Clinical Prognostic Factors During the Last One Month of Life in Terminally Ill Cancer Patients: A Retrospective Observational Study

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ABSTRACT

Objective: To explore the trajectory of clinical symptoms and biomarkers in the last four weeks of life in terminally ill cancer patients.
Study Design: Observational study.
Place and Duration of Study: Department of Oncology, Shijingshan hospital, Shijingshan Teaching Hospital of Capital Medical University, Beijing, China, between January 2017 and January 2020.
Methodology: This study evaluated 173 terminally ill cancer patients. Seventeen symptoms and fifteen biomarkers were identified. For sequential analysis, the authors divided the final four weeks of life into four time periods from the date of death. Ordinal multiple logistic regression analysis was used to explore the association between the changes in clinical parameters and the risk of death in a given period. Changes in clinical parameters across different time periods were evaluated using the Wilcoxon signed rank test.
Results: Abnormal consciousness; elevated ECOG (Eastern Cooperative Oncology Group) scores, neutrophil-to-lymphocyte ratio (NLR), blood urea nitrogen (BUN) to creatinine ratio, C-reactive protein (CRP)-to-albumin ratio; and decreased platelet (PLT) counts were independent factors ($p < 0.05$) for predicting closer death in the final month of life. All parameters above showed significant changes over time in the last month, although the starting time points for these changes varied.
Conclusion: Abnormal consciousness, elevated ECOG scores, NLR, BUN-to-creatinine ratio, CRP-to-albumin ratio, and decreased PLT counts are potentially useful markers for approaching death in terminally ill cancer patients. These findings are valuable for understanding the biology of death in terminally ill cancer patients. And to some extent, they may help clinicians recognise that a patient will die in the near future.

Key Words: Cancer, Ordinal regression analysis, Death, Terminal illness, Biomarkers.

INTRODUCTION

Predicting the duration of remaining life in terminally ill patients with cancer is of utmost importance as it may help avoid harmful and uncomfortable therapy and provide optimal end-of-life care for terminally ill patients. Given the unpredictable nature of the disease trajectory, it is often difficult for clinicians to predict the survival of terminally ill cancer patients. Several prognostic parameters have been validated to predict survival in terminally ill cancer patients.[1-4] Although objectively measurable clinical parameters are valuable sources of information, symptoms and signs may also be valuable.[5,6]

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In previous studies, survival time was evaluated from the day of hospitalisation to the day of death. These studies evaluated factors for the prediction of survival in terminally ill cancer patients within three days,[6] one week,[7] or two weeks.[2,8] However, only a few studies have explored the factors that predict survival within a month.[9] Moreover, clinical parameters and blood biomarkers were collected only once on the day of admission. The terminal stage of the disease is a continuous process, however, there have been few studies that have evaluated dynamic data in the final few weeks of terminally ill patients.[3,10]

Little is known about the changes in clinical symptoms, signs, and blood biomarkers in the last month before death. As such, this study aimed to explore the trajectory of clinical symptoms, signs, and biomarkers in the last four weeks of life in terminally ill cancer patients.

METHODOLOGY

This retrospective study was performed in the Oncology department at Shijingshan hospital, Shijingshan Teaching Hospital of Capital Medical University, Beijing, China. Patients with termi-

nally ill cancer who died in the Medical Oncology ward between January 2017 and January 2020 were enrolled consecutively. The inclusion criteria were: histologically confirmed solid tumour malignancies, age ≥18 years, absence of active anti cancer therapy in the last month of life owing to poor performance status or treatment-refractory disease, and availability of blood biomarkers and clinical signs or symptoms at four different time periods before death. The exclusion criteria were anti cancer therapy in the last month of life and death within 28 days after admission. This study was approved by the Ethics Committee of the Beijing Shijingshan Hospital. The requirement for patient informed consent was waived owing to the retrospective nature of the study. All data were anonymised before analysis.

Demographic data (age and gender) and clinical information were collected from our institutional electronic database. For sequential analysis, we divided the patients' final 4 weeks into four time periods from the date of death as T1= 0–7 days, T2= 8–14 days, T3= 15–21 days, and T4= 22–28 days. The symptoms or signs and blood test data for each period were then extracted. If a patient had more than one blood test result based on the same biomarker in one time period, the one measured approximately once per week was selected.

