Anorexia as a Risk Factor of Mortality in Patients with Advanced Lung Cancer Receiving Home-Base Palliative Care

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Research Article

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Abstract

Purpose

To determine the prevalence of anorexia among advanced lung cancer patients at the beginning of receiving home-based palliative care and to examine the predictive role of anorexia in survival of patients with advanced lung cancer.

Methods

In this retrospective study, we analyzed data from 918 advanced lung cancer patients who had received home-based palliative care between March 2010 and March 2020. We used Kaplan-Meier survival curves to determine the factors associated with survival time and applied the Cox proportional hazards model to examine the effect of anorexia on survival.

Results

The study included 918 patients with a mean age of 63.5 years; and 72.2% of them were men. Factors associated with shortened survival included gender, place of residence, weight loss, anorexia, nausea and Karnofsky performance status (KPS). In a multivariable Cox proportional hazards model, after adjusting for male gender, patient lives in city, and low KPS, we found that anorexia was an independent negative predictor of survival.

Conclusions

As an independent factor predicting the survival of patients with advanced lung cancer, anorexia should be taken seriously by medical staff. This predictive factor may serve as early risk identification indicator for healthcare workers who provide home-based palliative care, thereby providing personalized palliative care for advanced lung cancer patients.

1. Introduction

Lung cancer is currently the second most common malignant tumor disease in the world, accounting for about 11.4% of all cancer diagnoses, and has a high cancer-related mortality rate[1]. In recent years, it has been demonstrated that the survival rate of lung cancer patients at 5 years after diagnosis is only 10-20% [1]. Therefore, efforts to build preventative and curative interventions, accurately predicting the risk factors and developing personalized interventions for lung cancer are important[2, 3]. Unfortunately, clinician predictions of survival time are imprecise and optimistic[4, 5]. Although some studies have demonstrated that the prediction of lung cancer depends largely on age, sex, stage, histological type and treatment options, and antitumoral treatment[6, 7], there are still major limitations related to their

objectivity or measurability. At present, several published studies revealed that measurements by symptom for cancer patients have been preliminarily explored as an objective survival independent predictor[8].

The three most common symptoms of cancer patients at the end of life are fatigue, pain, and anorexia (appetite loss)[9, 10]. Notably, up to 57.9% of advanced cancer patients have experienced anorexia, especially among lung cancer patients. Anorexia is defined as the reduction and/or loss of appetite[11]. Cancer-related anorexia usually leads to reduced food intake[12] and it is also a major clinical problem, with a detrimentally effect on weight of patients, which may lead to a decline in the quality of life of patients and increased risk of death[12, 13]. Previous systematic reviews[13] on cancer patients described benefits associated with appetite status, and demonstrated that early detection of poor appetite and timely intervene on it before weight loss is important to improve the symptom burden of cancer patients[14]. Over the past years, several published studies further substantiated these findings[8, 15]. For example, Juliana and colleagues[8] investigated 522 stage IV lung cancer patients at a tertiary referral outpatient clinic in Brazil and found that anorexia and weight loss at diagnosis were associated with survival time. In addition, Bens and colleagues[15] also investigated the relationship between anorexia nervosa and breast cancer survival in women, and the results showed increased overall mortality after breast cancer diagnosis in women with a history of anorexia nervosa. Therefore, anorexia should be a factor worthy of attention for medical staff.

In the past two decades, the focus of care for patients with advanced cancer has undergone a major shift, from institution-based services to home-based palliative care[16]. Home-based palliative care is a supportive service that can help manage patient symptoms, address the care needs and psychosocial support[17]. A number of systematic literature reviews have shown that most people with advanced cancer and short life expectancy consider dying at home surrounded by family to be the “gold standard” for a good death[18, 19]. They want to stay at home for as long as possible at the end of their lives and home-based palliative care can help them fulfil this expectation[20]. In addition, home-based palliative care services not only provide personalized care at home based on the needs of the patient and caregivers, but also give the patient a greater sense of choice and comfort in the delivery of care[21]. Several studies have shown patients who receive home-based palliative care or dying at home have significantly longer survival than those who receive hospital care[22, 23]. To our knowledge, although palliative care for advanced cancer patients has been implemented for more than 30 years, but few investigators have examined predictive factors of home palliative care in terms of patient survival time. Although a preliminary study suggested association between anorexia and survival time among advanced lung cancer patients, this association may vary depending on the type of cancer and the location of palliative care. It is uncertain, in the current study, whether anorexia is associated with survival time in patients with advanced lung cancer receiving home-based palliative care.

