OPEN

Long-Term Survival of Patients With Cancer, Sepsis, and Vasopressor Requirements Based on Lactate Levels

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ABSTRACT: A prospective cohort study was conducted to evaluate the 1-year survival of cancer patients with sepsis and vasopressor requirements. Eligible patients were admitted a Comprehensive Cancer Center's ICU and were compared based on their admission lactate levels. Of the 132 included patients, 87 (66%) had high lactate (HL; > 2.0 mmol/L), and 45 (34%) had normal lactate (NL; ≤ 2.0 mmol/L). The 1-year survival rates of the two groups were similar (HL 16% vs. NL 18%; $p = 0.0921$). After adjustment for ICU baseline characteristics, HL was not significantly associated with a 1-year survival (Hazards ratio, 1.39; 95% CI, 0.94–2.05). Critically ill cancer patients with sepsis and vasopressor requirements, regardless of the lactate level, had 1-year survival of less than 20%. Large multicenter cancer registries would enable to confirm our findings and better understand the long-term trajectories of sepsis in this vulnerable population.

KEYWORDS: cancer; hematological; malignancies; lactate; sepsis; septic shock; solid tumors;

Sepsis is among the main causes of admission to the ICU in patients with cancer (1). The Third International Sepsis Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) incorporated a serum lactate level of greater than 2 mmol/L into the diagnostic criteria for septic shock (2). Although high lactate (HL) levels have been associated with increased mortality rates in patients with and without cancer, few studies have directly assessed the long-term survival of cancer patients fulfilling the Sepsis-3 criteria for septic shock (3–6). Our two retrospective cohorts of patients with cancer and septic shock showed a significantly higher short-term mortality rate between patients that fulfilled the Sepsis-3 criteria and those that did not (4, 5). However, both studies focused on short-term risk factors for mortality rather than the long-term survival. Therefore, we designed this prospective study to assess the 1-year survival of cancer patients with sepsis and vasopressor requirements based on their lactate level.

METHODS

We conducted an institutional review board-approved (RCR05-0982) prospective cohort study at The University of Texas MD Anderson Cancer Center from November 2019 to February 2020. Eligible patients were adults (≥ 18 yr old) with an oncologic disease who were admitted to the medical ICU with sepsis and hypotension and required vasopressor support within the first 12 hours of admission. Patients who developed sepsis after ICU admission were excluded.

Baseline demographics, body mass index, comorbidities, cancer diagnosis, Charlson Comorbidity Index, admission Sequential Organ Failure Assessment

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KEY POINTS

Question: Is there a long-term survival difference between cancer patients with sepsis and vasopressor requirements based on their lactate level?

Findings: In our prospective cohort of critically ill cancer patients with sepsis and shock, there was no significant difference in the 1-year survival between patients with lactate greater than 2 mmol/L (16.3%) and those with lactate less than or equal to 2 mmol/L (18.4%). After adjusting for confounders, high lactate remained not associated with 1-year survival.

Meaning: Lactate alone was not effective to determine long-term survival differences of critically ill cancer patients with sepsis and vasopressor requirements.

(SOFA) score, organ support, length of stay, short-term (ICU and 28-d) mortality rates, and 1-year survival rate were collected. Patients were classified into two groups based on their clinical phenotypes, sepsis, vasopressor requirements, and HL level (> 2 mmol/L) and those with sepsis, vasopressor requirements, and normal lactate (NL) level (≤ 2 mmol/L). The primary outcome was 1-year survival.

Data are presented as median (interquartile range [IQR]) and number (percentage) as appropriate. Differences between the groups were calculated with chi-square and Mann-Whitney *U* tests. Survival distributions were assessed with Kaplan-Meier plots, and differences between groups were assessed with the log-rank test. A Cox Proportional Hazards regression model was developed to identify the association between HL and 1-year mortality. *p* values of less than 0.05 were considered statistically significant.

RESULTS

A total of 132 patients were included. Of them, 87 (65.9%) had HL, and 45 (34.1%) had NL. Sixty-six patients (50%) had hematological tumors, 66 (50%) had solid tumors, and most patients had active malignancy (72.6%). The median SOFA scores at ICU admission were similar in both groups (12 [IQR, 8–15] vs. 10 [IQR, 8–12.5]; $p = 0.071$). Additional clinical characteristics are displayed in the **Table 1**.

