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ORIGINAL ARTICLE

Liver function tests may be useful tools for advanced cancer patient care: A preliminary single-center result

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Abstract Accurate prognostication in advanced cancer may facilitate better palliative care. An objective marker may be more applicable and appropriate than a subjective evaluation by physicians. The aim of this study was to evaluate liver function tests as useful prognostic factors for survival in patients with advanced cancer. We recruited advanced cancer patients from January 2007 to December 2009. Data on age, sex, cancer diagnosis, site of metastases, clinical symptoms, and performance status were collected at the time of admission to the palliative care unit. Analyzed laboratory data were obtained on the Day 1 of admission to the palliative care unit. A total of 522 patients were enrolled; 322 (61.7%) of them were males. The mean age was 60.6 ± 13.2 years. Multiple logistic regression analysis adjusting for age and sex demonstrated aspartate transaminase (AST) > 80 IU/L [odds ratio (OR) = 2.01, $p = 0.010$] and alanine transaminase > 80 IU/L (OR = 1.89, $p = 0.047$) were independently

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significant prognostic factors of death within 14 days. AST > 80 IU/L (OR = 3.67, $p = 0.017$) and albumin < 3.0 g/dL (OR = 1.98, $p = 0.048$) were independently significant prognostic factors of death within 6 months. Liver function tests may be useful prognostic factors for patients in the palliative care unit, in addition to being useful for patients with hepatobiliary cancer or liver metastasis. These biochemical tests of liver function with cutoff values can easily be used in palliative care.

Introduction

Care for increasing quality of life and symptom relief are the priority in shorter life expectancy such as when survival time is measured in days, whereas curative and therapeutic procedures would be practicable in patients with longer survival times such as months or years. Accurate prognostication of metastatic cancer patients is important to patients themselves as well as to their families and clinical providers. Patients and families can plan their limited survival days well [1,2], whereas clinicians can make appropriate medical decisions [3,4].

Although clinicians' subjective predictions and clinical symptoms can be helpful for prognostication, they tend to be overly optimistic and possibly inaccurate [5]. Prior literature indicated an accuracy of less than two-thirds for the estimation rate of clinicians' predictions [6]. Therefore, more accurate prediction tools for prognostication are warranted. Additionally, objective indicators will be more useful and easily applicable for less experienced health providers and for providing explanations to families. Studies have indicated the use of some biological markers to predict the survival of advanced cancer patients, including white blood cell (WBC) count, lymphocytes, C-reactive protein (CRP), lactate dehydrogenase (LDH), albumin (Alb), serum sodium (Na), uric acid, and blood urea nitrogen [7–12].

Research on the relationship between liver function tests and survival, especially in advanced cancer patients, is lacking. Some empirical findings aroused our interest to clarify the association between liver function tests and survival durations. Previous studies have investigated liver function tests as indicators of poor prognosis in hepatocellular carcinoma (HCC) [13,14], but fewer studies reported the association between liver function tests and prognosis of other cancer types.

We conducted the study by recruiting patients with advanced cancer and collecting data on cancer types, symptoms, and signs, and other serological variables including blood routine and biochemical parameters including AST, ALT, Alb, and prothrombin time (PT). The aim of this study was to identify whether liver function tests would be convenient and practicable parameters as an objective marker to predict the survival time of advanced cancer patients.

Materials and methods

This retrospective study recruited 522 advanced cancer patients who were admitted to a cancer palliative care unit in Southern Taiwan between January 2007 and December 2009. Advanced cancer patients were suggested by specialists to receive palliative care if curative cancer therapy was no longer applicable. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, and medical records and chart reviews were provided by the hospital. All enrolled patients underwent a blood examination on admission. Patients with acute liver failure or fulminant hepatitis that might have been induced by previous treatment, such as chemotherapy, or by viral infection, were excluded.

Patients' information including age, sex, primary cancer diagnosis, and site of metastases (especially liver) were collected at the time of admission to the palliative care unit. We recorded clinical symptoms including pain, edema, fatigue, tumor wound, cognitive impairment, anorexia, dysphagia, sleep disturbance, ascites, and jaundice. Pain severity was measured by a numeric rating scale (range, 0–10). Survival time (in days) was calculated from the day of admission to the day of death or leaving our palliative care unit, after which we conducted telephonic interviews for a duration of 6 months.