Seventeen symptoms and signs were identified, including three emotional and mental symptoms (anorexia, insomnia, consciousness), three physical functioning (the Eastern Cooperative Oncology Group (ECOG) performance status score, muscle, fatigue), four symptoms and signs related to nutrition (oral intake, oedema, pleural effusion and ascites), four gastrointestinal symptoms (jaundice, nausea and vomiting, diarrhoea, constipation), and other three symptoms and signs (temperature, pain, thrombus). Fifteen laboratory biomarkers were evaluated, including white blood cell (WBC count, reference range= male, 4-10×10^9/L; female, 3.5-9.5×10^9/L), platelet count (125–350×10^9/L), haemoglobin (male, 130–175 g/L; female, 115–150 g/L), serum glucose (700–1100 mg/L), albumin (40–55 g/L), BUN (81.2–200 mg/L), creatinine (2.5–12.0 mg/L), alanine aminotransferase (7–40 U/L), aspartate aminotransferase (15–40 U/L), and C-reactive protein (CRP, ≤3 mg/L).

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), blood urea nitrogen (BUN) to creatinine ratio, and CRP-to-albumin ratio were calculated. The cutoff values for WBC, BUN, creatinine, alanine aminotransferase and aspartate aminotransferase were based on the upper limit of the reference range. The median values of NLR and BUN-to-creatinine ratio were set as the cut-offs. The cutoff values of albumin, PLT, CRP, PLR, LMR, and CRP-to-albumin ratio were also set based on previous studies.[2,9,11-13]

In total, 32 variables were analysed; among them, 30 variables were selected based on previous studies,[2,3,7,9] and two more variables (LMR and BUN-to-creatinine ratio) were added.

Kolmogorov-Smirnov test was used to detect the normality of data. Non-normally distributed continuous data were expressed as medians with interquartile ranges, while categorical variables were presented as counts and percentages. Ordinal multiple

logistic regression analysis was used to explore the association between changes in clinical parameters and the risk of death in a given period. Factors that were statistically significant at the p<0.05 level in the univariate analysis was entered into multivariate analysis. Changes in clinical signs and biomarkers across different time periods were evaluated using the Wilcoxon signed rank test. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Beijing, China). A p-value of <0.05 was considered significant.

RESULTS

Five hundred and fifty-two cancer patients were identified from the institution's electronic database who had died in the Medical Oncology ward during the study period. Data of 198 patients were excluded because they had died within four weeks after admission. Sixteen patients who had received anti cancer therapy in the last one month of life and 165 patients who had incomplete blood count results, clinical symptoms and signs, were also excluded. A total of 173 eligible patients were included in the final analysis.

The study population included 96 (55.5%) men and 77 (44.5%) women. The median patient age was 71 years (range, 20–92), and 122 (70.5%) patients were aged ≥65 years. In total, 98 (56.6%) patients had distant metastases at the time of the initial diagnosis, and 75 (43.4%) patients had recurrent disease. The most common primary tumour sites were the gastrointestinal tract (n=50, 29%) and the lungs (n=39, 22.5%). The most common metastatic sites were the liver (n=74, 42.8%) and lung (n=44, 25.4%). In total, 116 (67.1%) patients had one or two metastatic organs, and 36 (20.8%) patients had no less than three metastatic organs. With respect to the history of cancer treatment, 57 (32.9%) patients had surgery, 28(16.2%) patients received radiotherapy, and 64 (37%) patients had chemotherapy. 3 (19.7%) patients received two kinds of anti cancer therapy, and 10(5.8%) patients had three kinds of anti cancer therapy. Hypertension (n=100, 57.8%) and Coronary heart disease (n=48, 27.7%) were the most common comorbidity.

Table I shows the results of univariate and multivariate analysis of parameters. In the univariate analysis, 16 parameters were statistically significant (p<0.05) and were entered into multivariate analysis. Finally, Six factors, namely, abnormal consciousness; increased ECOG performance status scores, NLR, BUN-to-creatinine ratio, CRP-to-albumin ratio; and decreased PLT were independent factors (p<0.05) for predicting closer mortality in the final month of life.

Table II depicts longitudinal changes in six identified factors during the final month of life. All of the above six parameters showed significant changes over time in the last month of life, although the starting time points for these changes varied. Consciousness disorders and worse performance status happened when approaching death. The NLR, BUN-to-creatinine ratio, and CRP-to-albumin ratio increased as death approached, whereas PLT values decreased.

