Effect of Hemoglobin on the Prognosis of Patients with Advanced Cancer in Palliative Care Settings

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Abstract

Background: Hemoglobin is a prognostic factor for many cancer patients. However, its effect on the prognosis of patients with advanced cancer receiving palliative treatment is still unclear.

Objective: The aim of this study was to assess whether hemoglobin can be used as a prognostic indicator for patients with advanced cancer receiving palliative treatment.

Methods: From July 2013 to October 2015, 368 consecutive patients were treated in the palliative treatment center of the Shanghai Cancer Center of Fudan University. The data for 105 patients were extended in the follow-up. The cut-off value selected for hemoglobin was 100 g/L.

Results: The median survival time of patients with low hemoglobin was shorter than that of patients with high hemoglobin (41 days vs. 84 days). In the follow-up readmission cohort ($n = 105$), the median survival time for patients with high hemoglobin (HHb $\rightarrow$ HHb) was 3.44 times longer than that of patients with low hemoglobin (HHb $\rightarrow$ LHb). Thus, both low hemoglobin and decreased hemoglobin were identified as independent prognostic factors for poor prognosis.

Conclusions: In palliative treatment, hemoglobin can be used as a stratification factor to determine the prognosis of advanced cancer patients.

Introduction

Cancer is a major public health problem and the number of cancer patients will increase worldwide, leading to serious health consequences^[1]. Advanced cancer poses a great challenge to treatment and is a common cause of death^[1]. Palliative care is an essential part of overall cancer treatment^[2]. In palliative care, clinicians need to predict the life expectancy of patients with advanced cancer because determining the possibility of impending death aids doctors in clinical decision-making to help patients and their families prepare for the future^[3, 4]. In the past few decades, several prognostic models have been proposed. The most commonly used prognostic model in palliative treatment is the Clinical Prediction of Survival; however, its inherent non-repeatability limits its accuracy and clinical application^[5]. Therefore, more accurate and easily detected indicators to predict the prognosis of patients with advanced cancer are greatly needed.

Hemoglobin (HB) is widely used in clinical examination^[6]. Low hemoglobin (HB) levels are common in cancer patients (approximately 30–77%)^[7]. Although the number of studies exploring the prognostic role of Hb levels has been increasing, the results are inconsistent and usually based on small samples. Few studies have reported the effect of low hemoglobin on the survival of patients with advanced cancer receiving palliative treatment.

Materials And Methods

Data collection and study cohort

Consecutive inpatients who were treated at the Department of palliative care, Shanghai Cancer Center (fuscc), Fudan University, Shanghai, China, were retrospectively enrolled between July 2013 and October 2015. We collected data on patients' age, sex, comorbidities, smoking status, family history, primary tumor location, tumor stage, nutritional status, and physical status (Eastern Cooperative Oncology Group, ECOG score) were obtained from the patient medical records. Hemoglobin levels were measured 1–3 days before the start of palliative care. According to the ESPEN guidelines for nutrition screening, an unintentional weight loss of > 5% in the previous three months or a food intake below 75% of the normal requirement in the preceding week were considered an abnormal nutritional status^[8]. The presence of concomitant disease was defined as self-reported cardiac disease, hypertension, diabetes, or any cerebrovascular disease.

Two cohorts of patients were identified in our study^[9]. Palliatively treated patients with malignancies in stages III-IV were classified as cohort 1, and the completeness of patient data was guaranteed. Patients in cohort 1 were classified after readmission to cohort 2. The effect of HB changes on OS was assessed. The last follow-up date was December 2015. The study was approved by the ethics committee of fuscc. Informed consent was waived due to the retrospective nature of the study.

Statistics analysis

Data are presented as the mean $\pm$ standard deviation (SD) for continuous variables and as totals and frequencies for categorical variables. The distributions of the clinicopathological features were tested using the Wilcoxon sum rank test, chi-squared test, or Fisher's exact test, as appropriate. The Kaplan-Meier method was used to plot the survival curves and the log-rank test was conducted to test differences between groups. Cox proportional hazards models were employed to estimate the magnitude of the association between the clinicopathological features and OS. X-tile version 3.6.1 (Yale University, New Haven, CT, USA) was used to determine the optimal cut-off value. All tests were two-sided, and *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed with SPSS (version 19.0), and R software (version 3.5.3) was used to draw survival curves.