Laboratory data on WBC count, platelet count, CRP level, hemoglobin level, serum aspartate transaminase (AST), alanine transaminase (ALT), serum creatinine, serum ammonia, serum Na, potassium (K), ionized calcium level (ion Ca), serum Alb, and PT with an international normalized ratio (INR) were obtained on the Day 1 of admission to the palliative care unit. The cutoff values for normal and abnormal laboratory data depended on our Kaohsiung Medical University Hospital normal laboratory range, except that ALT > 80 IU/L and AST > 80 IU/L were twice the normal range.

Statistical analyses were performed using SPSS version 19.0 for Windows (IBM Inc., Somers, NY, USA). The level of statistical significance was 0.05. The median survival times were estimated by the Kaplan–Meier method and the survival comparison was based on the log-rank test. Multiple logistic regressions were used to study outcomes of patients (died within 2 weeks to 6 months) associated with the liver function tests separately after adjusting covariates (including age and sex). We divided the patients into three groups (Patients without hepatobiliary cancer, Patients without liver metastasis, and Patients with hepatobiliary cancer and liver metastasis) and analyzed these groups separately to realize roles of liver function test, especially in advanced cancer patients without hepatobiliary involvement.

Results

Of the total patients studied, 84.9% with advanced cancer survived longer than 14 days; however, only 8.2% of these

patients survived more than 6 months. Survival rates in 1 month, 2 months, 3 months, 4 months, and 5 months were, respectively, 67.0%, 46.2%, 33.1%, 23.9%, and 15.3%. The demographic characteristics of these patients are shown in Table 1. The mean age was 60.6 ± 13.2 years, with the most common decade being the 50s (30.7%), followed by the 70s or older (25.3%) and the 60s (23.8%). The number of male patients was 322 (61.7%). The most common sites of cancer were the head and neck (19.9%), followed by the gastrointestinal tract (19.2%), hepatobiliary system (16.5%), and respiratory tract (15.7%), in a descending order. Of the total patients, 144 (27.6%) had been diagnosed with liver metastasis using medical images (abdomen sonography, magnetic resonance imaging, and computed tomography).

Table 2 shows the serological variables used in univariate analysis related to survival time. A significantly shorter survival time was observed in the following condition: AST > 80 IU/L ($p = 0.006$), ALT > 80 IU/L ($p = 0.018$), and Alb < 3.0 g/dL ($p < 0.023$). However, no statistical significance was observed in survival times between normal and abnormal data of WBC count, platelet count, CRP level, creatinine, Na, K, ammonia, and ion Ca.

Clinical symptoms occurring in these patients are shown in Table 3. We found that most symptoms, including cognitive impairment, fatigue, dysphagia, ascites, edema, jaundice, pain, sleep disturbance, and tumor fungating wound, were not associated with shorter survival times. However, the rate of anorexia was significantly higher with a shorter survival time ($p = 0.037$).

Multiple logistic regression analyses were used to clarify the odds ratio (OR) of liver function tests including AST, ALT, ammonia, PT_INR, and Alb on outcome (death within 2 weeks to 6 months) with adjustment for age and sex. We analyzed three groups including patients without hepatobiliary cancer, without liver metastasis, and with hepatobiliary involvement by the same method. The ORs [with 95% confidence interval (CI)] from multiple logistic regression analyses in those who died within 2 weeks are shown in Table 4. When these variables were categorized as dichotomous and adjusted for age and sex, AST > 80 IU/L (OR = 2.01, $p = 0.010$) and ALT > 80 IU/L (OR = 1.89, $p = 0.047$) were independently significant prognostic factors of death within 2 weeks. In patients without hepatobiliary cancer and in those without liver metastasis, AST > 80 IU/L, ALT > 80 IU/L, ammonia > 80 μg/dL, PT_INR > 1.2, and Alb < 3.0 g/L were not significantly associated with the prognosis of death within 2 weeks. However, if these patients had been followed-up for at least 6 months by telephone, as Table 5 reveals, AST > 80 IU/L (OR = 4.66, $p = 0.04$), Alb < 3.0 g/dL (OR = 2.37, $p = 0.03$), and PT_INR > 1.2 (OR = 3.38, $p = 0.049$) would significantly be associated with the outcome of death within 6 months in patients without hepatobiliary cancer.

Table 1 Demographic characteristics of recruited advanced cancer patients ($n = 522$).