Regarding organ support during the ICU stay, the need for invasive mechanical ventilation (50.6% vs. 51.1%; $p = 0.953$) and continuous renal replacement therapy (32.2% vs. 28.9%; $p = 0.698$) were not significantly different between the HL and the NL patients, respectively. The median number of vasopressors was higher for the HL patients (2 [IQR, 1–3] vs. 1 [IQR, 1–2]; $p = 0.002$). The short-term mortality rates were higher for the HL group than for the NL group; ICU mortality rates were 51.7% vs. 26.7% ($p = 0.006$); and 28-day mortality was 69% vs. 44.4% ($p = 0.006$).

Overall, the 1-year survival rate was 16.7%. There were no differences in survival between the overall HL and NL groups (16.3% vs. 18.4%, respectively; $p = 0.0921$; **Fig. 1*A***), and within the hematological tumors (21.4% vs. 19.2%; $p = 0.551$; **Fig. 1*B***) and solid tumors subgroups (11.8% vs. 17.4%; $p = 0.125$; **Fig. 1*C***). After adjusting for baseline characteristics, HL (HR, 1.39; 95% CI, 0.94–2.05) was not associated with lower survival in the Cox proportional hazards regression (**Table 2**).

DISCUSSION

In this prospective cohort of critically ill cancer patients with sepsis and vasopressor requirements the 1-year survival was 17.7%. The 1-year survival rates were similar between the HL (patients that met Sepsis-3 criteria for septic shock) and NL groups for the whole cohort and the hematological and solid tumor subgroups. Even after adjustment of baseline characteristics, there was no association between HL and 1-year survival.

Sepsis and septic shock survivors suffer cognitive and functional impairment and increased long-term mortality, even years after their sepsis-related admission (7–9). Buchman et al (7) reported that among Medicare beneficiaries from 2012 to 2017, the 1-year mortality of patients with sepsis was 66%, compared with 26% for patients with nonsepsis-related admissions. Furthermore, Courtright et al (8) evaluated the factors independently associated with 1-year mortality in sepsis survivors discharged to home healthcare. Among the highest risk factors for poor survival were cancer (odds ratio [OR], 3.66; 95% CI, 3.50–3.83), severe sepsis (OR, 1.30; 95% CI, 1.23–1.37), and septic shock (OR, 1.14; 95% CI, 1.05–1.24). Interestingly, within their cancer subgroup, septic shock was no longer associated with 1-year mortality (OR, 1.16; 95%

TABLE 1.
Clinical Characteristics and Outcomes by Lactate Level

Variable	Overall, *n* = 132	High Lactate, *n* = 87 (65.9%)	Normal Lactate, *n* = 45 (34.1%)	*p*
Age, median (IQR), yr	64 (52.25–69.75)	62 (50–71)	65 (54–69.5)	0.652
Male, *n* (%)	84 (63.6)	58 (66.7)	26 (57.8)	0.314
Body mass index, median (IQR), kg/m^2	26 (21.25–32.75)	27 (22–32)	25 (21–33.5)	0.600
Race, *n* (%)				
White	89 (67.4)	62 (71.3)	27 (60)	0.207
Black	17 (12.9)	8 (9.2)	9 (20)	
Asian	9 (6.8)	7 (8)	2 (4.4)	
Other	17 (12.9)	10 (11.5)	7 (15.6)	
Ethnicity, *n* (%)				
Hispanic	24 (18.2)	15 (17.2)	9 (20)	0.404
Non-Hispanic	108 (81.8)	72 (82.8)	36 (80)	
Charlson Comorbidity Index, median (IQR)				
Index	6 (4–9)	6 (4–9)	6 (5–8.5)	0.757
Estimated 10-yr survival rate	2 (0–53)	2 (0–53)	2 (0–21)	0.5
Hematological tumor, *n* (%)	66 (50)	40 (46)	26 (57.8)	0.199
Solid tumor, *n* (%)	66 (50)	47 (54)	19 (42.2)	0.199
Metastatic disease, *n* (%)	53 (80.3)	38 (80.9)	15 (78.9)	0.860
Cancer status, *n* (%)				
Active	96 (72.7)	62 (71.3)	34 (75.6)	0.861
Remission	6 (4.5)	4 (4.6)	2 (4.4)	
Relapse	30 (22.7)	21 (24.1)	9 (20)	
Lactate, median (IQR), mmol/L	2.55 (1.73–4.4)	3.5 (2.6–5.7)	1.6 (1.1–1.85)	< 0.001
Neutropenia[a], *n* (%)	39 (29.5)	26 (29.9)	13 (28.9)	0.873
Thrombocytopenia[b], *n* (%)	44 (33.3)	30 (34.5)	14 (31.1)	0.697
Sequential Organ Failure Assessment score, median (IQR)	11 (8–14)	12 (8–15)	10 (8–12.5)	0.071
Organ support				
Number of vasopressors, median (IQR)	1 (1–2)	2 (1–3)	1 (1–2)	0.002
Invasive mechanical ventilation, *n* (%)	67 (50.8)	44 (50.6)	23 (51.1)	0.953
Continuous renal replacement therapy, *n* (%)	41 (31.1)	28 (32.2)	13 (28.9)	0.698
Hospital LOS, median (IQR), d	13 (7–25.5)	12 (6–20)	14 (8–35.5)	0.125
ICU LOS, median (IQR), d	4 (2–7)	4 (2–7)	4 (2–8)	0.710
ICU mortality, *n* (%)	57 (43.2)	45 (51.7)	12 (26.7)	0.006
28-d mortality, *n* (%)	80 (60.6)	60 (69)	20 (44.4)	0.006