Results

Patient characteristics

A total of 368 qualified patients were identified for cohort 1 in this study. Of the 368 patients, 105 had readmission data and were selected for cohort 2. There were 201 males (54.62%) and 167 females (45.38%) in cohort 1. Most patients had stage IV disease (92.12%). In the classification of tumors, gastrointestinal tumors (189, 51.36%) accounted for the largest proportion of patients, while head and neck cancer (17, 4.62%) accounted for a relatively small proportion. Most patients received the best supportive care (275, 74.73%). There was no significant difference in the number of patients with ECOG <

3 (216, 58.69%) and ECOG $\geq$ 3 (152, 41.31%). Patients with poor nutritional status accounted for the vast majority of the study patients (289, 78.53%).

In cohort 2, there was a similar number of males (55, 52.38%) and females (50, 47.62%). Patients with stage IV disease (89, 84.76%) and gastrointestinal tumors (58, 55.24%) accounted for the vast majority of cases. Unlike cohort 1, cohort 2 had more patients who received palliative chemoradiotherapy (PCR) than best supportive care (BSC) (54 [51.43%] vs. 51 [48.57%]). There were far more patients with ECOG < 3 (79, 75.24%) than ECOG $\geq$ 3 (26, 24.76%). The number of patients with good nutritional status (41, 39.05%) was less than the number with poor nutritional status (64, 60.95%).

Table 1

Comparisons of baseline clinicopathological features based on Hb in cohort 1 (N = 368)

Clinicopathological features	N (%)	Hb		P value
		HHb (n = 236)	LHb (n = 132)	
Age (Mean ± SD)	368 (63.56±12.881)	64.42±12.423	62.04±13.576	0.09
Gender				0.008
Male	201(54.62%)	141(59.74%)	60(45.45%)	
Female	167(45.38%)	95(40.26%)	72(54.55%)	
Tumor stage				
III	29(7.88%)	20(8.47%)	9(6.82%)	0.572
IV	339(92.12%)	216(91.53%)	123(93.18%)	
Primary tumor site				0.709
Gastrointestinal tumors	189(51.36%)	118(50%)	71(53.79%)	
Thoracic cancers	83(22.55%)	56(23.73%)	27(20.45%)	
Urogenital neoplasms	60(16.31%)	36(15.25%)	24(18.18%)	
Head and neck cancers	17(4.62%)	12(5.08%)	5(3.79%)	
Other tumors	19(5.16%)	14(5.94%)	5(3.79%)	
Palliative care				0.004
PCR	93(25.27%)	71(30.08%)	22(16.67%)	
BSC	275(74.73%)	165(69.92%)	110(83.33%)	
Family history				0.372
No	260(70.65%)	163(69.07%)	97(73.48%)	
Yes	108(29.35%)	73(30.93%)	35(26.52%)	
ECOG				0.584
< 3	216(58.69%)	141(59.75%)	75(56.82%)	
≥ 3	152(41.31%)	95(40.25%)	57(43.18%)	
Comorbidity				0.998
No	223(60.59%)	143(60.59%)	80(60.61%)	
Yes	145(39.41%)	93(39.41%)	52(39.39%)	
Nutritional status				0.481
Normal	79(21.47%)	48(20.34%)	31(23.49%)	

Abnormal	289(78.53%)	188(79.66%)	101(76.51%)
Abbreviations: Hb, hemoglobin; SD, standard deviation; LHb, low Hb (pretreatment NC £ 100); HHb, high Hb (pretreatment NC > 100); BSC, best supportive care; PCR, palliative chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group			

Table 2

Comparisons of baseline clinicopathological features based on Hb in cohort 2 (N = 105)

