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PAPER

Survival prediction of anxious emotion in advanced cancer patients receiving palliative care

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Abstract

Background This study was carried out to investigate the prognostic value of baseline and dynamic changes in anxious emotion in advanced cancer patients undergoing palliative care.

Methods The association between anxious emotion and survival was investigated in a retrospective sample of 377 consecutive advanced cancer patients receiving palliative care from August 2013 to October 2015 and in an extended follow-up study of 106 of those patients.

Results The prevalence of anxious emotion was 24.93% (94/377) overall, 22.48% (47/209) in men and 27.97% (47/168) in women. Significant associations between baseline anxious emotion and overall survival (OS) were not found in the whole sample or in women. However, univariate and multivariate analyses showed that anxious emotion was an independent prognostic indicator of OS in men (hazard ratio [HR]: 1.811, $P = .003$). Moreover, findings showed that newly developed anxious emotion was significantly associated with poor OS in all readmitted patients (HR: 5.568, $P < .001$), in men (HR: 5.104, $P = .006$) and women (HR: 5.820, $P = .004$).

Conclusions Our study suggests that anxious emotion, especially dynamic changes in anxious emotion, needs to be monitored in advanced cancer patients; whether targeted interventions would prolong survival requires further studies.

KEYWORDS

advanced cancer, anxious emotion, oncology, palliative care, prognostic value

1 | INTRODUCTION

With an increasing incidence and mortality, cancer is the leading cause of death in China. An estimated 4 292 000 new cancer cases occurred in China in 2015, and 2 814 000 cases died from cancer.[1] Despite biomedical progress, the diagnosis of cancer and subsequent treatment are frightening experiences and present an intense emotional burden for most patients.

A negative emotional state is a natural psychological response that may occur throughout the entire trajectory of cancer, resulting from the perception of anxiety due to the inability to predict, control, or gain from the threatening situation.[2] Clearly, advanced cancer patients have increasing physical and emotional burdens toward the end of their life.[3,4] Many patients with advanced cancer experience negative moods, including anxiety, depression, stress, and fear, in anticipation of potential cancer-related complications or death.[5] There is a growing recognition that negative emotions can increase pain, weakness, and hopelessness; can even lead to suicide; can increase medical costs; and can disrupt patients'

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quality of life and therapeutic success.[5–7] Therefore, health policies in many countries throughout the last decade have prioritized detecting and addressing the psychological needs associated with cancer .[8] Although there are numbers of studies on depression and cancer, the studies on anxiety, especially evidence exploring the association between anxious emotion and survival, remained scarce and controversial.[9,10]

Health policies for cancer care promote the screening of patients for emotional distress, but the utility and validity of the screening instruments have been questioned.[8] Patients may have a poor compliance to mental health assessments via questionnaires, perhaps due to their complexity or patients' lack of interest.[11] The rate of valid questionnaires completed ranges from 24 to 84%.[12,13] In our palliative care unit, most patients had poor physical states and were too weak to complete questionnaires. To provide psychological assessments for all those patients is challengeable, and the standardized ultra-short 2 verbal questions were used consequently.

Therefore, this study aimed to explore the association between baseline anxious emotion and overall survival (OS) in advanced cancer patients and to assess the clinical influence of dynamic changes in anxious emotion on OS in a palliative care setting.

2 | METHODS

2.1 | Data source and study cohort

The palliative care unit in Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China, was established to provide symptom management and psychosocial and social support for cancer patients. Consecutive patients hospitalized at the palliative care unit between July 2013 and October 2015 were retrospectively reviewed. Demographic and clinical data were collected from the medical data platform of FUSCC by trained staff by using standardized data collection and quality control procedures. Emotional state was evaluated within 8 hours of admission, and all of those data were collected at the time of initiating palliative care. Written informed consent was obtained from all participants before commencing the research. The present study was approved by the Ethics Committee of FUSCC.