IQR = interquartile range, LOS = length of stay.
[a]Neutropenia: absolute neutrophil count < 500/μL.
[b]Thrombocytopenia: platelet count < 25,000/μL.

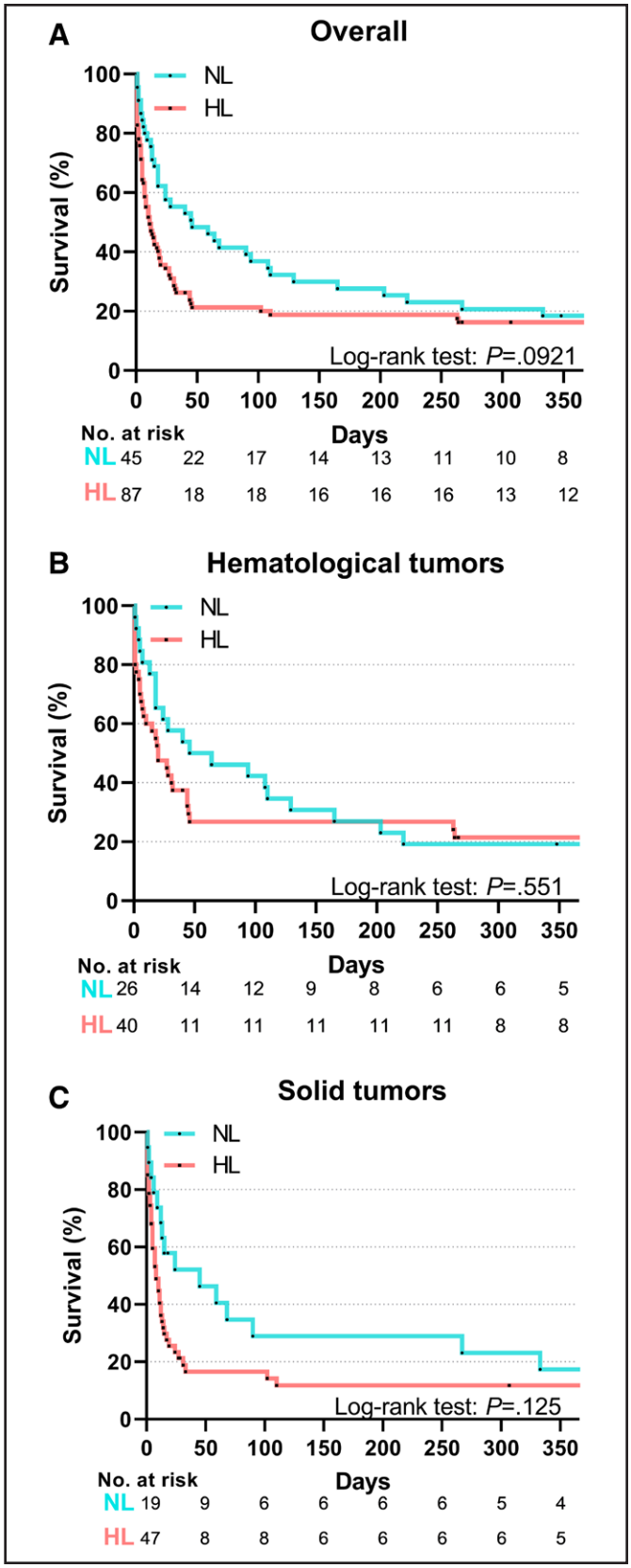

Figure 1. One-yr survival analysis comparing patients with high lactate (HL) and normal lactate (NL) levels. **A**, Complete cohort. **B**, Patients with hematological malignancies. **C**, Patients with solid tumors. Differences between the curves were assessed with the log-rank test.

CI, 0.96–1.40) (8). The latter parallels our 1-year survival findings. This observation suggests that the baseline oncologic disease burden surpasses the post-septic biological derangements. Whether similar physiologic, metabolic, and immunologic pathways interject between these two conditions is still to be determined and warrants further investigation (10).

Comparable to our findings, a South Korean epidemiological study reported a 1-year survival of 18.7% in cancer patients with septic shock. Of note, their definition of septic shock lacked serum lactate, mixing the two clinical phenotypes (11). Despite the lack of association seen in the present study between lactate and 1-year survival, lactate has been associated with long-term survival in the general sepsis population. In a noncancer cohort of septic patients admitted to a U.S. Veterans Affairs Hospital, increasing serum lactate was associated with increased odds for 1-year mortality (OR, 1.3; 95% CI, 1.1–1.6) (12).

Two-thirds (64.7%) of the Sepsis-3 task force agreed that lactate is a marker of cellular dysfunction (2). Lactate production and clearance, however, can be affected by acute and chronic concomitant processes such as liver and mitochondrial dysfunction, tissue hypoxia, adrenergic-induced aerobic glycolysis, and even cancer metabolism, as described by Warburg (13). This myriad of pathophysiological frameworks might explain why lactate is not a widely accepted target for resuscitation (13).