Characteristics	Total *n* (%)
Sex	
Male	322 (61.7)
Female	200 (38.3)
Age (y)	
<40	16 (3.1)
40–49	90 (17.2)
50–59	160 (30.7)
60–69	124 (23.8)
≥70	132 (25.3)
Primary cancer site	
Head and neck	104 (19.9)
Gastrointestinal tract	100 (19.2)
Hepatobiliary system	86 (16.5)
Respiratory system	82 (15.7)
Breast	36 (6.9)
Reproductive system	30 (5.7)
Urologic system	22 (4.2)
Pancreas	22 (4.2)
Hematologic system	18 (3.4)
Others	22 (4.2)
Liver metastasis	
Yes	144 (27.6)
No	378 (72.4)

Discussion

The present study clarified that elevated liver function tests may serve as useful prognostic factors of poor prognosis in advanced cancer patients. A higher AST level that was twice the upper limit of normal range (>80 IU/L) and hypoalbuminemia (Alb < 3.0 g/dL) were identified as being associated with the outcome of death within 6 months in all patients except those with hepatobiliary cancer. AST > 80 IU/L had a higher OR (5.65) of death within 6 months in patients with hepatobiliary involvement. However, elevations of AST and ALT were significantly related to the outcome of death within 2 weeks in all patients and in those with hepatobiliary involvement, but not in those without hepatobiliary involvement. The relationship between liver enzymes and prognosis has been discussed in HCC and liver diseases [13–15]. Chen et al. [13] and Changchien et al. [14] reported an ALT level two times higher than the upper limit of normal range and a higher AST/ALT ratio as significant prognostic factors of HCC patients to predict poor survival. However, these two studies focused on the association between HCC and liver enzymes, and not on all types of cancers. Our findings demonstrated that elevated AST would be an independently useful prognostic factor for the other cancer types. Proctor et al. [16] suggested that elevated AST (≥40 IU/L) has a higher hazard ratio of 1.71 for cancer-specific death in 5-year survivals, which is independent of the tumor site. Another cohort study in patients aged 75 years and more revealed an association between abnormal AST and increased cancer mortality (56% increase in the hazard ratio) [17]. However, research focusing on the relationship between advanced cancer patients and liver function tests was few. Our study offered an insight into the theory that AST would be a significant and valuable prognostic factor for the survival duration of advanced cancer patients.

Our study found serum Alb to be also an important prognostic factor of advanced cancer survival. Alb is

Table 2 Median survival time by serologic characteristics of study participants for following 6 months.

Characteristics	N^a (%)	Death (%)	Median (days)	95% CI	p^*
Survival time	522	479 (91.8)	49.5	22–117	
WBC ($10^3/\mu L$)					
≤10.0	207 (39.7)	185 (89.4)	62	50–74	0.065
>10.0	315 (60.3)	294 (93.3)	41	31–51	
Platelets ($10^3/\mu L$)					
≤150	112 (21.5)	105 (93.7)	46	18–74	0.482
>150	408 (78.5)	373 (91.4)	52	43–61	
Hemoglobin (g/dL)					
≤10.0	302 (57.9)	272 (90.1)	58	46–70	0.046
>10.0	220 (42.1)	207 (94.1)	39	28–50	
CRP (μg/mL)					
≤5.0	13 (2.8)	10 (76.9)	43	0–88	0.180
>5.0	459 (97.2)	424 (92.4)	49	40–58	
AST (IU/L)					
≤80	404 (77.4)	365 (90.3)	54	43–65	0.006
>80	118 (22.6)	114 (96.6)	38	15–61	
ALT (IU/L)					
≤80	452 (86.6)	411 (90.3)	54	44–64	0.018
>80	70 (13.4)	68 (97.1)	37	22–52	
Creatinine (mg/dL)					
≤1.5	413 (83.6)	380 (92.0)	50	40–60	0.651
>1.5	81 (16.4)	74 (91.4)	58	22–94	
Na (mmol/L)					
≤135	321 (63.1)	297 (92.5)	45	33–57	0.144
>135	188 (36.9)	169 (89.9)	57	44–70	
K (mmol/L)					
≤5.0	435 (85.0)	399 (91.7)	49	40–58	0.697
>5.0	77 (15.0)	70 (90.9)	68	40–96	
Ammonia (μg/dL)					
≤80	388 (74.3)	354 (91.2)	56	45–67	0.291
>80	134 (25.7)	125 (93.3)	40	33–47	
Ion Ca (mg/dL)					
≤5.5	320 (80.2)	290 (90.6)	55	43–67	0.467
>5.5	79 (19.8)	73 (92.4)	49	30–68	
PT_INR					
≤1.2	371 (71.1)	335 (90.3)	56	43–69	0.084
>1.2	151 (28.9)	144 (95.4)	41	33–49	
Albumin (g/dL)					
≤3.0	254 (48.7)	240 (94.5)	41	33–49	0.023
>3.0	268 (51.3)	239 (89.1)	60	46–74	

