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Prognostic significance of pretreatment serum levels of albumin, LDH and total bilirubin in patients with non-metastatic breast cancer

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Abstract

Liver function tests (LFTs) have been reported as independent predictors of non-liver disease-related morbidity and mortality in general population and cancer patients. In this study, we evaluated the relationship between pretreatment serum LFTs and overall survival (OS) in non-metastatic Caucasian breast cancer patients. Seven LFTs, including albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin and total protein, were measured in pretreatment serum from 2425 female Caucasian patients with newly diagnosed, histologically confirmed non-metastatic invasive breast cancer. Multivariate Cox model was used to estimate hazard ratio (HR) and 95% confidence interval (CI) for the association of individual LFTs with 5-year OS while adjusting for age, smoking status, pathological characteristics and treatment regimen. We found that serum albumin, LDH and total bilirubin were significantly associated with 5-year OS in multivariate Cox analyses. Patients with higher albumin level exhibited 45% reduced risk of death (HR = 0.55, 95% CI: 0.40–0.75) compared with those with lower albumin level. Patients with higher total bilirubin level had a nearly 40% reduction in the risk of death (HR = 0.62, 95% CI: 0.45–0.85) and patients with higher LDH levels had a 1.42-fold increased risk of death (HR = 1.42, 95% CI: 1.08–1.88). Furthermore, cumulative analysis showed a significant dose–response trend of significantly increasing risk of death with increasing number of unfavorable LFT levels. Our result highlighted the potential of using pretreatment serum levels of albumin, LDH and total bilirubin as prognostic factors for OS in patients with non-metastatic breast cancer.

Introduction

Breast cancer is the most frequently occurring cancer in women worldwide. The 5-year overall survival (OS) for non-metastatic stage breast cancer patients ranged from 72 to 100%; however, the 5-year survival for stage IV patients was a dismal 22%. Most patients with non-metastatic breast cancer will receive locoregional treatment, i.e. surgery with adjuvant radiotherapy on indication, and adjuvant systemic therapy which may consist of chemotherapy, endocrine therapy, target therapy or a combination of these treatments (1), whereas the primary treatment for metastatic breast cancer is systemic therapy. Modern breast cancer treatment can be tailored to individual tumor characteristics, therefore, being able to predict patients' prognosis will have tremendous clinical benefits by identifying most optional therapeutic options for certain subgroups of patients. Traditional prognostic variables, including tumor size, grade and lymph node status, have been integrated into the tumor, node and metastasis staging system and Nottingham prognostic index (2,3). Recently, several tumor-based molecular markers, such as the expression of estrogen receptor alpha, progesterone receptor and human epidermal growth factor receptor-2, have been strongly associated with OS (4). Furthermore, tumor-based gene expression profiling provided great promise in predicting

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Abbreviations

CI	confidence interval
HR	hazard ratio
LDH	lactate dehydrogenase
LFT	liver function test
OS	overall survival.

breast cancer outcome (5,6). For example, the PAM50 gene signature was approved by the U.S. Food and Drug Administration to assess a patient's risk of distant recurrence in postmenopausal women with node negative (stage I or II) or node positive (stage II), hormone receptor-positive breast cancer. However, the discriminatory accuracy with the addition of PAM50 to the clinical variables was still moderate with a concordance index of 0.78 (7). There is an urgent need to identify additional biomarkers which could improve the prediction of patient's prognosis. Since blood are easily accessible and minimally invasive, the identification of blood-based biomarkers are appealing and pose the great potential to enable accurate prediction of individual's clinical outcome and classify patients into differential prognostic subgroups.

Liver function tests (LFTs), a group of blood tests, usually consist of bilirubin, albumin, total protein, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase and lactate dehydrogenase (LDH). These tests are frequently included as baseline tests for many different clinical presentations and often obtained at initial consultation since they are associated with many aspect of liver function including cellular integrity, functionality and conditions related to biliary tract. There is increasing interest for using LFT variables as independent predictors of non-liver disease-related morbidity and mortality in general population and cancer patients (8,9). A few studies have investigated the associations of LFTs with mortality in breast cancer (10–13). In this study, we collected data from the large breast cancer patient population at the University of Texas MD Anderson Cancer Center and investigated the association of selected pretreatment LFTs with mortality in non-metastatic breast cancer patients. To our knowledge, this is the first study to assess a panel of LFTs in a large non-metastatic breast cancer patient population.