Table I: Univariate and multivariate analysis of symptoms, signs and biomarkers.

Variables	HR[a](95%CI)	p[a]	HR[b](95%CI)	p[b]
ECOG score				
0-3	1		1	
4	7.93(5.18-12.15)	<0.001	4.63(2.90-7.39)	<0.001
Temperature				
≤38℃	1			
>38℃	1.89(1.30-2.76)	0.001		
Consciousness				
Normal				
Abnormal	5.194(3.813-7.075)	<0.001	3.19(2.29-4.45)	<0.001
Oral take				
Normal	1			
Reduced	2.29(1.30-4.03)	0.004		
Minimal to sips or mouth care only	5.25(2.93-9.39)	<0.001		
Oedema				
No	1			
Yes	1.63(1.23-2.16)	0.001		
WBC				
≤10x10^9/L	1			
>10x10^9/L	2.12(1.62-2.78)	<0.001		
NLR				
≤9.55	1			
>9.55	2.43(1.85-3.20)	<0.001	1.71(1.20-2.44)	0.003
PLR				
≤100	1			
100-300	0.49(0.35-0.68)	<0.001		
≥300	0.57(0.39-0.85)	0.006		
LMR				
≥4	1			
<4	0.62(0.41-0.92)	0.019		
Platelet				
≥100×10^9/L	1			
<100×10^9/L	3.00(2.16-4.17)	<0.001	2.09(1.36-3.23)	0.001
BUN				
≤200mg/L	1			
>200mg/L	2.82(2.14-3.71)	<0.001		
Creatinine				
≤12.0mg/L	1			
>12.0mg/L	2.25(1.95-3.87)	<0.001		
Albumin[c]				
≥30g/L	1			
<30g/L	1.86(1.41-2.44)	<0.001		
CRP				
≤10mg/L	1			
10-50mg/L	1.63(0.93-2.87)	0.091		
50-100mg/L	2.72(1.53-4.85)	0.001		
>100mg/L	4.24(2.43-7.38)	<0.001		
CRP-to-albumin ratio[c]				
≤4.85x10^{-3}	1			
>4.85x10^{-3}	2.75(2.01-3.78)	<0.001	1.69(1.10-2.61)	0.018
BUN-to-creatinine ratio				
≤27.23	1			
>27.23	2.25(1.72-2.96)	<0.001	1.47(1.05-2.06)	0.024

HR, hazard ratio; 95% CI means 95% confidence interval for HR; [a]Univariate analysis; [b]Multivariate analysis; [c]Missing data, 3 for albumin and CRP to albumin ratio respectively.

Table II: Longitudinal changes in six identified factors during the final month of life.

Variables	Time period from death						
	T4	p	T3	p	T2	p	T1
ECOG	1(1,2)	<0.001	4(3,4)	<0.001	4(4,4)	<0.001	4(4,4)
Consciousness (2:normal, 1:abnormal)	2(2,2)	0.248	2(2,2)	<0.001	2(1,2)	<0.001	1(1,2)
Platelet	198.00(142.50,279.50)	0.001	189.00(118.50,243.50)	<0.001	153.00(98.00,224.50)	<0.001	127.00(68.50,194.00)
CRP-to-albumin ratio	1.88(0.74,3.83)	0.386	2.38(1.44,4.00)	0.010	2.98(1.44,4.74)	<0.001	4.37(2.37,6.48)
NLR	7.00(4.63,10.55)	0.006	8.63(5.38,13.81)	0.001	9.79(6.21,16.33)	<0.001	14.47(8.28,23.10)
BUN-to-creatinine ratio	22.28(17.33,32.18)	0.001	27.23(19.80,37.13)	0.002	29.70(19.80,42.08	<0.001	34.65(23.51,50.74)

T1: 0-7 days, T2: 8-14 days, T3: 15-21 days, T4: 22-28 days. Wilcoxon signed rank test was used to evaluate longitudinal changes of six identified factors.

Furthermore, the BUN-to-creatinine ratio, NLR, and ECOG performance status scores increased significantly from the fourth time period to the first time period (p<0.05). The PLT showed a significant reduction from the fourth time period to the first time period (p<0.05). The rate of abnormal consciousness and the CRP-to-albumin ratio increased significantly from the third week to the first week (p<0.05), but without statistical significance from the fourth week to the third week.