*Values of p by log-rank test of the Kaplan–Meier method.
ALT = alanine transaminase; AST = aspartate transaminase; CI = confidence interval; CRP = C-reactive protein; PT_INR = prothrombin time with an international normalized ratio; WBC = white blood cell.
[a] Numbers may not add up due to missing data.

produced by the liver and may represent liver synthetic function [18]. Serum Alb levels were used widely to identify malnutrition and systemic inflammation response [19]. We noticed that advanced cancer patients are commonly associated with hypoalbuminemia, which is related to cachexia, edema, and organ function decline in clinical practice. The literature demonstrated that mild hypoalbuminemia (Alb < 3.5 g/dL) would increase mortality in patients with advanced cancer [9,20]. Wyld et al. [21] indicated moderate hypoalbuminemia (<3.0 g/dL) to be a poor prognostic factor in patients with advanced breast cancer. Lower serum Alb levels are common in advanced cancer patients, and a previous study indicated that these may lead to higher mortality rates due to malnutrition and inflammation [22]. Our results supported the literature and recommended hypoalbuminemia (<3.0 g/dL) as a practicable prognostic factor of shorter survival in advanced cancer patients.

We found increased PT to be a prognostic factor of a shorter survival time in advanced cancer patients. The prognostic significance of abnormal PT in cancer patients was inconsistent in previous researches, which did not focus on advanced cancer patients [23,24]. Our study demonstrated the probably significant prognostic importance of

Table 3 Median survival time by clinical characteristics of study participants for following 6 months.

	N (%)	Death (%)	Median (d)	95% CI	*p**
Survival time	522	479 (91.8)	49.5	22—117	
Cognitive impairment					
Yes	66 (12.6)	59 (89.4)	49	19—79	0.625
No	456 (87.4)	420 (92.1)	49	40—58	
Fatigue					
Yes	516 (98.9)	474 (91.9)	50	41—59	0.643
No	6 (1.1)	5 (83.3)	34	5—64	
Anorexia					
Yes	422 (80.8)	389 (92.2)	45	35—55	0.037
No	100 (19.2)	90 (90.0)	65	39—91	
Dysphagia					
Yes	158 (30.3)	139 (88.0)	45	27—63	0.440
No	364 (69.7)	340 (93.4)	52	42—62	
Ascites					
Yes	74 (14.2)	69 (93.2)	35	19—51	0.210
No	448 (85.8)	410 (91.5)	54	44—64	
Edema					
Yes	144 (27.6)	129 (89.6)	40	19—61	0.921
No	378 (72.4)	350 (92.6)	52	42—62	
Jaundice					
Yes	56 (10.7)	54 (96.4)	36	21—51	0.057
No	466 (89.3)	425 (91.2)	54	44—64	
Pain					
0—4	393 (75.3)	360 (91.6)	45	35—55	0.670
5—6	53 (10.2)	49 (92.5)	69	45—93	
7—10	76 (14.5)	70 (92.1)	50	29—71	
Sleep disturbance					
Yes	32 (6.1)	27 (84.4)	63	27—99	0.324
No	490 (93.9)	452 (92.2)	49	40—58	
Tumor fungating wound					
Yes	60 (11.5)	56 (93.3)	42	33—51	0.509
No	462 (88.5)	423 (91.6)	54	44—64	

*Values of *p* and 95% CI by log-rank test of the Kaplan—Meier method.
CI = confidence interval.

prolonged PT in advanced cancer patients. Abnormal coagulation function was found commonly in cancer patients due to clinical progression and tumor burden [24,25]. Prolonged PT may be related to liver synthetic dysfunction, bleeding tendency, severe sepsis, and disseminated intravascular coagulation, which are frequently combined with advanced cancer and a shortened survival time. Although the detailed mechanism of abnormal PT in advanced cancer is unclear, our findings recognized the possible relationship between prolonged PT and short survival in advanced cancer patients. Hyperammonemia usually occurs in liver diseases, and hyperammonemia also results from renal disease, gastrointestinal bleeding, and chemotherapy, [26]. Kumar et al. [27] indicated an association between hyperammonemia and poor outcome in liver diseases. We hypothesized a relation between ammonia and prognostication in advanced cancer patients, but it was not significant in our study. Further studies are needed to better understand this aspect.