Materials and methods

Patient population and data collection

This study included 2425 female Caucasian patients with newly diagnosed, histologically confirmed, non-metastatic invasive breast cancer (stage I–III). All patients were recruited at the University of Texas MD Anderson Cancer Center. All patients signed an informed consent before taking part in the study. There were no other recruitment restrictions on age, pathological features and treatments. Information on ethnicity, smoking history and family history of breast cancer was assessed by self-administered questionnaires. Clinical and pathological data, treatment regimen and follow-up information were abstracted from medical charts. Albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, LDH and total protein were measured as part of a standard panel of tests evaluating patients' overall condition before treatment at the baseline visit. These tests were performed within 30 days after the diagnosis and before any treatment by the Department of Laboratory Medicine at MD Anderson Cancer Center. The study was approved by the MD Anderson Cancer Center Institutional Review Board.

Statistical analysis

The endpoint of this study was OS, which was defined from the date of diagnosis to the date of death or the latest follow-up. In this study, we presented the results for the 5-year OS. STATA software, version 10 (StataCorp, College Station, TX) was used for statistical analyses. Chi-square test or Fisher's exact test was used to analyze the differences in patients' host characteristics. Patient age was categorized into <50 and ≥50 years of age. Tumor size was categorized into ≤1 cm, <1 cm to ≤2 cm, >2 cm to ≤3 cm, >3 cm to ≤4 cm, >4 cm to ≤5 cm and >5 cm. Axillary lymph node positivity was categorized into 0, 1 or 2, 3 or 4, 5–8, 9–19 and ≥20. Nuclear grade was categorized into grade I, II and III. Smoking status was categorized into never, former and current. Other stratified factors, including first-degree relative breast cancer history, lymph vessels invasion and treatment regimens, were divided into two categories (yes versus no).The LFTs were dichotomized using cut-off points derived from spline modeling procedure which identified the optimal categorization through minimizing the distance between estimated and observed outcome values among subjects in the same category as described in detail by O'Brien (14), since over 90% of marker levels were within normal range. The association of the three significant markers, albumin, LDH and total bilirubin, were non-linear as illustrated by the spline curves shown in Supplementary Figure 1, available at *Carcinogenesis* Online. Multivariate Cox proportional hazards model was used to assess the effect of each LFT variable on 5-year OS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by fitting the multivariate Cox model while adjusting for age, smoking status, pathological features, first-degree relative breast cancer history and treatment regimens. Kaplan–Meier survival analysis and log-rank tests were used to assess the differences in OS by individual LFTs. The cumulative effects of multiple unfavorable LFT levels were evaluated for the three tests that showed statistical significance in the main analysis. For all analyses, a P value of <0.05 was considered statistically significant.

Results

Patient characteristics

This study included 2425 female Caucasian patients with non-metastatic invasive breast cancer. The median age of all patients was 54 years (range: 22–98). There were 1030 patients having stage I tumor (42.47%), 1011 (41.69%) and 384 patients (15.84%) having stage II and III tumor, respectively. A total of 1,281 patients had negative axillary lymph nodes (52.82%), and 644 having lymph vessel invasion (26.56%). Estrogen receptor status included positivity (n = 1872, 77.20%), negativity (n = 538, 22.19%) or unknown (n = 15, 0.62%). About 64.6% (n = 1566) of all patients were positive for progesterone receptor status, 34.64% (n = 840) negative and 0.78% (n = 19) unknown. As for Her2 status, 81.20% (n = 1969) was negative, 14.93% (n = 362) positive and 3.88% (n = 94) unknown. The majority of patients had adjuvant hormone therapy (n = 1709, 70.47%), and 653 had neoadjuvant chemotherapy (26.93%). Totally, 1159 patients (47.79%) received adjuvant chemotherapy (Table 1).

Association of pretreatment LFT with OS

We analyzed the association of the seven routine pretreatment serum LFTs with 5-year OS. Three LFTs including albumin, LDH and total bilirubin were significantly associated with 5-year OS in multivariate Cox analyses, adjusting for age, smoking status, pathological characteristics, first-degree relative breast cancer history and treatment regimens (Table 2, Figure 1). Patient with higher albumin level (>3.9 g/dl) were at 45% reduced risk of death (HR = 0.55, 95% CI: 0.40–0.75, P = 0.0002) compared with those with lower albumin level (≤3.9 g/dl). For bilirubin, patients with total bilirubin level >0.2 mg/dl had better 5-year OS and their risks of death reduced nearly 40% compared with that of patients with total bilirubin level ≤0.2 mg/dl (HR = 0.62, 95% CI: 0.45–0.85, P = 0.003). The albumin and bilirubin remained significant at $P < 0.007$ (= 0.05/7) after the Bonferroni correction for multiple comparisons. Patients with higher LDH levels (>469 U/l) had a 1.42-fold increased risk of death compared with patients with lower LDH levels (≤469 U/l) (HR = 1.42, 95% CI: 1.08–1.88,

