Serum Creatinine as a Clinical Parameter for Patients with Cancer in End-of-Life: a retrospective cohort study in an acute palliative care unit

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Abstract

Background: Prognosis prediction is a challenge for clinicians caring for patients with cancer in end-of-life. Although previous studies have shown several biological parameters to be prognostic factors, it remains unclear which factors can predict the exact prognosis. Additionally, blood tests for patients with terminal cancer are limited, it is practically difficult to utilize usual parameters as prognostic factors. Therefore, a universal, readily available, and the cost-effective clinical parameter is needed to predict the survival times of patients with cancer in end-of-life regardless of age, sex, or cancer type.

Methods: We analyzed the medical records of 280 patients admitted to the palliative care unit at Korea University Guro Hospital from July 2019 to June 2021. After analysis of survival time according to patients' clinical parameters, Kaplan-Meier survival curves using Serum Creatinine (Scr) levels (cut-off: 1.2 mg/dL) were plotted and compared using the log-rank test. Finally, using stepwise selection, multivariable Cox proportional hazard model was used to identify significant prognostic factors.

Results: Patients with high Scr (≥1.2 mg/dL) had shorter median survival than those with normal levels (12 days vs 23 days). Multivariate Cox proportional hazard model identified male (HR=1.47; P=0.019), stomach cancer (HR=1.88; P=0.020), poor performance status (HR=1.56; P=0.004), leukocytosis (HR=1.81; P<0.001), high AST (HR=1.57; P=0.004), and high Scr (HR=1.54; P=0.022) as significantly associated with shorter survival time.

Conclusions: High Scr was significantly associated with poor survival in patients with cancer near end-of-life. This readily available and simple clinical parameter might be helpful in predicting prognosis in palliative care settings.

Introduction

Prognostication is important for patients and caregivers in end-of-life care to make their limited lifetime meaningful and for physicians to establish appropriate care plans [1]. However, it is difficult to predict the survival time of patients in end-of-life because of the diverse disease courses and various physiological characteristics of an individual. Therefore, predicting the prognosis is a challenging task for clinicians caring for patients with cancer in end-of-life.

Clinicians may estimate the survival time of patients by integrating the subjective and objective findings. Subjective findings include the clinician's prediction of survival and symptoms such as dyspnea, anorexia, and delirium [2–4]. Objective findings include biological parameters such as white blood cells (WBC), lymphocytes, albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, cortisol, uric acid, C-reactive protein (CRP), and lactate dehydrogenase (LDH) [5–14]. However, it remains unclear which factors can predict the exact prognosis of patients with terminal cancer. This gains importance in a palliative care setting, where only basic blood tests, such as complete blood count (CBC), renal function tests, and liver function tests, are required to assess a patient's status and minimize discomfort; additional tests are needed depending on the patient's condition. Therefore, a

universal, readily available, and cost-effective clinical parameter is necessary to predict the survival time of patients with cancer in end-of-life, regardless of age, sex, or cancer type.

Creatinine (Cr) is an amino acid compound derived from creatine and creatine phosphate [15]. Serum Cr (Scr) has generally been used as a standard biomarker to evaluate renal function [16]. Several studies have suggested that a high Scr level is associated with poor prognosis in patients with cancer owing to renal dysfunction and cancer progression [17–20]. Since renal function in patients with terminal cancer declines for various reasons, such as multiple organ failure, dehydration, and nephrotoxicity of cancer treatment, it is assumed that the deterioration of renal function is related to prognosis. However, Scr is not included as a prognostic factor in representative prognostic models, such as the Palliative Prognostic Score, Palliative Prognostic Index, and Prognosis in Palliative Care Study [21–23]. Although a few studies have suggested a relationship between renal function and prognosis of patients with terminal cancer, factors that are not routinely measured in a palliative care setting, such as CRP, LDH, and uric acid, have been included [24–25].

The purpose of this study was to investigate the prevalence of abnormal Scr levels in patients with terminal cancer in an acute palliative care unit and evaluate whether Scr can be a universal, readily available prognostic factor in patients with cancer in end-of-life.

