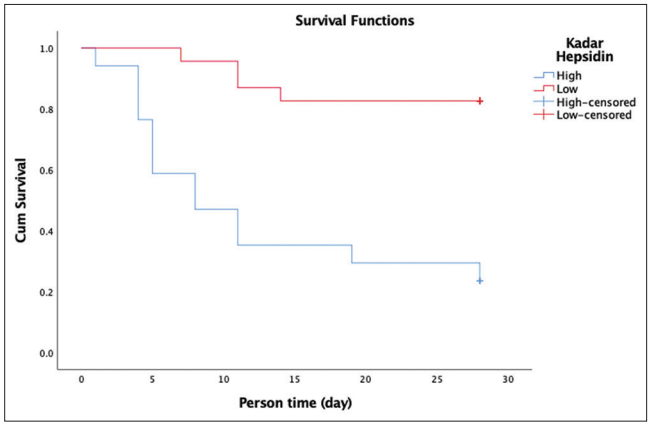

Figure 2: Kaplan-Meier curve based on hepcidin levels

Table 4: Mean, median, and overall survival of subjects based on hepcidin levels

Category of hepcidin levels	Mean (days)	95% CI	Median (days)	95% CI	Overall survival (%)
High	13.23	8.15–18.32	8.0	1.95–14.05	23.5
Low	25.00	22.29–27.71	-	-	82.6
All subject	20.00	16.74–23.26	-	-	57.5

CI: Confidence interval.

Hazard ratio (HR) and Adjusted HR of hepcidin levels and sepsis severity

The hazard ratio (HR) of the variable hepcidin levels is 7.28 (95% CI 2.35–22.55), p < 0.001, which means that at any time the group of subjects with high hepcidin levels has a probability of death 7.28 times compared to the group of subjects with low hepcidin levels. In the multivariate analysis by including the sepsis severity variable into the analysis, hepcidin levels are independently associated with mortality with an adjusted HR of 7.91 (2.51–24.91), p < 0.001 (Table 5).

Table 5: Hazard ratio and adjusted hazard ratio of hepcidin levels and sepsis severity

Variable	HR (95% CI)	p	Adjusted HR (95% CI)	p
Sepsis severity	5.71 (2.14–15.26)	0.001*	6.46 (2.31–18.05)	< 0.001*
Hepcidin	7.28 (2.35–22.55)	< 0.001*	7.91 (2.51–24.91)	< 0.001*

HR: Hazard ratio, CI: Confidence interval.

Discussion

The results of our study revealed higher mortality in patients with high hepcidin levels than in patients with low hepcidin levels. The effect of hepcidin levels on mortality is statistically significant and is independently associated with sepsis severity. These results are consistent with the study of Jiang *et al*. who found that serum hepcidin levels have the highest predictive value compared to other parameters related to inflammatory anemia. The predictive value of hepcidin in predicting mortality is related to its role as an acute-phase biomarker in severe infectious and inflammatory conditions [6].

The mechanism of regulation of hepcidin levels is very complex. Besides being influenced by an increase of proinflammatory cytokines, the regulation of hepcidin levels is also influenced by serum iron levels and the rate of erythropoiesis. In sepsis, there is increased scavenging of erythrocytes by macrophages and suppression of erythropoiesis by inflammatory cytokines. Both conditions cause an increase of serum iron concentration which induces an increase of hepcidin levels [10], [11]. Increased hepcidin levels cause a decrease in iron export by macrophages and cause an increase in intracellular iron. Iron restriction can limit the availability of iron for the growth of pathogenic bacteria, but the increase of free iron in the cytoplasm can increase oxidative stress, mitochondrial dysfunction, cell death, and tissue damage. The degree of tissue damage or organ dysfunction due to sepsis is proportional to the degree of intracellular iron accumulation [4].

In advanced cancer, there is an increase in hepcidin levels which correlate with an increase in interleukin-6 (IL-6) levels [12]. Another study also found that elevated serum hepcidin levels in advanced cancer patients correlated with T-stage and the occurrence of metastases [13], [14], [15].

Conclusions

Cancer patients with sepsis who have high hepcidin levels have a lower survival than patients with low hepcidin levels at 28 days of follow-up. Hepcidin levels can be used as a predictor of mortality in cancer patients with sepsis. Further studies are needed to determine the appropriate therapy in septic patients based on hepcidin levels to improve survival.

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