Table 1. Host characteristics of breast cancer patients

Variables	Class	Dead *N* (%)	Alive *N* (%)	*P* value[a]
Age, median (range)		54 (22–98)		
Smoking status	Never	124 (8.95%)	1262 (91.05%)	
	Former	51 (6.68%)	712 (93.32%)	
	Current	37 (13.41%)	239 (86.59%)	0.003
First-degree relative breast cancer history	N	190 (9.55%)	1799 (90.45%)	
	Y	22 (5.05%)	414 (94.95%)	0.002
TNM stage	I	37 (3.59%)	993 (96.41%)	
	II	87 (8.61%)	924 (91.39%)	
	III	88 (22.92%)	296 (77.08%)	<0.001
Nuclear grade	I	6 (3.26%)	178 (96.74%)	
	II	50 (4.58%)	1042 (95.42%)	
	III	156 (13.58%)	993 (86.42%)	<0.001
Tumor size	0–1 cm	41 (6.56%)	584 (93.44%)	
	1–2 cm	48 (5.13%)	888 (94.87%)	
	2–3 cm	39 (9.26%)	382 (90.74%)	
	3–4 cm	26 (14.69%)	151 (85.31%)	
	4–5 cm	16 (16.49%)	81 (83.51%)	
	5+ cm	42 (24.85%)	127 (75.15%)	<0.001
Node positivity	0	64 (5.00%)	1217 (95.00%)	
	1 or 2	47 (7.83%)	553 (92.17%)	
	3 or 4	21 (9.59%)	198 (90.41%)	
	5–8	33 (20.89%)	125 (79.11%)	
	9–19	29 (23.02%)	97 (76.98%)	
	≥20	18 (43.90%)	23 (56.10%)	<0.001
Lymph vessels invasion	N	109 (6.12%)	1672 (93.88%)	
	Y	103 (15.99%)	541 (84.01%)	<0.001
Neoadjuvant chemotherapy	N	92 (5.19%)	1680 (94.81%)	
	Y	120 (18.38%)	533 (81.62%)	<0.001
Adjuvant chemotherapy	N	145 (11.45%)	1121 (88.55%)	
	Y	67 (5.78%)	1092 (94.22%)	<0.001
Adjuvant hormone therapy	N	111 (15.50%)	605 (84.50%)	
	Y	101 (5.91%)	1608 (94.09%)	<0.001

TNM, tumor, node and metastasis.
[a]*P* value for the differences in patients' host characteristics between dead and alive.

P = 0.01). In subgroup analysis stratified by stage, we found that albumin levels were associated with OS regardless of stages. LDH appeared to only influence OS in stage II and III patients. The association of bilirubin with OS appeared to the strongest in stage I patients (Table 3). In subgroup analysis stratified by molecular subtypes, we observed similar estimated HRs for albumin and total bilirubin while the estimates for LDH were more evident in HR-positive and human epidermal growth factor receptor-2-enriched subgroups.

Cumulative effects of unfavorable LFT levels

We then conducted a joint analysis to test whether patients with more unfavorable pretreatment LFT levels had worse OS compared with those with fewer unfavorable LFT levels (Table 4, Figure 2) Compared with patient without any unfavorable LFT level, patients with 1, 2 and 3 unfavorable LFT levels exhibited progressively increased risks of death with HRs of 1.39 (95% CI: 1.00–1.94), 2.56 (95% CI: 1.72–3.79), and 3.34 (95% CI: 1.61–6.93), respectively. The 5-year OS rates were 94.11, 91.30, 83.96 and 72.73% for patients with 0, 1, 2 and 3 unfavorable LFT levels, respectively (log-rank *P* < 0.0001).