At present, only one retrospective study[8] summarizing the effects of anorexia on advanced lung cancer patients' survival time has been conducted. It included a tertiary referral outpatient clinic involving 522 participants, and the results demonstrated that the synergistic effect of weight loss and anorexia may be

effective in improving survival time in patients with advanced lung cancer. But whether anorexia was an independent predictor of survival time among patients with advanced lung cancer is not fully elucidated. In view of this, we have undertaken to describe the prevalence of anorexia in patients with advanced lung cancer receiving home-based palliative care and, to identify the influencing factors associated with the occurrence of anorexia, and to comprehensively assess the independent predictive role of anorexia on overall survival in patients with advanced lung cancer.

2. Methods

2.1 study population

This was a retrospectively study. This study reviewed medical record of 937 patients received home-based palliative care in the hospice unit of Zhongnan Hospital of Wuhan University between March 2010 and March 2020. The inclusion criteria for participants in this study were include:(1) patient who aged 18 years or older; (2) patients who were diagnosed with an incurable advanced lung cancer; (3) patients who completed the questionnaires on the same day of their receiving home-based palliative care. While patients who were unable to give informed consent or treated partially in other hospitals were excluded. Finally, nineteen patients with unknown detailed information were excluded, leaving 918 patients eligible for data analysis. This study was approved by the institutional review board of Wuhan University school of health sciences. (no. 2021-YF-0061)

2.2 Patient assessment

Information from the electronic medical records was obtained on age, gender, marital status, clinical characteristics and Karnofsky performance status (KPS) scores the date of home-based palliative care started and the date of death. We also assessed symptoms related to the tumor such as weight loss, insomnia, appetite, and nausea. The symptoms reported by the patients were assessed according to Cancer Pain and Quality of Life Questionnaire for Chinese Cancer Patients (CPQLQ-CCC)[24]. CPQLQ-CCC consists of 12 questions, patients rated each question on a Likert scale from 1 to 5. Scoring 3 points or higher indicates that the patients have a higher burden of symptoms. Presence of anorexia was defined as the cancer patient's loss or disappearance of appetite for a long time, resulting in a decrease in appetite, less than two-thirds of the normal intake or inability to eat, with or without weight loss. The affirmative response to one of the following questions used in order to evaluate anorexia: (1) In past month, are you eating less because of decreased appetite? (Yes/ No); (2) In past month, do you eat less than two-thirds of what you used to eat? (Yes/ No); The patients' performance status was estimated according to the KPS scale. The KPS score was categorized into low (score 10-50) and high (60-100)[25]. Survival time was defined as the interval from the date of enrollment in home-based palliative care until the day of death.

2.3 Data analysis

The collected data were analyzed using IBM SPSS Statistics (version 25.0). Characteristics of patients were summarized using means (standard deviation) and frequencies (percentages). Normally distributed measures were expressed as mean and standard deviation and differences were analyzed using the t-test for comparison between the two groups. Non-normally distributed measures were expressed as median and interquartile range, and differences were analyzed using the non-parametric Mann-Whitney U test. Count data were expressed as frequencies (percentages) and differences were analyzed using the chi-square test and Fisher's exact test. The Kaplan-Meier survival analysis and log-rank tests were used to assess differences in survival times of all patient characteristics. Kaplan-Meier's method was used to evaluate the association between appetite status and survival at the beginning of the home-based palliative care program. The impact of covariates and appetite status on survival by using the univariate and multivariate Cox proportional hazard regression analysis. The predictors that showed significance ($p < 0.05$) in the univariate analysis were enter in multivariate analysis. For all analysis, a conventional criterion of statistical significance ($p < 0.05$) was applied.

3. Results

We identified 918 participants with an average of age 63.5 years. Of the patients in the study, 663(72.2%) were male, and 255(27.8%) were female. Median and mean survival times were 65 and 109 days, respectively. Patients live in cities was reported by 67.0% of patients, and 85.1% of patients were married. Of these, the most common symptoms weight loss (80.8%), insomnia (65.6%), and anorexia (64.4%). The demographic data and symptoms of the patients with and without anorexia were reported in Table 1. The majority of patients with anorexia were male (69.1% and 30.9%, $p < 0.05$) compared to those with normal appetite. It was also higher in anorexic patients who has weight loss ($p < 0.01$), insomnia ($p < 0.01$), constipation($p = 0.02$), and nausea($p < 0.01$) than those with normal appetite.