We suppose that many factors may influence liver function in advanced cancer patients. Potential reasons of liver function impairment in advanced cancer patients may include the direct effect of tumor, liver metastasis, chemotherapeutic drugs, and infection. The combination of liver function impairment and cancer-related complication may aggravate their progression and shorten survival time. In addition, malnutrition in advanced cancer patients has been a common cause of death, which may be related to tumor progression or cancer treatment. Malnutrition may also be associated with inflammation response and therefore may affect liver function greatly. Furthermore, previous studies suggested cytokines as mediators for cancer cachexia [28], and cachexia may result in hypoalbuminemia. Therefore, low Alb levels are thought to be reasonably related to poor prognosis in advanced cancer patients and even accelerate patients' death.

Our findings indicate that anorexia may predict shorter survival in advanced cancer patients. Anorexia is a common symptom in patients with elevated liver enzymes. We suppose that the association between anorexia and impaired liver function may predict poor prognostication. The literature demonstrates that the metabolic activity in the liver would increase in cancer, and it may stimulate the hepatic receptors and lead to suppression of appetite [29].

Table 4 Liver function of advanced cancer patients who died within 2 weeks, using multiple logistic regressions with adjustment for age and sex for each model.

	All patients (n = 522)	Patients without hepatobiliary cancer (n = 436)	Patients without liver metastasis (n = 378)	Patients with hepatobiliary cancer and liver metastasis (n = 28)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
AST > 80 IU/L	2.01 (1.18—3.43)*	1.86 (0.93—3.70)	1.74 (0.91—3.32)	2.60 (1.23—5.47)*
ALT > 80 IU/L	1.89 (1.01—3.54)*	1.83 (0.85—3.96)	2.13 (0.97—4.65)	1.63 (0.71—3.78)
Ammonia > 80 μg/dL	0.84 (0.48—1.49)	0.56 (0.24—1.28)	0.75 (0.37—1.52)	1.16 (0.55—2.44)
Albumin < 3.0 g/dL	1.17 (0.72—1.91)	0.88 (0.50—1.54)	0.98 (0.55—1.74)	2.59 (1.10—6.10) *
PT_INR > 1.2	1.03 (0.61—1.75)	0.75 (0.37—1.51)	1.32 (0.71—2.46)	2.87 (0.88—9.37)

*$p < 0.05$.
ALT = alanine transaminase; AST = aspartate transaminase; CI = confidence interval; OR = odds ratio; PT_INR = prothrombin time with an international normalized ratio.

Table 5 Liver function of advanced cancer patients who died within 6 months, using multiple logistic regressions with adjustment for age and sex for each model.

	All patients(n = 522)	Patients without hepatobiliary cancer (n = 436)	Patients without liver metastasis (n = 378)	Patients with hepatobiliary cancer and liver metastasis (n = 28)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
AST > 80 IU/L	3.67 (1.27–10.66)*	4.66 (1.06–20.49)*	2.74 (0.80–9.33)	5.65 (1.22–26.09)*
ALT > 80 IU/L	3.64 (0.85–15.50)	4.78 (0.63–36.06)	3.94 (0.52–29.83)	5.54 (0.69–44.3)
Ammonia > 80 μg/dL	1.35 (0.63–2.91)	1.37 (0.51–3.67)	1.72 (0.64–4.65)	1.13 (0.39–3.30)
Albumin < 3.0 g/dL	1.98 (1.01–3.88)*	2.37 (1.07–5.22)*	1.70 (0.77–3.77)	2.47 (0.81–7.49)
PT_INR > 1.2	2.20 (0.95–5.06)	3.38 (1.01–11.33)*	1.86 (0.69–5.00)	2.87 (0.88–9.37)

*$p < 0.05$.

Moreover, organ failure may occur in cancer patients with anorexia due to malnutrition, eventually leading to increased mortality [30]._ENREF_28 Thus, our study predicted that anorexia might predict poor survival in advanced cancer patients.

In our study, the number of patients who died within 2 weeks was less than those who died within 6 months. It may result in significant findings due to more analyzed patients and our result was compatible with the above possibility. Our findings may demonstrate an association between liver function tests and prognostication in advanced cancers, but to understand the mechanism or causality further research is needed. In addition, we investigated whether jaundice was related to short survival in advanced cancer patients. Although jaundice did not predict short survival in our study, it was less objective than serum bilirubin levels. Further research may be designed to analyze the association between serum bilirubin levels and survival duration.

In conclusion, liver function tests may be noticeable prognostic factors of survival time in advanced cancer patients, in addition to being useful for patients with hepatobiliary cancer or liver metastasis. Biochemical tests may be more certain and objective. Our study revealed that two times higher AST and ALT levels, prolonged PT, and hypoalbuminemia are likely to be prognostic factors of poor survival in advanced cancer patients. These parameters provide new insights into the prognostication in advanced cancer.

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