Discussion

In this study, we demonstrated that pretreatment serum albumin, total bilirubin and LDH levels were associated with 5-year OS in patients with non-metastatic invasive breast cancer, and the results remained significant for albumin, LDH and bilirubin after adjusting for multiple comparisons using the stringent Bonferroni method, whereas alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase or total protein levels were not associated with OS. Furthermore, there was a cumulative effect of those three unfavorable markers (lower albumin level, higher LDH level and lower total bilirubin level) on patients' survival. To illustrate the improvement of the three markers on the prediction of breast cancer survival, we calculated area under the time-dependent receiver operating characteristic curves (AUC) for censored survival data using two models. The clinical model included the traditional prognostic factors (age, nuclear grade, tumor size, number of positive lymph nodes, detection mode, lymphoma or vascular invasion), whereas the clinical + marker model included the three markers in addition to the clinical variables described above. The AUC increased from 0.748 for the clinical model to 0.766 for the clinical + marker model.

Serum albumin is one of the mostly commonly used markers for assessing patients' nutritional status. Albumin is produced by the liver and is the major protein in blood, acting as a key antioxidant, detoxifier and transporter of important nutrients. In advanced cancer patients, the levels of serum albumin fall sharply, because malnutrition and systematic inflammatory response to tumors both suppress albumin synthesis (15). The prevalence of malnutrition among breast cancer patients

Table 2. Association of biomarker levels with 5-year OS

Lab test	Dead (*N*)	Alive (*N*)	Adjusted HR[a] (95% CI)	*P* value
Albumin (g/dl)				
≤3.9	56	363	1 (reference)	
>3.9	156	1850	0.55 (0.40–0.75)	0.0002
ALP (IU/l)				
≤79	108	1296	1 (reference)	
>79	104	913	1.25 (0.95–1.65)	0.11
ALT (IU/l)				
≤19	120	1075	1 (reference)	
>19	92	1138	0.79 (0.59–1.04)	0.09
AST (IU/l)				
≤37	121	1377	1 (reference)	
>37	28	222	1.40 (0.91–2.15)	0.12
LDH (IU/l)				
≤469	100	1319	1 (reference)	
>469	112	894	1.42 (1.08–1.88)	0.01
Total bilirubin (mg/dl)				
≤0.2	51	330	1 (reference)	
>0.2	159	1868	0.62 (0.45–0.85)	0.003
Total protein (g/dl)				
≤6.9	15	180	1 (reference)	
>6.9	118	1152	1.02 (0.57–1.81)	0.96

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Adjusted for age, smoking status, first-degree relative breast cancer history, pathological characteristics and treatment.

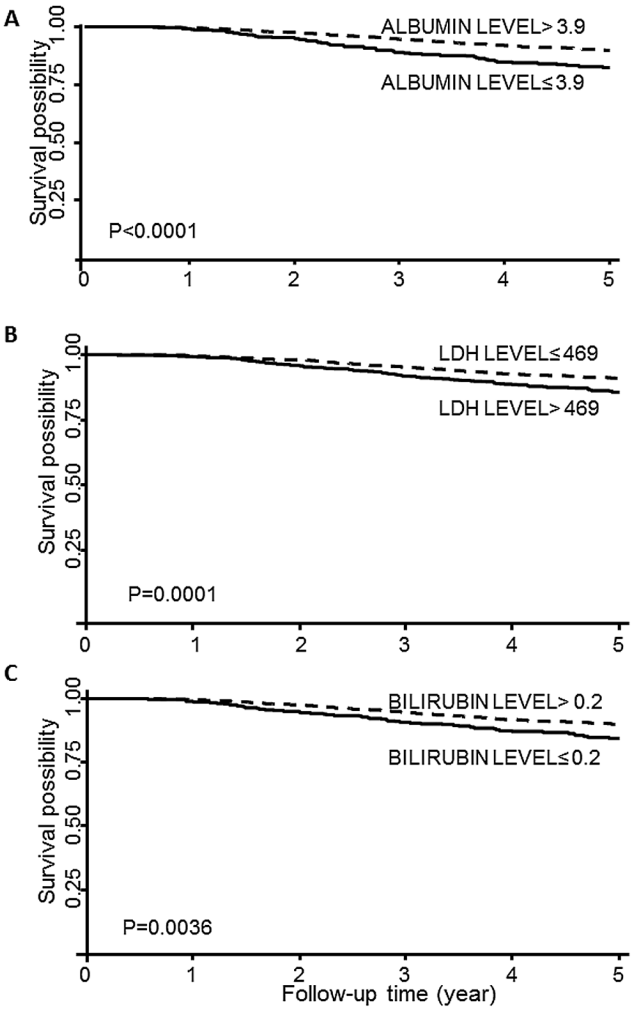

Figure 1. The Kaplan–Meier curves showing 5-year OS among breast cancer patients according to pretreatment albumin levels (**A**), LDH levels (**B**) and total bilirubin levels (**C**).