Methods

Participants

This retrospective study reviewed the medical records of 280 patients with terminal cancer, admitted to the palliative care unit at Korea University Guro Hospital from July 2019 to June 2021. Among the 280 patients, those with incomplete laboratory data including hemoglobin (Hb), WBC, AST, ALT, albumin, and Cr were excluded from this study (N = 5). Patients who were repeatedly hospitalized and discharged within the study period were considered single cases based on the last hospitalization (N = 63). Finally, 212 patients were eligible for statistical analysis. Patients whose survival data were unavailable owing to discharge, were censored (N = 28). Ethical approval was obtained from the Institutional Review Board of Korea University Guro Hospital (Registration Number: K2021-2502-001).

Patient demographics and clinical information including sex, age, admission or transfer-in date, discharge date, date of death, primary cancer site, performance status, pain intensity, use of total parenteral nutrition (TPN), and laboratory findings were collected from electronic medical records. Survival time was defined from the date of admission to the date of death or was censored. The primary cancer site was categorized according to the International Classification of Disease-10 (ICD-10). Performance status was assessed using the Eastern Cooperative Oncology Group performance scale (ECOG-PS), and ECOG-4 was considered poor performance status [26]. Pain intensity was measured using the Numerical pain Rating Scale (NRS) [27]. Patients were assessed using ECOG-PS and NRS at the time of admission or transfer-in, by physicians or trained palliative care nurses. In our palliative unit,

baseline laboratory examinations were performed within 3 days of admission, and additional tests were performed when the patient's condition changed. Hb, WBC, albumin, AST, ALT, and Cr levels, which are considered essential laboratory parameters, were selected for our analysis. If blood tests were repeated within 3 days of admission, the results of the first test were analyzed.

Scr was dichotomized at the cut-off value of 1.2 mg/dL, since Scr above 1.2 mg/dL was considered pathological. Leukocytosis was defined as WBC $\geq$ 11.0 10^3/μL as suggested by previous research [24]. Anemia was defined as Hb < 10.0 g/dL based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5). Serum albumin, AST, and ALT levels were divided by the abnormal cut-off level of in-hospital standards.

Statistical Analysis

Descriptive data were expressed as medians (interquartile range; IQR) for continuous variables and numbers (%) for categorical variables. The Kaplan-Meier method was used to compute the median survival time and 95% confidence interval (CI) of each group. Kaplan-Meier survival curves according to Scr groups were plotted and compared with the log-rank test. A univariable Cox proportional hazard model and a multivariable Cox proportional hazard model using stepwise selection were used to identify significant prognostic factors. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated. All statistical analyses were carried out using SAS version 9.4(SAS Institute, Cary, NC, USA). The level of statistical significance was $P < 0.05$.

Results

The demographic and cancer-related characteristics of the patients are presented in Table 1. Among the 212 patients, 54.7% (N = 116) were male and 64.2% (N = 136) were 65 years or older. The most common primary cancer site was the lungs (N = 46, 21.7%), and 44.8% (N = 95) of the patients had a poor performance status. The median survival time of the patients was 16 days (95% CI: 8.0-32.5).

Table 1
Demographics and cancer-related characteristics of patients (N = 212)

	Median (IQR) or n (%)
Sex	
Male	116(54.7)
Female	96(45.3)
Age, yrs	
≥65	136(64.2)
<65	76(35.9)
Cancer site (ICD-10)	
Lung (C33-34)	46(21.7)
Liver (C22)	29(13.7)
Ovary, Cervix (C53,56)	22(10.4)
Urinary tract (C64-68)	21(9.9)
Colon (C18-21)	21(9.9)
Stomach (C16)	17(8.0)
Pancreas (C25)	16(7.6)
Breast (C50)	12(5.7)
Gallbladder, biliary tract (C23-24)	8(3.8)
Prostate (C61)	6(2.8)
Lymphoma (C83-85)	3(1.4)
Others	11(5.2)
ECOG-PS	
4 (Poor performance status)	95(44.8)
≤3	117(55.2)
TPN use	
Yes	29(13.7)
No	183(86.3)
NRS	

	Median (IQR) or n (%)
0–3 (mild)	181(85.4)
4–6 (moderate)	29(13.7)
7–10 (severe)	2(0.9)
Laboratory parameter	
Hemoglobin, g/dL	9.6(8.3–11.1)
White blood cells, 10^3/μL	9.3(6.6–14.0)
Albumin, g/dL	2.8(2.6–3.2)
AST, IU/L	34.5(21.0–73.0)
ALT, IU/L	19.5(12.0–46.0)
Creatinine, mg/dL	0.7(0.5–1.3)
Censored[a]	28(13.2)
Survival time[b]**, days**	16(8.0-32.5)
Abbreviations: *ICD-10* International Classification of Disease-10, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *TPN* total parenteral nutrition, *NRS* Numerical pain Rating Scale, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *IQR* interquartile range	
[a]Survival data were not available due to discharge	
[b]Defined from the date of admission to the date of death or censored	