Two cohorts of patients were identified for 2 different study purposes. First, the potential relationship between baseline emotional state and OS was examined. Patients who met the following inclusion criteria were enrolled to cohort 1: (a) a hospitalization for palliative care, (b) the presence of various cancers confirmed by histopathology or at least cytology, (c) ability to evaluate baseline emotional state within 8 hours of admission, and (d) availability of all clinical data. Patients with benign or early stage (I and II) tumors and those without an emotional assessment were excluded from the analysis. The patients in this cohort were divided into the subgroup of anxious emotion (AE) and nonanxious emotion (NAE) according to the baseline emotional assessments. Second, the relationship between changes in emotional states after palliative care and OS was explored. The patients in cohort 1 who had a second admission to our unit were enrolled into cohort 2. To achieve this study aim, we categorized patients into 4 subgroups based on their emotional assessments at the 2 hospitalizations: (a) both of the assessments were NAEs, i.e., from NAE to NAE (NAE → NAE) group; (b) both of the assessments were AEs (AE → AE); (c) from AE to NAE (AE → NAE) group; and (d) from NAE to AE (NAE → AE) group. The demographic characteristics, disease-specific factors, and emotional state assessments were also obtained at the second admission.

Patients' anxious emotional state was assessed by well-trained clinical nurse specialists according to the literature.[14] They have long been engaged in palliative care for advanced cancer patients and were trained to assess the AE by using the standardized ultra-short 2 verbal questions. The case-finding ability of the ultra-short 2 verbal questions is given by an area under the curve (AUC) of 0.831 and the screening ability area under the curve of 0.673, which has superior efficiency than the Hospital Anxiety and Depression Scale (14 items), Distress Thermometer (1 item), and Psychological Distress Inventory (13 items).[15] The 2 verbal questions were administered by asking "are you anxious/scared/stressed?" and "how anxious/scared/stressed have you been in the previous week?" Abnormal nutritional status was defined as an unintentional weight loss greater than 5% in the previous 3 months or a food intake below 75% of the normal requirement in the preceding week according to the European Society for Clinical Nutrition and Metabolism's guidelines for nutrition screening.[16] Concomitant disease was defined as self-reported cardiac disease, hypertension, diabetes, or any cerebrovascular disease. The last follow-up was in December 2015. Overall survival time was defined as the period from the date of initial treatment in the palliative care unit of FUSCC to death from any cause or the last follow-up (if death not known).

2.2 | Statistics analysis

Frequencies and proportions were reported for categorical variables, and comparisons were conducted by using the χ^2 or Fisher's exact test as appropriate. Survival rates were estimated by the Kaplan-Meier method, and differences between groups were determined by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox proportional hazard models to estimate the association of AE with OS. All of the tests were 2-sided, and *P* less than .05 was considered statistically significant. Data analyses were performed by using SAS 9.3 (Cary, NC, USA).

3 | RESULTS

3.1 | Demographic and clinical characteristics

A total of 405 patients were retrieved from the database. Two patients diagnosed with benign lesions, 18 patients with early tumor stages (stages I and II), and 8 coma patients who lacked a psychological assessment were excluded. Thus, 377 eligible advanced cancer patients (stages III and IV) were identified in cohort 1. Of the 377 patients, 106 with readmission information were selected for cohort 2 (Figure S1).

The median duration of follow-up was 446 days, the median age was 64 years old, and the prevalence of AE was 24.93% (94/377) in cohort 1. The demographic and clinical characteristics are provided in Table S1. Specifically, 209 patients were male (55.44%), and 168

patients were female (44.56%). The proportion of patients with AE was 22.49% (47/209) and 27.98% (47/168) in men and women, respectively. Almost all patients were married (94.43%), and approximately 85% had an educational level above middle school. There were 23 patients with stage III tumors (6.10%), and 354 patients had tumors in stage IV (93.90%). Approximately half of the enrolled patients had gastrointestinal tumors (52.52%), almost a quarter had thoracic cancer (22.55%), 15.6% had urogenital cancer (59/377), and patients with head and neck neoplasms and other tumors were the minority, accounting for 4.24% and 5.04%, respectively. Most of the enrolled subjects had no smoking history, no concomitant disease, and no family history of cancer. However, 70.8% of the patients had an abnormal nutrient status. Over half of the patients had been hospitalized for more than 2 weeks (54.38%). In cohort 2, the distribution of demographic and clinical characteristics was similar to that in cohort 1 (Table S2). Clinicopathological features of the patients with (n = 106) and without readmission (n = 271) were listed in Table S3.