reported by two French studies was 20.5% (16) and 18.3% (17), respectively. A Korean study also showed over 51% of female breast cancer patients had moderate to high risk of malnutrition (18). Malnutrition can cause many clinical consequences, including decreased life quality, reduced treatment response and increased treatment-related toxicity. Serum albumin has been used to assess severity of disease, disease progression and prognosis. Numerous studies have evaluated the association of serum albumin levels with the survival of cancer patients and the results are fairly consistent: lower serum albumin levels are an independent indicator of worse survival of various cancers (8). Several studies with relatively small sample sizes have consistently reported the prognostic value of serum albumin in breast cancer patients. Heys *et al.* (12) reported that pretreatment serum albumin, lymph node involvement and advanced stage were independent prognostic factors of worse survival using 77 large and locally advanced breast cancer patients treated with neoadjuvant chemotherapy. In another study of 180 consecutively treated breast cancer patients, Lis *et al.* (13) found that normal levels of baseline serum albumin levels reduced the risk of death by 72% compared with low levels. Only tumor stage had a larger impact on survival than serum albumin levels. In the third study of 145 patients with hepatic metastases from breast cancer, Wyld *et al.* (11) identified low albumin, advanced age and estrogen receptor negativity as independent predictors of poor survival. To our knowledge, this current study is the largest study to evaluate pretreatment serum albumin levels in breast cancer patients and is the only study that has sufficient sample size to exclusively focus on early stage patients. Our results are consistent with previous finding for other cancer sites (19–22) and provide the strongest evidence that lower serum albumin level was a prognostic factor for poor survival in early stage breast cancer patients regardless of stages.

LDH is a key enzyme in the conversion of pyruvate to lactate during anaerobic conditions. LDH is associated with metabolic activities, inflammation, tissue injury and neoplasms. Hypoxia in tumor microenvironment leads to high LDH levels. Many studies have shown that LDH level could be used to estimate tumor bulk and activity and predict treatment response and prognosis. High serum LDH levels have been reported to be a prognostic marker for poor survival in several different cancer types (23–27). Few studies with relatively small sample sizes and focusing on metastatic breast cancer patients have assessed the prognostic role of serum LDH level. Yamamoto *et al.* (28) found that an elevation of serum LDH significantly contributed to poorer survival among metastatic breast cancer patients in Japan. A recent study reported that serum LDH level correlate strongly with survival in patients with bone metastasis from breast cancer (10). Our study showed that higher levels of LDH predicted worse 5-year OS in non-metastatic breast cancer patients which was consistent with previous reports. Furthermore, it appeared that the prognostic effect of LDH was only evident in stage II and III patients, but not in stage I patients. It is likely that higher LDH levels indicate high tumor activities and occult metastasis, which may not be evident in stage I tumors. It is also possible that stage I breast cancer patients had excellent survival, and the 5-year follow-up is not long enough to see the OS difference in stage I patients.

Table 3. Association of biomarker levels with 5-year OS stratified by stage and molecular subtypes

	Stage I			Stage II			Stage III		
Lab test	Dead (*N*)	Alive (*N*)	HR[a] (95% CI)	Dead (*N*)	Alive (*N*)	HR[a] (95% CI)	Dead (*N*)	Alive (*N*)	HR[a] (95% CI)
Albumin (g/dl)									
≤3.9	8	153		26	167		22	43	
>3.9	29	840	0.62 (0.28–1.38)	61	757	0.60 (0.37–0.96)	66	253	0.46 (0.27–0.80)
LDH (IU/l)									
≤469	22	597		39	547		39	175	
>469	15	396	0.98 (0.50–1.92)	48	377	1.44 (0.91–2.26)	49	121	1.59 (1.02–2.50)
Total bilirubin (mg/dl)									
≤0.2	12	113		19	171		20	46	
>0.2	25	871	0.25 (0.12–0.51)	67	749	1.02 (0.60–1.74)	67	248	0.51 (0.30–0.88)
	HR positive			HER2 enriched			Triple negative		
Lab test	Dead (*N*)	Alive (*N*)	HR[a] (95% CI)	Dead (*N*)	Alive (*N*)	HR[a] (95% CI)	Dead (*N*)	Alive (*N*)	HR[a] (95% CI)
Albumin (g/dl)									
≤3.9	28	242		11	61		16	44	
>3.9	78	1280	0.54 (0.34–0.86)	26	264	0.58 (0.27–1.29)	51	228	0.68 (0.35–1.33)
LDH (IU/l)									
≤469	50	930		16	188		33	151	
>469	56	592	1.66 (1.11–2.47)	21	137	2.00 (0.97–4.11)	34	121	0.89 (0.51–1.54)
Total bilirubin (mg/dl)									
≤0.2	25	228		7	58		19	37	
>0.2	79	1282	0.65 (0.41–1.03)	30	265	0.84 (0.32–2.22)	48	234	0.51 (0.28–0.93)