Table 2 shows the median survival time in relation to the patient characteristics. Male, stomach cancer, poor performance status, leukocytosis, high AST, high ALT, and high Scr were significantly associated with a shorter median survival time. 26.9% (N = 57) of the patients showed high Scr and their median survival was 12 days (95% CI: 9–15), while those with normal Scr had a median survival of 23 days (95% CI: 17–27).

Table 2
Survival time in relation to patient characteristics

	n(%)	Median survival days (95% CI)	p-value[a]
Sex			0.008
Male	116(54.7)	15(13–21)	
Female	96(45.3)	25(17–29)	
Age, yrs			0.392
≥65	136(64.2)	22(16–26)	
<65	76(35.8)	16(12–21)	
Cancer site (ICD-10)			
Lung (C33-34)	46(21.7)	15(12–25)	0.197
Liver (C22)	29(13.7)	17(9–23)	0.121
Ovary, Cervix (C53,56)	22(10.4)	29(15–52)	0.05
Urinary tract (C64-68)	21(9.9)	28(15–42)	0.076
Colon (C18-21)	21(9.9)	27(11–40)	0.122
Stomach (C16)	17(8.0)	16(6–22)	0.045
Pancreas (C25)	16(7.6)	16.5(11–28)	0.651
Breast (C50)	12(5.7)	26(4–44)	0.991
Gallbladder, biliary tract (C23-24)	8(3.8)	16(2–51)	0.813
Prostate (C61)	6(2.8)	32(5-)	0.561
Lymphoma	3(1.4)	15(4–30)	0.401
Others	11(5.2)	13(2–28)	0.279
ECOG-PS			0.005
4 (Poor performance status)	95(44.8)	15(12–16)	
≤3	117(55.2)	23(18–29)	
TPN use			0.367
Yes	29(13.7)	13(10–25)	
No	183(86.3)	19(16–24)	
NRS			0.518

	n(%)	Median survival days (95% CI)	p-value[a]
0–3 (mild)	181(85.4)	19(15–24)	
4–6 (moderate)	29(13.7)	17(11–25)	
7–10 (severe)	2(1)		
Hemoglobin, g/dL			0.499
<10.0 (Anemia)	121(57.1)	19(15–24)	
≥10.0 (Normal)	91(42.9)	17(13–27)	
White blood cells, 10^3/μL			0.004
≥11.0 (Leukocytosis)	84(39.6)	13(11–15)	
<11.0 (Normal)	128(60.4)	23(17–28)	
Albumin, g/dL			0.553
<2.5 (hypoalbuminemia)	37(17.5)	15(8–21)	
≥2.5 (Normal)	175(82.5)	21(16–25)	
AST, IU/L			< 0.001
>36 (High)	99(46.7)	15(12–18)	
≤36 (Normal)	113(53.3)	25(17–30)	
ALT, IU/L			0.002
>36 (High)	62(29.2)	13(9–16)	
≤36 (Normal)	150(70.8)	23(17–28)	
Creatinine, mg/dL			0.001
≥1.2 (High)	57(26.9)	12(9–15)	
<1.2 (Normal)	155(73.1)	23(17–27)	
Abbreviations: *ICD-10* International Classification of Disease-10, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *TPN* total parenteral nutrition, *NRS* Numerical pain Rating Scale, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *95% CI* 95% confidence interval			
[a]Log-rank test			

Figure 1 presents the Kaplan-Meier curves plotted using Scr levels; patients with high Scr levels survived for a shorter time than those with normal levels (P = 0.001, log-rank test).

Independent prognostic factors analyzed from the Cox proportional hazard models are shown in Table 3. Univariate Cox hazard model analyses revealed that male (HR = 1.49; P = 0.009), poor performance status (HR = 1.50; P = 0.006), leukocytosis (HR = 1.54; P = 0.005), high AST (HR = 1.65; P = 0.001), high ALT (HR = 1.62; P = 0.003), and high Scr (HR = 1.75; P = 0.001) were associated with a shorter survival time. A multivariable Cox hazard model using stepwise selection revealed that male (HR = 1.47; P = 0.019), stomach cancer (HR = 1.88; P = 0.020), poor performance status (HR = 1.56; P = 0.004), leukocytosis (HR = 1.81; P < 0.001), high AST (HR = 1.57; P = 0.004), and high Scr (HR = 1.54; P = 0.022) were significantly associated with poor prognosis.

