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## Effect of Conjugated Hyperbilirubinemia on the Prognosis of Patients Hospitalized in Intensive Care Unit at Kariadi Hospital, Semarang

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### ABSTRACT

**Background:** In critically-ill patients, liver dysfunction plays a significant role on patient's morbidity and mortality in the intensive care unit (ICU). Metabolic, hemodynamic and inflammatory factors also contribute in liver damage. Bilirubin is one of clinical markers for liver dysfunction. Some literatures indicated that patients with hyperbilirubinemia have higher mortality rate. The aim of this study was to assess the death prognosis of critically-ill patients with hyperbilirubinemia.

**Method:** This study was an observational, prospective, and cohort study. All patients at the ICU of Kariadi hospital with hyperbilirubinemia were consecutively recruited over 8-month period from May 1<sup>st</sup> 2008 to January 31<sup>st</sup> 2009. Hyperbilirubinemia was defined as serum bilirubin levels  $\geq 1.3$  mg/dL for at least 72 hours and no hyperbilirubinemia was observed when the patients were admitted to the hospital.

**Results:** Of 79 subjects who fulfilled inclusion criteria, the incidence of hyperbilirubinemia in critically-ill patients was 39.2%. About 56 subjects were enrolled in the study. Among them, 28 subjects showed hyperbilirubinemia and the other 28 subjects were included in the control group. There was no significant difference regarding the baseline characteristics of hyperbilirubinemia group and non-hyperbilirubinemia group. At the end of the study, the mortality rate in hyperbilirubinemia patients were 60.7% and 21.3% in the non-hyperbilirubinemia patients. The relative risk (RR) of death was 2.8 (95% CI = 1.3 - 6.1;  $p = 0.003$ ).

**Conclusion:** The incidence of hyperbilirubinemia was high in critically ill-patients hospitalized in the ICU of Kariadi hospital. The incidence of death between non-hyperbilirubinemia and hyperbilirubinemia subjects was significantly different. The significant relative risk of death indicates that hyperbilirubinemia may have influences on the mortality rate of critically-ill patients hospitalized in the ICU.

**Keywords:** liver dysfunction, hyperbilirubinemia, death

### INTRODUCTION

In critically-ill patients who have multi organ failure (MOF), liver dysfunction frequently occurs. Liver dysfunction is considered less dangerous and less threatening than the respiratory, cardiovascular, or renal failure, since it has been frequently overlooked.<sup>1</sup>

Liver dysfunction in critically-ill patients may occur due to shock, impaired liver circulation, decreased oxygen supply, and inflammation. Such condition, often called shock liver syndrome, explains the state of shocked liver in critically-ill patients. Pathophysiology of the syndrome may include hemodynamic disorders, metabolic, and inflammatory factors.<sup>2</sup> Conjugated bilirubin levels have not often been examined in patients without visible jaundice. However, Brienza et al found evidences that patients who had mild hyperbilirubinemia ( $> 2.0$  mg/dL) and went to surgery had higher mortality rate, as well as in patients with sepsis, multiple injuries, totally parenteral nutrition and mechanical ventilation supported by positive end expiratory pressure.<sup>1,3,4,5</sup>

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The aim of this study was to assess the effect of conjugated hyperbilirubinemia on the prognosis of patients who all been treated in the intensive care unit. Moreover, the aim was also to assess the death prognosis in critically-ill patients with hyperbilirubinemia who had all been treated in the intensive care unit (ICU) of Kariadi hospital.

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**METHOD**

In order to assess the prognosis of critically-ill patients who had hyperbilirubinemia, we conducted an observational study with cohort design. We studied dependent and independent variables. The dependent variable was the number of death of patients who were hospitalized in the ICU of Kariadi hospital; while the independent variable was conjugated hyperbilirubinemia level. However, we did not investigate the confounding variables.