HR positive: ER+ or PR+, HER2–; HER2 enriched: HER2+, regardless of ER and PR; Triple negative:
ER–, PR–, HER2–. ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor.
[a]Adjusted for age, smoking status, first-degree relative breast cancer history, pathological characteristics and treatment.

Table 4. Cumulative effect of unfavorable LFT levels associated with 5-year OS

Number of adverse tests	Dead (*N*)	Alive (*N*)	Adjusted HR[a] (95% CI)	*P*
0	57	910	1 (reference)	
1	97	1018	1.39 (1.00–1.94)	0.0535
2	47	246	2.56 (1.72–3.79)	<0.0001
3	9	24	3.34 (1.61–6.93)	0.0012

[a]Adjusted for age, smoking status, first-degree relative breast cancer history, pathological characteristics and treatment.

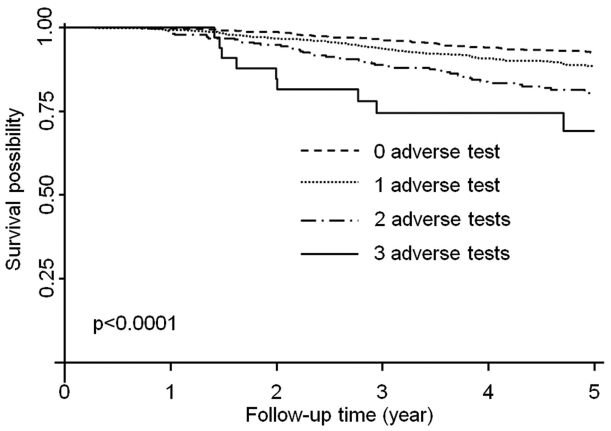

Figure 2. Kaplan–Meier cumulative survival plots for 5-year OS according to unfavorable marker score.

Oxidative stress contributes to carcinogenesis. Bilirubin is a potent antioxidant and has been shown to protect against cancer development. Lower serum bilirubin level has been linked to increased risk of cardiovascular diseases and cancer (29,30). The relationship of serum bilirubin level with survival has been evaluated in metastatic breast cancer patients (11,31), and the results showed that hyperbilirubinemia was associated with worse survival. However, our study revealed that non-metastatic breast cancer patients with higher total bilirubin levels had better OS compared with those with lower bilirubin levels. This discrepancy may be due to the differences in patient population. The above two mentioned studies focused on heavily pretreated advanced breast cancer patients or breast cancer patients with liver metastasis. Therefore, serum bilirubin level may have different predictive effect in metastatic and non-metastatic breast cancer patients.

Serum biomarkers are promising clinical prognostic factors in cancer patients. However, single biomarker may not have sufficient predictive power for clinical application. The combination of multiple biomarkers through the cumulative analysis can improve the predictive power (19,32), as evidenced by previous attempts of calculating prognostic scores (33). In our study, we found the patients with the most unfavorable LFT levels had worst 5-year OS (5-year OS rates for patients without unfavorable LFT versus patients with three unfavorable LFTs: 94.11 versus 72.73%), supporting the potential of combining multiple prognostic factors.

The major strength of this study is the large sample size of non-metastatic breast cancer patients who received treatment at a single institution. The follow-up time was relatively long. Our study provides strong evidence supporting that pretreatment serum levels of albumin, LDH and bilirubin are prognostic factors for OS in non-metastatic breast cancer. These results

suggest that evaluation of these three biomarkers may be useful for predicting prognosis in non-metastatic breast cancer. This study has a couple of limitations. Our study focused on Caucasian patients; therefore, additional studies are needed before it can be generalized to other ethnic groups. In addition, validation of our findings in an independent population is warranted.

In conclusion, our study was based on the large patient cohort of 2425 non-metastatic breast cancer patients. These results suggest that evaluation of serum albumin, bilirubin and LDH may be useful for predicting prognosis in non-metastatic breast cancer.

Supplementary material

Supplementary Figure 1 can be found at http://carcin.oxfordjournals.org/

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