Table 3
Independent prognostic indices of survival (Cox proportional hazard model)

	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	p-value	**HR (95% CI)**	p-value
Sex				
Male	1.49(1.10–2.01)	0.009	1.47(1.07–2.03)	0.019
Female	ref.		ref.	
Age, yrs				
≥65	0.88(0.65–1.19)	0.402		
<65	ref.			
Cancer site (ICD-10)				
Lung (C33-34)	1.25(0.89–1.75)	0.208		
Liver (C22)	1.37(0.91–2.05)	0.129		
Ovary, Cervix (C53,56)	0.60(0.35–1.02)	0.057		
Urinary tract (C64-68)	0.65(0.40–1.06)	0.086	0.47(0.27–0.81)	0.006
Colon (C18-21)	0.66(0.38–1.14)	0.132		
Stomach (C16)	1.68(1.00-2.82)	0.052	1.88(1.10–3.21)	0.020
Pancreas (C25)	1.12(0.67–1.88)	0.659		
Breast (C50)	1.00(0.51–1.95)	0.992		
Gallbladder, biliary tract (C23-24)	0.90(0.37–2.19)	0.817		
Prostate (C61)	0.75(0.28–2.02)	0.570		
Lymphoma	1.61(0.51–5.06)	0.414		
Others	1.39(0.75–2.57)	0.293		
ECOG-PS				
4 (Poor performance status)	1.50(1.12–2.01)	0.006	1.56(1.15–2.10)	0.004
≤3	ref.		ref.	
TPN use				
Yes	1.20(0.80–1.81)	0.378		

	Univariable analysis		Multivariable analysis[a]	
No	ref.			
NRS		0.564		
0–3 (mild)	ref.			
4–6 (moderate)	0.98(0.64–1.50)	0.924		
7–10 (severe)	0.34(0.05–2.45)	0.285		
Hb, g/dL				
<10.0 (Anemia)	1.11(0.82–1.49)	0.509		
≥10.0 (Normal)	ref.			
White blood cells, 10^3/μL				
≥11.0 (Leukocytosis)	1.54(1.14–2.07)	0.005	1.81(1.30–2.50)	< .001
<11.0 (Normal)	ref.		ref.	
Albumin, g/dL				
<2.5 (hypoalbuminemia)	1.12(0.76–1.65)	0.562		
≥2.5 (Normal)	ref.			
AST, IU/L				
>36 (High)	1.65(1.23–2.22)	0.001	1.57(1.16–2.14)	0.004
≤36 (Normal)	ref.		ref.	
ALT, IU/L				
>36 (High)	1.62(1.18–2.21)	0.003		
≤36 (Normal)	ref.			
Creatinine, mg/dL				
≥1.2 (High)	1.75(1.26–2.44)	0.001	1.54(1.07–2.24)	0.022
<1.2 (Normal)	ref.		ref.	

Abbreviations: *ICD-10* International Classification of Disease-10, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *TPN* total parenteral nutrition, *NRS* Numerical pain Rating Scale, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HR* hazard ratio, *95% CI* 95% confidence interval

[a]Multivariable Cox hazard model using stepwise selection

Discussion

In this study, we identified the prevalence of high Scr in patients with terminal cancer in an acute palliative care unit. We also confirmed that Scr, sex, performance status, WBC count, and AST were strongly associated with the survival of patients in end-of-life.

Previous studies have noted that high Scr is a significant prognostic factor in patients with various types and stages of cancer; high preoperative Scr in renal cell carcinoma is associated with impaired 5-year cancer-specific survival [17]; high Scr in ovarian cancer is related to age at first diagnosis and predicts poor prognosis [18]; high Scr is an independent predictor of lower overall survival in colorectal cancer patients [19], and independent risk factors in vulvar cancer patients [20]. Therefore, we hypothesized that the survival time of cancer patients in end-of-life can be associated with Scr, which was investigated in this study.