DISCUSSION

Survival prediction is still challenging among terminally ill patients. In our study, six factors that independently predicted mortality among terminally ill cancer patients were identified. The ECOG scores, PLT, NLR, and BUN-to-creatinine ratio changed significantly from the fourth week to the first week before death. Consciousness and the CRP-to-albumin ratio significantly changed from the third week to the first week before death. It appeared that the changes in ECOG scores, PLT, NLR, and BUN-to-creatinine ratio occurred earlier than did the changes in consciousness and CRP-to-albumin ratio as death approaches in this population.

Tayor *et al.* identified that renal function worsened (as measured by abnormal serum urea and creatinine levels) in the last 2 weeks of life among patients with cancer.[10] Similarly, the current study observed increased BUN and creatinine levels over the last 4 weeks of life (results not shown). However, serum urea and creatinine levels were the only significant factors of mortality in the univariate analysis but not in the multivariate analysis. The BUN-to-creatinine ratio has been demonstrated to be a predictor of mortality in various diseases.[14,15] The current study also found that the BUN-to-creatinine ratio is an independent factor of mortality, with the ratio increasing with the time closer to death. To date, little is known about the association between this variable and death in patients with terminally ill cancer. One of the distinguishing features of our study was the evaluation of the BUN-to-creatinine ratio in the final month of life. Compared with the value of BUN or creatinine alone, the increase in the BUN-to-creatinine ratio is more valuable in helping clinicians recognise that a patient will die in the near future.

Markers of the systemic inflammatory response, such as the levels of WBC or its components and CRP, have been found to play an important role in cancer development and progression.[16,17] Increased NLR and decreased PLR are associated with poor outcomes in several malignancies.[13,18] However, this study found that only elevated NLR was associated with a worse prognosis in the last month of life, similar to a previous study.[3] The most commonly used cutoff values for NLR varied from 2 to 5.[19] In this study, NLR continuously increased with the time closer to death and was higher than in previous studies.[5,19] This could partly be because the population involved terminally ill cancer patients with only 1

month of survival, while previous studies focused on patients with earlier stages of cancer.

Serum albumin levels in cancer patients are often low because of poor nutritional status. Importantly, increased CRP-to-albumin ratio has been recently found to be associated with the worse general conditions and short-term survival in terminally ill cancer.[9] Similarly, the current study demonstrated that the CRP-to-albumin ratio is also a significant predictor of closer death, with the CRP-to-albumin ratio increased with time closer to death.

Most predictive models included performance status as a predictor.[1,5,7] In this study, ECOG sores changed significantly over time in the last 1 month and proved to be an independent factor. This is consistent with the findings by Kim *et al.* and Chiang *et al.*[5,7] In contrast to those by Ichihashi *et al.*[1] Abnormal consciousness was also a strong predictor, similar to the report by Chiang *et al.*,[7] but in contrast to the report by Kim *et al.*[5]

The study has some limitations. First, this was a single-centre retrospective study, and thus, the generalisability of the results needs to be evaluated in future studies. Second, the sample size was small because only patients with all the pre-established symptoms and biomarkers in the four time periods were evaluated, and such patients are extremely rare. However, it will prevent an error >0.1 when the sample size is 10 folds or more of the variable number.[20] In the current study, 16 variables were included in the multivariate analysis; and a sample size of at least 160 was required{Harrell, 1996 #38;Harrell, 1996 #38}. The sample size satisfied this criterion. Third, there were several primary organs in this study, and it is currently unclear whether the trends in clinical parameters in the final month vary by primary organ. Research by primary organs will be carried out in the future.

CONCLUSION

Abnormal consciousness; increased ECOG scores, NLR, BUN-to-creatinine ratio, CRP-to-albumin ratio; and decreased PLT counts are potentially useful markers for predicting closer mortality in terminally ill cancer patients. These findings are valuable for understanding the biology of death in these patients. And to some extent, they may help clinicians recognizing that a patient will die in near future.

ETHICAL APPROVAL:
This study was approved by the Ethics Committee of Beijing Shijingshan Hospital.

PATIENTS' CONSENT:
The requirement for patient informed consent was waived owing to the retrospective nature of the study. All data were anonymised before analysis.

COMPETING INTEREST:

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

AUTHORS' CONTRIBUTION:

HS, HL: The design of the study, acquisition and analysis of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

ZZ, LY: Analysis of data and Critical revision of the manuscript for important intellectual content.

All the authors have approved the final version of the manuscript to be published.

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