The study population was patients who were hospitalized in the ICU. The inclusion criteria were patients who were treated in the ICU, patients with total bilirubin levels  $\geq 1.3$  mg/dL on day 3 or more following the intensive treatment, patients who had given informed consent, including the consent from their family. The exclusion criteria were patients who had history of liver disease characterized by history or signs of chronic liver disease; patients with positive viral seromarker, blunt trauma, and extrahepatic obstruction; patients who died or discharged from the ICU < 48 hours after treatment.

Each patient in the ICU who had hyperbilirubinemia was compared to another patient who did not have hyperbilirubinemia. They were interviewed to confirm the study outcome. The collected data was tested and the results showed no significant difference between the hyperbilirubinemia group and non-hyperbilirubinemia group. Continuous data which was normally distributed was tested by using the student t-test; while data with abnormal distribution was tested by using Mann Whitney test. Categorical or nominal variables were tested by Chi-square test or Fisher test. Univariate analysis of the study outcome was applied for variables that did not show any significant difference; while analysis of stratification for relative risk assessment was performed if there was significant difference between both groups. The proportion of significance level of the variables was tested by calculating relative risk (RR) and was expressed as the level of significance  $\alpha = 0.05$  and 95% confidence interval (CI). The statistical analysis was performed by using SPSS version 15.

**RESULTS**

The study was conducted between May 1<sup>st</sup> 2008 to January 31<sup>st</sup> 2009. Of the 552 patients treated in the ICU, 478 patients did not meet the inclusion criteria. Patients who fulfilled the criteria were included as the study patients and were categorized into two cohort groups, i.e. 31 patients in hyperbilirubinemia group and 48 patients in the non-hyperbilirubinemia group.

**Table 1. Characteristic of the patients with different test**

Variable	Hyperbilirubinemia	Non hyperbilirubinemia	p
Age > 60 years	9 (32.1%)	14 ( 50.0%)	0.174@
Acute respiratory distress syndrome	3 (10.7%)	7 (25.0%)	0.592@
Febris	6 (21.4%)	5 (17.8%)	0.787@
Heart failure	18 (64.3%)	12 (42.8%)	0.108@
Surgery patient	7 (25%)	5 (17.8%)	0.515@
Severe sepsis	14 (50%)	13 (46.4%)	0.174@
Ventilator positive end-expiratory pressure > 12 cm H <sub>2</sub> O	3 (10.7%)	2 (7.1%)	0.639@
Hyperglycemia/hypoglycemia	4 (14.3%)	10 (35.7%)	0.121@
Thrombocyte abnormality	13 (46.4%)	11 (39.3%)	0.415@
Sodium level abnormality	15 (53.6%)	9 (32.1%)	0.105@
Ureum	88.7 ± 58.9	106.4 ± 111.6	0.926@
Potassium	4.3 ± 0.8	4.7 ± 1.5	0.21@
Heart rate	112.9 ± 17.1	113.3 ± 25.6	0.878@
Pulse	104.1 ± 16.1	105.7 ± 17.7	0.724□
Systolic blood pressure	122.4 ± 27.8	120.2 ± 38.9	0.807□
Diastolic blood pressure	72.5 ± 18.9	69.3 ± 22.4	0.556□
Hemoglobin	11.6 ± 2.5	10.9 ± 2.7	0.352□
Hematocyte	35.9 ± 8.3	33.1 ± 8.2	0.209□

Note: @: X<sup>2</sup> , @: Fisher's exact test, ©: Mann Whitney, □: t-test

The study found that the incidence of liver dysfunction in the ICU at Kariadi hospital was 39.2%. Among them, there were 28 patients with hyperbilirubinemia and 28 patients who were non-hyperbilirubinemia. The mean age was 42 years; with the lowest age of 14 years and the highest age was 80 years. In average, the patients were at 41.66 years of age; while the median age was 55 years. At the end of the study, the mortality rate in hyperbilirubinemia patients were 60.7% and 21.3% in the non-hyperbilirubinemia patients. The relative risk (RR) of death was 2.8; (95% CI = 1.3 - 6.1; p = 0.003).