There are several explanations for the relationship between Scr and remaining life expectancy of patients with terminal cancer. The major contributor for high Scr in patients with cancer may be decreased renal function. Usually, Cr, urea, and uric acid levels are estimated to evaluate the extent of renal dysfunction. Among them, Scr is the most widely used blood test value that indicates renal function [28]. Cr, a low-molecular-weight protein, is metabolized by non-enzymatic phosphorylation in muscle cells at a constant rate and is mainly eliminated through the kidney [29]. It is filtered through the glomerulus and excreted from the proximal tubules. Renal impairment is common in patients with cancer owing to cancer itself, multiple organ failure, and postoperative complications or chemotoxicity [30–32].

In addition, Cr metabolism is linked to cancer progression and metastasis through several mechanisms. Cr is the end product of creatine and creatine phosphate metabolism and is utilized as an essential energy source [15]. Creatine is transported into the muscle and phosphorylated by creatine kinase (CK). Previous studies have shown that CK is upregulated during cancer progression [33]. As cancer cells use creatine as a readily available energy source, the end product of creatine increases [34]. Thus, high Scr in patients with terminal cancer is related to the state of cancer progression and is considered a prognostic factor.

We found that the prevalence of high Scr was approximately 27%, and the median survival time of high Scr group was 12 days. Although increased Scr has been reported in patients with terminal cancer as death approaches, there has been limited data on the prevalence of high Scr in these groups [35, 36]. A multi-center study of terminally ill cancer patients in Korea demonstrated that 11.0% of patients had high Scr, but with different cut-off values (≥ 1.5 mg/dL) [24].

Medical judgement on active dying is important in palliative care. A minimum of 2 weeks preparation is required for patients and their caregivers to face a dignified death. During this period, the palliative care team must provide specific preparations for their last moments as well as physical, mental, and spiritual comfort. In Korea, the standard for judging whether the ‘Hospice, Palliative Care, and Life-sustaining Treatment Decision-making Act’ is enforced is based on the physician’s medical judgment on the last

days of life [37]. From this point of view, a median survival time of 12 days in patients with high Scr has a special meaning; Cr, a relatively cost-effective and simple blood test value, can be helpful in medically identifying active dying without additional unnecessary inconveniences.

Consistent with previous findings, leukocytosis and high AST levels were associated with the survival time of patients with cancer in end-of-life [5, 7, 24]. Leukocytosis was related to the general condition of the patient and inflammation, and abnormal liver function tests are related to liver metastases, infections, direct effects of tumors, and chemotherapeutic drugs. Therefore, leukocytosis and high AST levels are related to poor prognosis, reflecting the poor general condition of patients with terminal cancer.

This study has several limitations. First, some confounders, such as body mass index (BMI) could not be analyzed because of the retrospective design. In general, the weight and height of patients in palliative care units are rarely measured because of their poor condition or the unnecessary discomfort it can cause them. In addition, a study of patients with terminal cancer revealed that BMI did not significantly influence their survival time, and measured body weight may not be accurate owing to the presence of ascites or lymphedema [38]. Second, we did not exclude patients with renal cancer or chronic kidney disease, which might strongly affect Scr levels. Furthermore, this was a single-center study that cannot represent general patients with cancer in end of life. Therefore, a multi-center, larger study is required.

Nonetheless, we confirmed an association between relatively simple blood test parameters and survival time in a palliative care setting, particularly regarding the usefulness of Scr. Further studies are warranted to explore the validity and reliability of Scr as an independent prognostic factor.

Conclusions

In conclusion, we identified that high Scr is significantly associated with poor survival time in patients with cancer in end-of-life. A readily available and simple clinical parameter might be helpful in predicting prognosis and making care plans in palliative care settings.

Abbreviations

WBC: White Blood Cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; LDH: lactate dehydrogenase; CBC: complete blood count; Cr: Creatinine; Scr: Serum Creatinine; TPN: total parenteral nutrition; ICD-10: International Classification of Disease-10; NRS: Numerical pain Rating Scale; CI: confidence interval; HR: Hazard ratios; CK: creatine kinase.

Declarations

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Not applicable.

Author's contributions

YJL and YSC designed this study and participated in all the study stages. CWL and JYP were responsible for the acquisition of the data. SYH carried out data analysis. All authors contributed to data interpretation. YJL wrote the first draft of this manuscript. YSC and SHK carried out critical revisions for intellectual content. YSC and SHK contributed equally as corresponding authors. All authors have read and approved the final version.