3.2 | Association of anxious emotion and changes in anxious emotion with clinicopathological features

The proportion of NAE in cohort 1 was 75.06% (283/377). Comparisons of demographic and clinicopathological characteristics were made between patients with and without AE (Table S1). Anxious emotion was significantly higher in patients with an abnormal nutritional status than in those with a normal status (28.46% vs 15.89%, P = .030). No other significant differences were observed between the NAE and AE groups (P > .05).

In cohort 2, changes in anxious emotional status were compared regarding clinicopathological features. Most of the patients remained without AE (70.75%); 11 patients had NAE after palliative care, and 13 patients had worse emotional assessments after palliative care. No statistically significant associations were found between the changes in AE and clinicopathological features (Table S2).

3.3 | Associations between overall survival and anxious emotion and changes in anxious emotion

In cohort 1, the patients were divided into NAE and AE groups, in which the median survival time was 57 (95% CI: 48-74) days and 35 (95% CI: 21-46) days, respectively (P = .204). Significant associations between baseline AE and OS were not found in the whole sample (Table 1 and Figure 1A). However, we hypothesized that emotional status might differ by gender, and further analyses were conducted to compare OS stratified by gender. Male advanced cancer patients with AE had a significantly shorter median survival time than male patients without AE (26 vs 64 days, P = .017). For women, the median survival time of NAE and AE patients was 53 (95% CI: 38-68) and 38 (95% CI: 21-84) days, respectively (P = .617). As expected, the univariate survival analysis showed that men in the AE group were significantly associated with a worse OS than those with NAE (HR: 1.542, P = .017; Table 1 and Figure 1B). After controlling for several potential confounders in the multivariable Cox proportional hazard models, AE remained significantly (HR: 1.811, P = .003) associated with OS in men (Table 1). On the other hand, there was no significant relationship between baseline AE and OS in women (Table 1 and Figure 1C).

In cohort 2, the patients were categorized into 4 subgroups, i.e., NAE → NAE, AE → AE, NAE → AE, and AE → NAE. We hypothesized that the patients who changed from NAE to AE (NAE → AE) would have the worst OS. Further subgroup analyses were performed on the associations of emotional changes with OS stratified by gender (Table 2). Univariate analyses showed that the patients whose emotional status is from NAE to AE had a much poorer OS (HR: 4.837, P < .001). For the patients with baseline NAE, the median survival time in patients with newly developed AE was significantly shorter than in patients without newly developed AE (60 vs 178 days, P < .001). In the subgroup analysis stratified by gender, the HRs of patients who switched from NAE to AE were approximately 7.8 and 3.6 times that of emotionally stable patients (NAE → NAE) in men and women, respectively. Both male and female patients with newly developed AE (changing from NAE to AE) had significantly shorter survival times than patients with stable emotions (namely NAE → NAE; 62 vs 188 days and 57 vs 132 days). However, male cancer patients who had baseline AE still had a worse survival than the controls, even if their emotional status improved (HR: 3.331, P < .001). The Kaplan-Meier survival curves depicted that the NAE → AE group had the worst survival (Figure 2). When demographic and disease-specific factors were adjusted for, similar results were obtained (Table 2).

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate the influence of AE on OS in advanced cancer patients in a palliative care

TABLE 1 Unadjusted and adjusted HRs for overall survival stratified by genders and pretreatment emotional status in cohort 1 (N = 377)

	Unadjusted			Adjusted[a]		
Genders + PES	HR	95% CI	P	HR	95% CI	P
NAE (n = 283)	Reference	–		Reference		
AE (n = 94)	1.185	0.911-1.541	.204	1.194	0.912-1.564	.197
Male + NAE (n = 162)	Reference			Reference		
Male + AE (n = 47)	1.542	1.077-2.208	.017	1.811	1.229-2.668	.003
Female + NAE (n = 121)	Reference			Reference		
Female + AE (n = 47)	0.906	0.615-1.335	.617	0.735	0.483-1.118	.150

HR, hazard ratio; CI, confidence interval; AE, anxious emotion; NAE, nonanxious emotion; PES, pretreatment emotional status.