Clinicopathological features	N (%)	Hb		<i>P</i> value
		Descending	Ascending	
Age (Mean ± SD)	105(62.92±12.012)	63(62.11±11.278)	42(64.14±13.081)	0.398
Gender				0.69
Male	55(52.38%)	34▯53.97%▯	21▯50%▯	
Female	50(47.62%)	29▯46.03%▯	21▯50%▯	
Tumor stage				0.438
III	16▯15.24%▯	11▯17.46%▯	5▯11.91%▯	
IV	89▯84.76%▯	52▯82.54%▯	37▯88.09%▯	
Primary tumor site				0.653
Gastrointestinal tumors	58▯55.24%▯	33▯52.38%▯	25▯59.53%▯	
Thoracic cancers	14▯13.33%▯	8▯12.69%▯	6▯14.28%▯	
Urogenital neoplasms	24▯22.86%▯	17▯26.99%▯	7▯16.67%▯	
Head and neck neoplasm	6▯5.71%▯	4▯6.34%▯	2▯4.76%▯	
Other tumors	3▯2.86%▯	1▯1.59%▯	2▯4.76%▯	
Palliative care				0.3
PCR	54▯51.43%▯	35▯55.56%▯	19▯45.24%▯	
BSC	51▯48.57%▯	28▯44.44%▯	23▯54.76%▯	
Family history				0.226
No	73▯69.52%▯	41▯65.08%▯	32▯76.19%▯	
Yes	32▯30.43%▯	22▯34.92%▯	10▯23.81%▯	
ECOG				0.854
< 3	79▯75.24%▯	47▯74.60%▯	32▯76.19%▯	
≥ 3	26▯24.76%▯	16▯25.40%▯	10▯23.81%▯	
Comorbidity				0.218
No	65▯61.90%▯	42▯66.67%▯	23▯54.76%▯	
Yes	40▯38.10%▯	21▯33.33%▯	19▯45.24%▯	
Nutritional status				0.288
Normal	41▯39.05%▯	22▯34.92%▯	19▯45.24%▯	

Abnormal	64[60.95%]	41[65.08%]	23[54.76%]
Abbreviations: Hb, hemoglobin; SD, standard Deviation; BSC, best supportive care; PCR, palliative chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group			

Determination of the Hb cut-off value

In the clinical environment, it is common to convert continuous variables to binary variables. In this study, the patients were divided into "high" and "low" groups, which was convenient for diagnostic or prognostic predictions. However, for patients with advanced cancer, the accepted clinical threshold was not available. Using X-tile based on a minimum p-value algorithm^[10], the optimal cut-off value for Hb was determined to be 100 g/L. Therefore, the patients with HB levels greater than 100 g/L were assigned to the high HB (HHB) group and the patients with HB levels less than or equal to 100 g/L were part of the low HB (LHB) group.

Association of Hb with clinicopathological features

The relationships between the clinicopathological features and Hb (low vs. high) for cohort 1 are shown in Table 1. There were no differences in age, tumor site, family history, ECOG, nutritional status, or comorbidity between the HHB and LHB groups. In contrast, palliative treatment and gender were significantly associated with Hb. The characteristics of cohort 2 are shown in Table 2, where patients were divided into descending (changes < 0) and ascending (changes > 0) groups. There was no significant difference in the proportion of patients with specific clinicopathological features between the two groups.

Association of Hb with OS

Patients in cohort 1 were divided into HHb and LHb groups. The survival time for the HHB group was significantly longer than that of the LHB group (median survival time: 84 days [95% CI 61–107] vs. 41 days [95% CI 31–51], *P* < 0.001) (Figure 2). Multivariate Cox proportional hazard model showed that tumor stage, ECOG score, palliative treatment, and Hb were independent prognostic factors for OS. After controlling for important confounding variables, HB was still significantly correlated with OS (HHB vs. LHB, HR 0.733, 95% CI 0.558–0.909) (Table 3).