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Availability of data and materials

The data supporting the conclusions of this article and detailed information about these data is included within the article.

Ethics approval and consent to participate

We conducted all procedures according to the principles of the Declaration of Helsinki. The Institutional Review Board (IRB) of Korea University Guro Hospital reviewed and approved the study protocol (Registration Number: K2021-2502-001). Informed consent requirements were waived by the IRB of KUMC owing to the retrospective design of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Figures

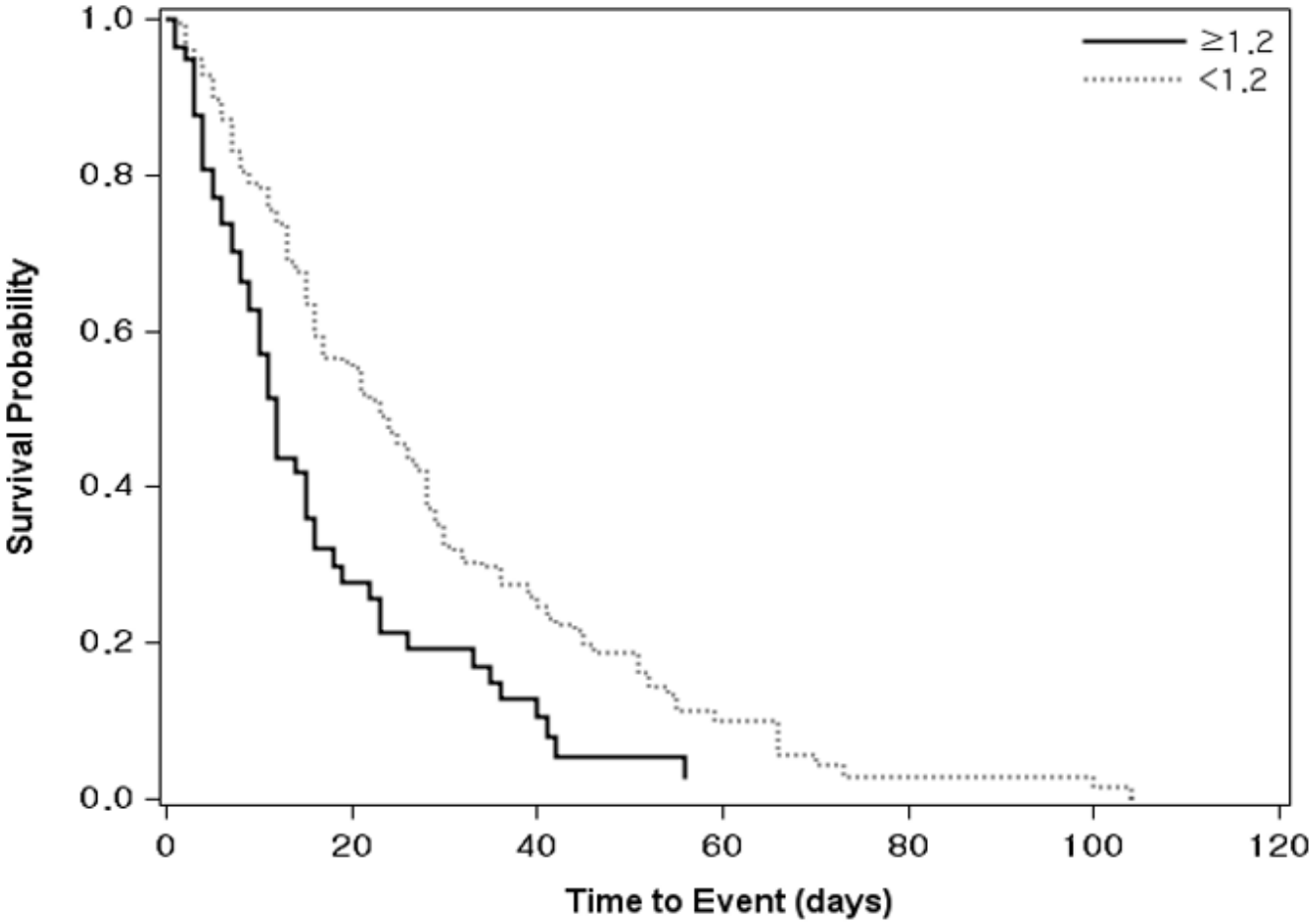

Figure 1

Kaplan-Meier survival curves plotted by serum creatinine levels