The results of the survival time according to participant characteristics were presented in Table 2. Male sex, place of residence, weight loss, anorexia, nausea, and KPS score were significantly associated with median survival time. But other common cancer related symptoms such as insomnia and constipation were not significantly associated with survival time.

Kaplan-Meier survival curve drawn by appetite status was shown in Figure 1. Anorexia patients had shorter overall survival than normal appetite patients ($p < 0.001$). Median survival for normal appetite patients was 156 days (5 months, 95% CI=77.72-100.28), and for anorexia patients it was 87 days (3 months, 95% CI=42.53-53.46).

Six predictors of univariate analysis were included in the multivariate Cox proportional hazards model. The results of the multivariable extended Cox regression model analysis were presents in Table 3. Five of predictors were significantly associated with poor survival. The anorexia was significantly associated with survival time. (HR=1.431; $p < 0.001$). Additionally, male sex (HR=1.332; $p < 0.001$), patient living in the city (HR=0.783; $p = 0.001$), nausea (HR=1.240; $p = 0.015$), and KPS score (HR=0.650, $p < 0.001$) were

significantly associated with survival time. But we found that whether the patients have weight loss was not significantly associated with survival time.

4. Discussion

This study investigated the prevalence of anorexia in patients with advanced lung cancer and confirmed whether anorexia was associated with survival time in patients with advanced lung cancer. The results of this study showed that anorexia was very common in patients with advanced lung cancer and that the trend of anorexia onset was different between male and female lung cancer patients. Most of the patients who had anorexia were accompanied by symptoms such as insomnia, constipation, weight loss and nausea. Another finding was that gender, place of residence, nausea, KPS score and anorexia were significantly associated with survival time. The findings of the current study indicated that anorexia was associated with a higher HR, thereby signaling a high risk of death. The correlation between anorexia and low survival remained strong after controlling for other predictors of survival. These results were consistent with previous research results and provide additional support.

Anorexia was a rather common symptom and one of the most challenging symptoms among advanced cancer[26], which was a multifactorial syndrome occurred when the reduction of food intake and abnormal metabolism make patients with advanced cancer more vulnerable[27]. Current treatment relies on the use of nutritional support or pharmacological treatment[28]. Furthermore, our results suggested that anorexia was a predictor for survival in the patients with lung cancer. Three different factors contribute to explaining the reasons of it. Firstly, up to 12-68% of lung cancer patients experience dysphagia and can cause much suffering, thereby can reduce the desire for food[29]. Secondly, as the disease progresses in patients with advanced cancer, they will take a lot of pain medication and these medications may cause nausea and vomiting, which can lead to anorexia. Finally, since our survey was based on the home-based palliative care patient's participation, the home environment and eating habits also play a role in affecting patients' appetite. Due to the special nature of the diet of patients with advanced cancer, they may encounter conflicts with family food and pressure from family members to "eat more" during meals that cause the patient to feel angry and upset, leading to emotional anorexia patients[30]. Therefore, in the future care of patients with advanced lung cancer, firstly, we need to provide patients with appropriate pharmacological interventions in response to nausea, vomiting and loss of appetite in order to control their symptoms; secondly, we need to identify the underlying cause of the loss of appetite and provide patients and their caregiver with individualized non-pharmacological interventions such as dietary advice, psychological interventions and acupuncture/acupressure.

We also found that sociodemographic factors such as gender and residence were associated with shorter survival time. The finding was consistent with results published by other institutions. For instance, Cook and colleagues[31] extracted data concerning cancer from the *Surveillance Epidemiology and End Results Database* and found that for the vast majority of cancer, mortality rates were higher among males than females. The reason for the discrepancy may be the difference of living habits and living environment between men and women. For example, smoking has been proved to be an important risk factor for

advanced lung cancer, smoking remained highly prevalent among adult men, which may lead to higher mortality rates for men than women[32, 33]. Furthermore, we also found the mortality rates were higher among rural than urban areas. One reason is that there are great differences between urban and rural areas in terms of economic development level, medical and health care resources and industrialized air pollution. With the economic development of rural areas in China, industrialization is spreading to rural areas, and the living environment of more and more rural residents is destroyed[33]. Another reason is the insufficient development of multidisciplinary teams and medical teams in rural China, where patients can't get timely medical resources, and this has likely impact on survival rate among advanced lung cancer. As a result, the incidence and mortality of lung cancer in rural areas are higher than those in urban areas.