We evaluated cohort 2 to verify the prognostic significance of dynamic changes in Hb by dividing into ascending and descending groups. We found that patients who changed from the HHb group pretreatment to LHb after the second admission had the worst OS (LHb → LHb median survival time [109, 95% CI 49–169] vs. LHb → HHb median survival time [104, 95% CI 0–276] vs. HHb → LHb median survival time [68, 95% C: 45–90] vs. HHb → HHb median survival time [234, 95% CI 168–300], *P* = 0.013)

(Figure 3). The related subgroups were further analyzed and significant results were obtained after adjusting for demographic and disease-specific factors (Table 4).

Table 3

Multivariate Cox regression analysis for Hb (N = 368)

Prognostic factors	Hb Model [#]	
	Adjusted HR (95% CI)	P value
Gender (male vs. female)	0.834(0.634-1.034)	0.09
Age	0.998(0.988-1.008)	0.635
Primary tumor site	1.008(0.376-1.640)	0.156
Tumor stage (IV vs. III)	7.089(2.710-11.469)	0.001
ECOG (< 3 vs. ≥ 3)	0.606(0.461-0.751)	0.001
Nutritional status (normal vs. abnormal)	1.068(0.763-1.373)	0.879
Palliative care (PCR vs. BSC)	0.573(0.401-0.745)	0.001
Comorbidity (yes vs. no)	0.855(0.640-1.071)	0.151
Family history (yes vs. no)	1.217(0.915-1.520)	0.203
HHb vs. LHb	0.733(0.558-0.909)	0.006
Abbreviations: Hb, hemoglobin; HR, hazard ratio; CI, confidence interval; LHb, low Hb (pretreatment ≤ 100); HHb, high Hb (pretreatment > 100); BSC, best supportive care; PCR, palliative chemoradiotherapy; ECOG, Eastern Cooperative		

Oncology Group.

[#]The potential prognostic factors used for adjustment in the Cox regression model controlling for gender; age; primary tumor site; tumor stage; ECOG; nutrient status; palliative care; comorbidity; family history.

Table 4

Adjusted HRs for overall survival stratified by changes in Hb in cohort 2 (N = 105)

Hb	Hb Model [#]	
	Adjusted HR (95% CI)	<i>P</i> value
Ascending	Reference	
Descending	0.684(0.366-1.002)	0.051
LHb → LHb	Reference	
LHb → HHb	1.841(0.211-3.472)	0.828
HHb → LHb	4.003(1.421-6.585)	0.004
HHb → HHb	0.701(0.293-1.109)	0.098
Abbreviations: Hb, hemoglobin; HR, hazard ratio; CI, confidence interval; LHb, low Hb (pretreatment ≤ 100); HHb, high Hb (pretreatment > 100). [#] The potential prognostic factors used for adjustment in the Cox regression model controlling for gender, age, primary tumor site, tumor stage, ECOG, nutrient status, palliative care, comorbidity, and family history.		

Discussion

Although tremendous progress has been made in the treatment of cancer, the likelihood of treatment failure for patients with advanced disease remains high. Survival assessment is necessary for risk stratification and further clinical decision-making. However, no significant biomarkers have been widely used in survival assessment. Hemoglobin is an indicator measured in almost all hospitals in China. In our study, we evaluated the prognostic impact of Hb on patients with advanced cancer.

This study is the first to investigate the dynamic changes of hemoglobin in patients with advanced cancer in the palliative treatment environment. We established a Hb cut-off value of 100 g/L and found that patients with a low Hb had a poorer survival time than patients with high Hb with advanced cancer. Furthermore, patients that transitioned from high Hb levels to low Hb levels between the first and second hospital admission were at a greater risk of a poor prognosis. In conclusion, pretreatment and dynamic peripheral hemoglobin levels represent convenient and intuitive markers to predict aggressiveness in patients with advanced cancer.