Regardless of its strengths, this study has the limitations associated with its observational design. The relatively small cohort and subgroup sizes could opaque relevant clinical differences. Larger cancer registries that include patients with septic shock defined using Sepsis-3 criteria are needed and could help elucidate the impact of sepsis in their long-term survival; however, such research endeavors can be challenging, especially in critically ill patients (14).

CONCLUSIONS

Regardless of their lactate level, critically ill cancer patients with sepsis and vasopressor requirements displayed a 1-year survival of less than 20%. Large multicenter cancer registries that include patients with sepsis and septic shock would enable a better understanding of the trajectories in this vulnerable population.

TABLE 2.
Summary of Cox Proportional Hazards Regression

	Univariable Analysis		Multivariable Analysis	
Characteristics	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Malignancy				
Hematologic	Reference			
Solid	1.45 (1–2.1)	0.052		
Cancer status				
Remission	Reference			
Active	2.93 (0.92–9.32)	0.069		
Relapse	2.92 (0.88–9.75)	0.081		
Metastasis				
No	Reference			
Yes	4.21 (1.86–9.51)	0.001		
Lactate (Sepsis-3)				
Normal lactate	Reference			
High lactate	1.39 (0.94–2.05)	0.1		
Invasive mechanical ventilation				
No	Reference			
Yes	1.79 (1.23–2.62)	0.003		
Severe neutropenia[a]				
No	Reference			
Yes	1.12 (0.75–1.68)	0.568		
Severe thrombocytopenia[b]				
No	Reference		Reference	
Yes	1.55 (1.05–2.28)	0.026	2.86 (1.54–5.33)	0.001
Charlson Comorbidity Index				
1 U increase	1.12 (1.05–1.19)	0.001	1.20 (1.04–1.38)	0.014
Lactate				
1 U increase	1.09 (1.04–1.15)	0.001	1.09 (1.01–1.17)	0.032
Sequential Organ Failure Assessment score				
1 U increase	1.11 (1.05–1.16)	< 0.001	1.10 (1.02–1.20)	0.021

HR = hazard ratio.
[a]Severe neutropenia: absolute neutrophil count < 500/μL.
[b]Thrombocytopenia: platelet count < 25,000/μL.

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