Moreover, in our studies, clinical characteristics of patients other than anorexia such as nausea and low KPS score was associated with shorter survival time. There have been a large number of studies and clinical trials demonstrated that nausea was a common clinical issue among advanced cancer[34], which was consistent with our results. The etiology of nausea may be related to post-chemotherapy nausea and opioid-induced nausea[35]. To our knowledge, chronic nausea may cause complications, such as anorexia and diminished quality of life[35]. If the symptoms are not controlled, it may also threaten the survival of patients with advanced cancer. Likewise, the KPS score was also one of the factors in the Cox proportional hazards model that affected their survival, which was consistent with the results reported by Witteler and colleagues[25]. The KPS scoring system is a reliable method to measure the performance of patients, which is widely used in the performance assessment of cancer patients[36]. Lower KPS scores can represent to poorer physical health. For patients, what matters is not the percentage score of KPS, but the disease status and complications, and impact of these two items on patient's disease burden. Therefore, KPS as one of the indicators of overall survival prediction is completely understandable, because poorer survival is usually related to more and more severe symptoms and greater disease burden. It is noteworthy that weight loss not affect mortality in our sample of patients. Contrary to our study, prior study has demonstrated that weight loss is an important predictor of shorter survival[37], which may be explained by the criteria for clinically significant weight loss (>5%) has not been applied in our study, and self-reported weight loss is the potential reason for inaccuracy[38]. Another explanation is that clinical weight loss may differ for various tumor types. Therefore, future research could explore the impact of weight loss based on standard weight measurements on the survival time of patients with advanced lung cancer.

It is worth highlighting, home-based palliative care as a new treatment of care can offer patients many benefits, some of which including managing symptoms, reducing psychological distress and improving quality of life[21, 39]. Our results suggest that patients with advanced lung cancer who participate in palliative care at home have many symptoms, of which anorexia accounts for a higher proportion. Most patients with advanced cancer experience symptoms throughout the course of the disease, and symptoms tend to become more severe as death approaches. If poorly managed, these symptoms can have a considerable impact on patients' survival. Our team was a trained, interdisciplinary palliative care team whose purpose is to provide drugs, manage symptoms and give personalized care to patients. At

present, in our samples, there are many treatment methods for anorexia among advanced cancer patients, such as swallowing therapy, psychosocial support and giving dietary advice[40, 41]. Despite home-based palliative care being an advantageous model of care, challenges still exist in managing the burden of symptoms. Therefore, it is necessary to instill knowledge of anorexia management to both the home-based palliative care nurses and physicians.

There are acknowledged limitations to interpreting our results. Firstly, this study is only representative of one home-based palliative care center in China, study results may not generalize to every palliative unit. Secondly, as with all retrospective studies, our study relies heavily on reviewing data, which was clinically documented for patient care, so there may be a potential for recording bias. Thirdly, we could not calculate the time from cancer diagnosis to death because these data are not available. Finally, we only used simple tools to assess the anorexia of patients, and the diagnostic criterion of anorexia was omitted. Therefore, for high quality evidence, more large scaled longitudinal studies are required in the future.

Conclusion

Overall, this study has provided evidence that anorexia has a higher prevalence in patients with advanced lung cancer, and it was associated with higher mortality. Anorexia can be used in combination with other clinical factors to predict the survival of patients with lung cancer receiving home-based palliative care. However, current evidence is based on limited number of studies and primarily in home-based palliative care patients. More studies should be therefore carried out to verify our findings to provide reference for making individualized treatment plans in palliative care and improving patient well-being.

Declarations

Funding: The author declares no financial support.

Conflicts of interest: The authors declare no competing interests.

Availability of data and material□Not applicable

Code availability□Software application

Ethics approval: As approved by the institutional review board of Wuhan University school of health sciences, informed consent from patients was not necessary because of the retrospective design of this study.

Consent to participate: Not applicable

Consent for publication: Not applicable.

Author's contributions

- 1.Study design: JiaXin Cui and Lanhui Tan.
- 2.Methodology: JiaXin Cui and Pei Fang.
- 3.Formal analysis and investigation: Jia-Xin Cui, Zifen An and Jia-Yi Du;
- 4.Writing-original draft preparation, Jia-Xin Cui.
- 5.Writing-review and editing: Lan-Hui Tan and Li-Ping Yu.