[a]Cox regression model controlling for age, marital status, educational level, tumor stage, primary tumor site, family history, smoke history, nutrient status, concomitant disease, and hospital stay.

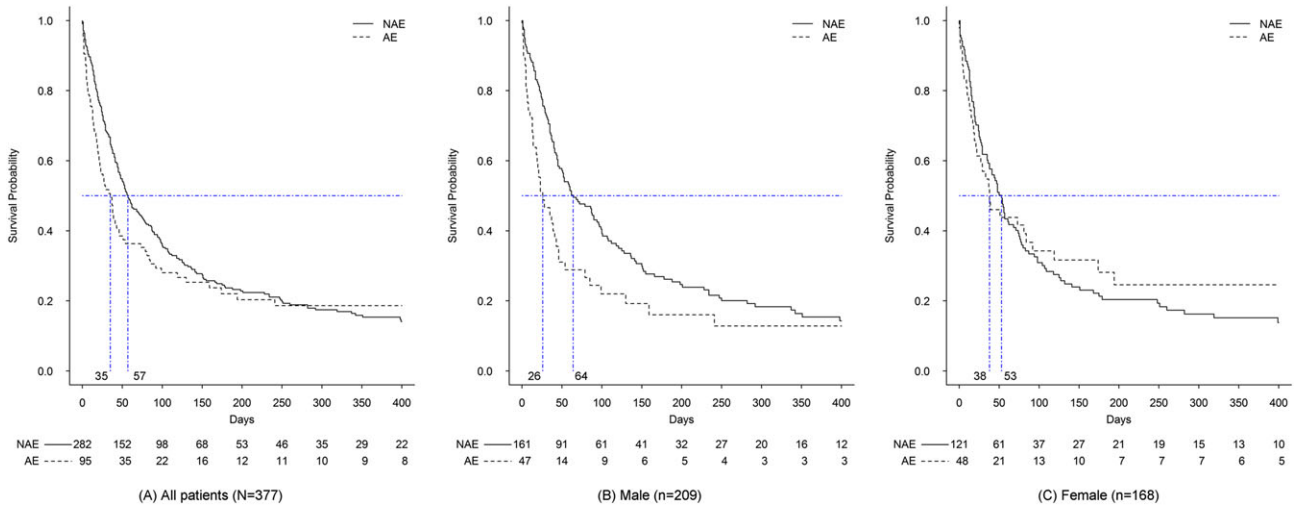

FIGURE 1 Overall survival of patients with palliative care stratified by genders and pretreatment psychological status in cohort 1. AE, anxious emotion; NAE, nonanxious emotion

TABLE 2 Unadjusted and adjusted HRs for overall survival stratified by genders and changes in emotional status in cohort 2 (N = 106)

	Unadjusted			Adjusted[a]		
Genders + ESC	HR	95% CI	*P*	HR	95% CI	*P*
All patients						
NAE → NAE	Reference			Reference		
AE → AE	1.027	0.371-2.842	.958	1.309	0.422-4.063	.641
AE → NAE	0.952	0.434-2.088	.902	0.890	0.378-2.045	.783
NAE → AE	4.837	2.502-9.352	<.001	5.568	2.680-11.57	<.001
Male						
NAE → NAE	Reference			Reference		
AE → AE	0.688	0.163-2.905	.611	1.350	0.191-9.563	.764
AE → NAE	3.331	1.133-9.796	.029	6.083	1.574-23.51	.009
NAE → AE	7.827	2.753-22.258	<.001	5.104	1.611-16.17	.006
Female						
NAE → NAE	Reference			Reference		
AE → AE	1.259	0.290-5.476	.759	2.589	0.491-13.66	.262
AE → NAE	0.566	0.170-1.882	.353	0.646	0.163-2.564	.535
NAE → AE	3.621	1.477-8.878	.005	5.820	1.749-19.36	.004

HR, hazard ratio; CI, confidence interval; AE, anxious emotion; NAE, nonanxious emotion; ESC, emotional status changes.