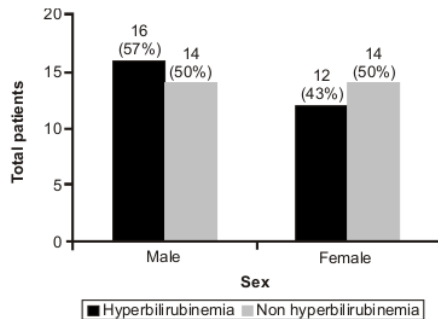


Figure 1. Characteristic of the patients by sex

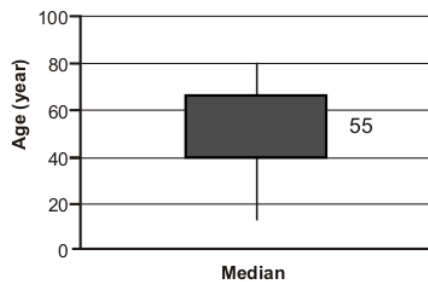


Figure 2. Characteristic of the patients by age

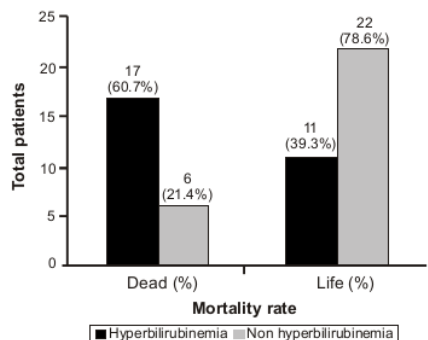


Figure 3. Correlation between hyperbilirubinemia and mortality

## DISCUSSION

Of patients who were treated at the ICU of Kariadi hospital, we found the incidence of liver dysfunction as many as 39.2%. Such result is greater than that the results obtained by Ebert (22%) and Grau et al (23%).<sup>6,7</sup>

It may occur because we included various risk factors in this study.

The correlation between hyperbilirubinemia and mortality at the ICU can be seen on figure 3. It shows that there were 17 (60.7%) patients who had hyperbilirubinemia and experienced the outcome of death; while there were only 11 (39.3%) patients who had the outcome death in non-hyperbilirubinemia group. Thus, the case fatality rate in critically-ill patients who were hospitalized in intensive care with liver dysfunction was 60.7%. The study indicates that the relative risk of death in patients with hyperbilirubinemia was 2.8 times (CI 95% = 1.3; RR < 6.1; p = 0.003). Such result suggests that the existence of hyperbilirubinemia in patients, who were treated in the ICU, will increase the risk of death by 2.8 times. Therefore, hyperbilirubinemia seems to have influence on the prognosis of patients hospitalized in the ICU. These results are consistent with the study results conducted by Stavitz et al who reported that the death reached 50% in patients with acute liver failure who were treated in intensive care unit.<sup>8</sup>

Acute jaundice may also act as a marker of sepsis, multisystem organ failure (MSOF), or may reflect transient hypotension (shock-liver), right-sided heart failure, the metabolic breakdown of red blood cells, or pharmacologic toxicity. Such condition should lead us to suspected liver dysfunction and he patients may experience shock or sepsis, which increases the risk of death. Death caused by liver dysfunction may occur through extensive necrosis, followed by encephalopathy. It may also occur through liver failure, encephalopathy, brain edema, coagulopathy, hypoglycemia, electrolyte disturbances, respiratory problems, renal failure and secondary infection. Bleeding and coagulopathy hemodynamic disturbances may result, which leads to death.<sup>9-15</sup>

Our study result indicates that the incident of hyperbilirubinemia should be concerned and further studies should be carried out about liver dysfunction in critically-ill patients who were hospitalized in the ICU. The assessment of hyperbilirubinemia performed on day 3 after the sign of jaundice may become the weakness in our study.

## CONCLUSION

The incidence of hyperbilirubinemia is frequently high in critically-ill patients who were hospitalized in the ICU of Kariadi hospital. This study demonstrates that there was significant difference regarding the incidence of death between non hyperbilirubinemia and hyperbilirubinemia patients. The significant relative risk of death indicates that hyperbilirubinemia has important influence on the mortality of critically-ill patients hospitalized in the intensive care unit.

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