Ludwig et al.^[11] found that the incidence of anemia in 11,453 patients with various cancers was 41%. In patients with advanced tumors and those receiving radiotherapy or chemotherapy, the incidence of anemia is as high as 90%^[12], especially in patients with more aggressive tumors. This finding may be related to the complex interactions between the immune system, tumor microenvironment, and cancer cells^[13,14]. In general, cancer-related anemia has various causes, including blood loss, functional iron deficiency, erythropoietin deficiency due to kidney disease, and the relationship between cancer and bone marrow^[15]. Tumor cells can activate macrophages, promote the secretion of inflammatory factors (e.g., gamma-interferon, IL-1, and tumor necrosis factor), which can reduce Hb concentrations by altering the

hematopoietic environment^[16, 17], inhibiting erythropoiesis and erythropoietin, and impairing the erythropoietin response of erythroid progenitor cells^[18,19]. In addition, bone marrow failure is common in patients with bone metastases and leads to low Hb levels^[20]. Patients at later tumor stages and greater tumor burden have more inflammatory factors secreted by tumor cells, a higher incidence of anemia, and a worse prognosis^[21]. Hypoxia is an important link in the occurrence and development of malignant tumors^[22], while anemia will aggravate the degree of hypoxia in tumor tissues and affect the stability of chemotherapeutic drugs in the process of diffusion. Moreover, the production of oxygen-free radicals reduces the damaging effect of chemotherapeutic drugs on the DNA of tumor cells, thus reducing drug efficacy^[23]. Tissue oxygenation disorders stimulate the high expression of angiogenic factors, which promotes the occurrence and development of tumors, reduces drug sensitivity, increases the probability of blood transfusion after chemotherapy, damages organ function, reduces the quality of life, and increases postoperative mortality.

A meta-analysis involving 60 studies showed that anemia increased the overall risk of death in tumor patients by 65%^[24]. Previous studies showed that anemia might impact the biological characteristics and prognosis of tumor patients, reduced the response to chemotherapy, and promoted tumor recurrence and metastasis, which is an independent risk factor of poor prognosis^[25]. Studies have reported that anemia may or may not be a bad prognostic factor in patients with advanced gastric cancer^[26,27]. These results may be related to the inconsistent reference criteria for anemia used in the different studies. The U.S. National Cancer Institute (NCI) and the World Health Organization (WHO) define their own anemia diagnosis and classification standard. The Chinese Society of Clinical Oncology (notes) is based on clinical practice and the treatment of cancer-related anemia classification^[28]. The different standards in defining the normal Hb range and anemia are different for these entities based on slightly different severity classifications. Therefore, to unify the criteria, we first established a threshold value for Hb as a tool to predict the prognosis of patients with advanced cancer.

Although this study provides important insights into the relationship between Hb levels and the prognosis of patients with advanced cancer, it has some limitations. This study was limited to a retrospective single-center design with inherent limitations, such as selection bias, possible confounders, and relatively low sample size. Therefore, larger prospective multi-institutional studies with more clinical markers are needed to validate the relationship between Hb and poor prognosis. Overall, we demonstrated for the first time that Hb is a strong independent predictor of shortened survival after palliative treatment in patients with advanced cancer. As an easily accessible and inexpensive biomarker, Hb deserves further research into future clinical practice for risk stratification and may enable more accurate clinical decision-making for patients with advanced cancer.

Conclusions

In conclusion, in palliative treatment, hemoglobin can be used as a stratification factor to determine the prognosis of advanced cancer patients. Patient survival time can be estimated from the changes after

haemoglobin treatment.

Declarations

Author contributions

All authors made substantial contributions to one or more of the following: study conception and design (XHL, WWC); acquisition of data or analysis (XHL, WWZ, MLC, XLG, MHL, ZZ, CYZ); interpretation of data (XHL, WWZ, CHB, ZZ). XHL and CHB drafted the article, and all other authors contributed to critically revising the article for important intellectual content. All authors provided their final approval of the version to be published.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Figures

Figure 1

X-tile analysis was performed to determine the optimal cut-off values using the data of cohort 1. The optimal cut-off value for HB was 100 ($x^2 = 15.85$, $P = 0.0026$).

Figure 2

Overall survival of patients under palliative care stratified by pretreatment Hb (cohort 1). Abbreviations: LHb, low Hb (pretreatment ≤ 100); HHb, high Hb (pretreatment > 100)

Figure 3

Overall survival of patients under palliative care stratified by changes in Hb (cohort 2). Abbreviations: LHb, low Hb (pretreatment ≤ 100); HHb, high Hb (pretreatment > 100)