[a]Cox regression model controlling for age, marital status, educational level, tumor stage, primary tumor site, family history, smoke history, nutrient status, concomitant disease, and hospital stay.

setting. In cohort 1, significant association between baseline AE and OS was not found in the whole sample or in women. However, men with AE were found to have a significantly shorter survival time than men without AE, after controlling for sociodemographic and disease-related features. In addition, patients with newly developed AE showed a poor OS in all readmitted patients, both men and women. These results suggest that AE, especially dynamic changes in AE, may serve as independent prognostic indicators of OS. Anxious emotion needs to be monitored and taken into account when making survival prediction or clinical decisions in advanced cancer patients during tumor follow-up.

The psychological health of cancer patients is poorly studied worldwide, especially in China. For one, clinicians, patients, and families usually pay more attention to physical diseases than psychological diseases. Additionally, few domestic cancer hospitals have psychological wards. Thus, psychological care for cancer patients is widely misunderstood, underdiagnosed, undertreated, and considered a complex medical task. As a treatable problem in cancer patients, AE deserves greater attention.

Negative emotions have been reported to increase the risk of mortality after organ transplantation, heart failure, and clinical recurrence of inflammatory bowel disease.[2,17,18] However, studies on the relationship between AE and OS in cancer patients are still limited, especially in mixed advanced cancer patients. In our study, we found that 24.93% of the advanced cancer patients suffered from AE, a figure consistent with previous studies, which reported that

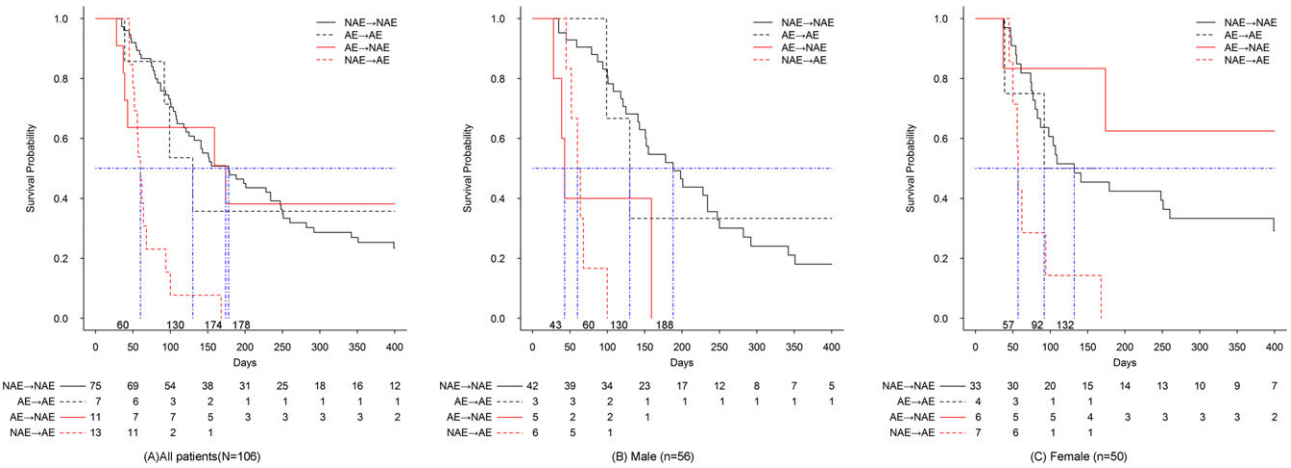

FIGURE 2 Overall survival of patients with palliative care stratified by genders and changes in psychological status in cohort 2. AE, anxious emotion; NAE, nonanxious emotion