All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1. Baseline Characteristics of Patients

variable		Total (n=918)		Anorexia [n=591]		Normal appetite [n=327]		p value
		n	%	n	%	n	%	
Age	>70	679	74.0%	429	72.6%	250	76.5%	0.201
	≤70	239	36.0%	162	27.4%	77	23.5%	
Sex	Male	663	72.2%	440	74.5%	233	69.1%	0.043
	Female	255	27.8%	151	25.5%	104	30.9%	
Living condition	Living with relatives	896	97.6%	578	97.8%	318	97.2%	0.600
	Others	22	2.4%	13	2.2%	9	2.8%	
Place of residence	City	615	67.0%	395	66.8%	220	67.2%	0.891
	countryside	303	33.0%	196	33.2%	107	32.8%	
Economic source	Salary or pension	460	50.1%	285	48.2%	175	53.5%	0.156
	Family support	390	42.4%	255	43.1%	135	41.3%	
	Government support	51	5.6%	37	6.3%	14	4.3%	
	Savings	17	1.9%	14	2.4%	3	0.9%	
Education	<6 years	288	31.4%	184	31.1%	104	31.8%	0.469
	7-12years	351	38.2%	234	39.6%	117	35.8%	
	>12 years	279	30.4%	173	29.3%	106	32.4%	
Marital status	Married	781	85.1%	496	83.9%	285	87.2%	0.188
	Single	137	14.9%	42	16.1%	95	12.8%	
Weight loss	Yes	742	80.8%	522	88.3%	220	67.3%	<0.01
	No	176	19.2%	69	11.7%	107	32.7%	
Insomnia	Yes	602	65.6%	411	69.5%	191	58.4%	<0.01
	No	316	34.4%	180	30.5%	136	41.6%	
Constipation	Yes	378	41.2%	259	43.8%	119	36.4%	0.028
	No	540	58.8%	332	56.2%	208	63.6%	
Nausea	Yes	166	18.1%	132	22.3%	34	10.4%	<0.01
	No	752	81.9%	459	77.7%	293	89.6%	

Primary caregivers	Spouse	464	50.5%	289	48.9%	175	53.5%	0.180
	Others	454	49.5%	302	51.1%	152	46.5%	
KPS scores	60	327	35.6%	157	26.6%	170	52.0%	<0.001
	50	591	64.4%	434	73.4%	157	48.0%	

Table 2 Survival time in relation to patient characteristics

Variables		n	Median survival, days (95% CI)	p value
Age, years	≥70	239	107(87-127)	0.338
	≤70	679	113(103-124)	
Sex	Male	663	100(91-110)	<0.001
	Female	255	142(120-164)	
Live alone	Yes	22	185(48-323)	0.127
	No	896	110(101-119)	
Place of residence	City	615	123(110-135)	<0.001
	Rural area	303	88(77-99)	
Education	<6 years	288	114(96-132)	0.823
	7-12years	351	107(94-120)	
	>12 years	279	115(98-133)	
Weight loss	Yes	742	103(94-112)	0.001
	No	176	149(119-178)	
Insomnia	Yes	602	109(98-121)	0.352
	No	316	116(101-131)	
Appetite	Anorexia	591	87(78-96)	<0.001
	Normal appetite	327	156(136-176)	
Constipate	Yes	378	104(91-116)	0.120
	No	540	118(107-129)	
Nausea	Yes	166	85(70-96)	0.002
	No	752	117(106-128)	
KPS scores	≥60	327	149(131-167)	<0.001
	≤50	591	90(81-101)	

Table 3 Independent prognostic indices of survival (Cox proportional hazards model)

Variables	Univariable analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	p value
Male patients	1.329(1.148-1.539)	<0.001	1.332(1.145-1.548)	<0.001
Patient lives in city	0.779(0.678-0.897)	0.001	0.783(0.680-0.902)	0.001
Anorexia (yes)	1.674(1.458-1.922)	<0.001	1.431(1.233-1.660)	<0.001
Nausea(yes)	1.300(1.097-1.540)	0.002	1.240(1.044-1.473)	0.015
Weight loss(yes)	1.326(1.121-1.568)	0.001	1.058(0.886-1.263)	0.535
KPS scores(high)	0.625(0.545-0.717)	<0.001	0.650(0.565-0.749)	<0.001

HR hazard ratio, CI confidence interval

Figures

Figure 1

Kaplan-Meier survival curves of advanced lung cancer patients plotted by appetite level