approximately 7.6 to 44% of cancer patients experienced anxiety disorder.[19,20] The only important factor associated with AE among advanced cancer patients in the present study was nutritional status. Patients with an abnormal nutritional status were more likely to experience AE than patients with a normal nutritional status (P = .030), which was also consistent with previous findings.[21] The inconsistencies were that female patients, young patients, single patients, and those with more advanced disease, concomitant disease, or a specific type of cancer such as head and neck cancer or thoracic cancer were reported to be significantly predisposed to psychological disorders in previous studies,[22–26] while our results suggested that patients with these clinical features might be vulnerable to AE, but the differences were not significant (P > .05). Although AE has been studied as a factor with a possibly unfavorable effect on cancer progression in some studies,[10] a significant association between AE and survival was not found in the overall sample in our study. However, men with AE had a significantly increased rate of mortality compared with men without AE after stratification by gender (P = .003). The association between AE and OS was also not observed in women. Studies on the gender differences in the association between AE and OS are mainly lacking, although it is known that the prevalence of anxiety is higher in female cancer patients than in male cancer patients.[22] These differences should, however, be considered with caution, as the evidence for gender-specific effects of anxiety is scarce and the findings on cancer mortality and anxiety are inconsistent [9,10]. More in-depth studies should be conducted to enable a better understanding of the effects of gender.

Another strength of our study is the inclusion of dynamic changes in emotional assessment because people's emotions will probably change throughout the cancer trajectory, as supported by the literature.[27] Thus, the use of baseline or cross-sectional assessment of emotional variables may present a flaw in the study design. Our study found that patients with newly developed AE had significantly shorter survival times than patients with stable emotions (i.e., NAE → NAE) in all readmitted patients, in men and in women (P < .001). Our analyses using baseline emotional assessments resulted in partially different findings from the analyses that include the dynamic changes in emotions, reinforcing the importance of considering emotional changes over time. Some previous studies did not find a significant association between psychological disorders and survival which may have been due to a neglect of gender differences or dynamic changes in emotions. These results may support the value of a more detailed assessment of psychological disorders in patients with advanced cancer. Our study suggests that dynamic changes in AE need to be monitored and targeted for intervention in future studies to clarify the role of psychosocial influences on survival in cancer patients.

The mechanisms between AE and poor patient outcomes have been increasingly investigated. However, there is no general agreement on the contributing biological or psychosocial basis of AE. Possible explanations for the associations have been suggested, including a direct effect on neuro-endocrinological and/or immunologic systems or an indirect effect via changes in behavior. Potential physiological pathways have been shown to contribute to the crosstalk between AE and the development, progression, and control of cancer, including the sympathetic nervous system, hypothalamic pituitary adrenal axis, stress hormones, cellular immunity, inflammation, angiogenesis, invasion, anoikis, and changes in gene expression, as well as telomere length and telomerase activity, which could interact with the tumor microenvironment to promote factors favoring tumor growth.[28–30] The most likely biobehavioral mechanisms underlying the relationship between AE and survival include poor adherence to anticancer treatment, fewer social networks, and disruptions of circadian rhythms such as sleep/activity.[31] In addition, AE may reflect a poor clinical state, which would be associated with an increased mortality in cancer patients. These factors together may lead to accelerate cancer progression.

Several limitations should be noted. First, the data were retrospectively collected at a single tertiary care center, which may limit the external validity of the findings. Second, as the AE in our study was assessed by evaluation interviews that lacked a diagnostic

rating scale, the validity of our findings regarding the association between AE and survival may be limited. Thus, further studies on the issue may be recommended to provide conclusive outcomes.

In conclusion, our study is the first to date in which baseline AE and dynamic changes in AE were found to be predictors of OS in advanced cancer patients in the specific research area of psycho-oncology. Dynamic assessments and interventions targeting these noninvasive and easily evaluated parameters in advanced cancer patients should be recommended as an essential part of cancer care with the potential to improve not only psychological well-being and quality of life but also clinical outcomes.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to 1 or more of the following: the study conception and design (WZ and WC), acquisition of data or analysis (WZ, ZW, HJ, MC, XG, ML, ZZ, and HW), and interpretation of data (WZ, ZW, HJ, JC, and PW). WZ and ZW drafted the article, and the other authors contributed to revising the article critically for important intellectual content. All authors provided their final approval of the version to be published. PW and WC are the guarantors of this work and responsible for the integrity of the work.

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SUPPORTING INFORMATION

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