

Use of Antidepressant Medications Moderates the Relationship Between Depressive Symptoms and Hospital Length of Stay in Patients with Advanced Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article

Key Words. Depression • Antidepressive agents • Cancer • Hospitalization • Length of stay

ABSTRACT

Background. Among patients with cancer, depressive symptoms are associated with worse clinical outcomes, including greater health care utilization. As use of antidepressant medications can improve depressive symptoms, we sought to examine relationships among depressive symptoms, antidepressant medications, and hospital length of stay (LOS) in patients with advanced cancer.

Materials and Methods. From September 2014 to May 2016, we prospectively enrolled patients with advanced cancer who had an unplanned hospitalization. We performed chart review to obtain information regarding documented depressive symptoms in the 3 months prior to admission and use of antidepressant medications at the time of admission. We compared differences in hospital LOS by presence or absence of depressive symptoms and used adjusted linear regression to examine if antidepressant medications moderated these outcomes.

Results. Of 1,036 patients, 126 (12.2%) had depressive symptoms documented prior to admission, and 288 (27.8%) were taking antidepressant medications at the time of admission. Patients with depressive symptoms experienced longer hospital LOS (7.25 vs. 6.13 days; $p = .036$). Use of antidepressant medications moderated this relationship; among patients not on antidepressant medications, depressive symptoms were associated with longer hospital LOS (7.88 vs. 6.11 days; $p = .025$), but among those on antidepressant medications, depressive symptoms were not associated with hospital LOS (6.57 vs. 6.17 days; $p = .578$).

Conclusion. Documented depressive symptoms prior to hospital admission were associated with longer hospital LOS. This effect was restricted to patients not on antidepressant medications. Future studies are needed to investigate if use of antidepressant medications decreases LOS for patients hospitalized with advanced cancer and the mechanisms by which this may occur. *The Oncologist* 2019;24:117–124

Implications for Practice: This study investigated the prevalence of documented depressive symptoms in patients with advanced cancer in the 3 months prior to an unplanned hospitalization and the prevalence of use of antidepressant medications at time of hospital admission. The relationship of these variables with hospital length of stay was also examined, and it was found that documented depressive symptoms were associated with prolonged hospital length of stay. Interestingly, antidepressant medications moderated the relationship between depressive symptoms and hospital length of stay. These findings support the need to recognize and address depressive symptoms among patients with advanced cancer, with potential implications for optimizing health care utilization.

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INTRODUCTION

Patients with cancer often experience depressive symptoms, which influences their treatment outcomes and quality of life [1–18]. Studies suggest that approximately 10%–25% of patients with cancer experience depressive symptoms, which can be unrecognized and undertreated because of the overlap of patients' symptoms related to their underlying illness, side effects of cancer therapies, and pre-existing mood disorders [19–24]. Notably, research has demonstrated that patients with cancer and depressive symptoms may receive less guideline-concordant cancer treatment and more aggressive care near the end of life and that they often experience inferior survival compared with patients without depressive symptoms [8–18]. Moreover, studies have linked depressive symptoms to poor physical and psychological well-being as well as diminished quality of life among patients with cancer [1–7]. Thus, there is a pressing need to understand better the relationship between patients' depressive symptoms and their clinical outcomes.

Recently, research has demonstrated that depressive symptoms are associated with greater health care utilization in patients with cancer, particularly longer hospital length of stay (LOS) [25–27]. However, although therapies are available to help address depressive symptoms in patients with cancer, prior studies have not investigated the potential impact of such therapies on the use of health care services. Clinicians frequently use antidepressant medications to treat depressive symptoms among patients with cancer, and studies have shown that the use of antidepressant medications can help decrease psychological distress in this population [21, 22, 28, 29]. In addition, research has demonstrated that proactive use of antidepressant medications for patients with cancer may help prevent the development of depressive symptoms [30–32]. However, further research is needed to clarify relationships among depressive symptoms, use of antidepressant medications, and health care utilization in patients with cancer. Specifically, as patients with cancer often prefer to avoid time in the hospital [33, 34], efforts to understand the effects of addressing patients' depressive symptoms on their hospital LOS are critically important.

In this study, we sought to evaluate associations among depressive symptoms, use of antidepressant medications, and hospital LOS in hospitalized patients with advanced cancer. In addition, we explored whether the use of antidepressant medications moderated the relationship between patients' depressive symptoms and their hospital LOS. We hypothesized that patients with documented depressive symptoms prior to hospital admission would have a longer hospital LOS than patients without depressive symptoms. We further hypothesized that the use of antidepressant medications would moderate this relationship, such that the association between depressive symptoms and hospital LOS would be stronger in those not treated with antidepressant medications. By studying the relationships among depressive symptoms, use of antidepressant medications, and hospital LOS in patients with cancer, we hope to provide evidence supporting the importance of recognizing and addressing depressive symptoms in this population.

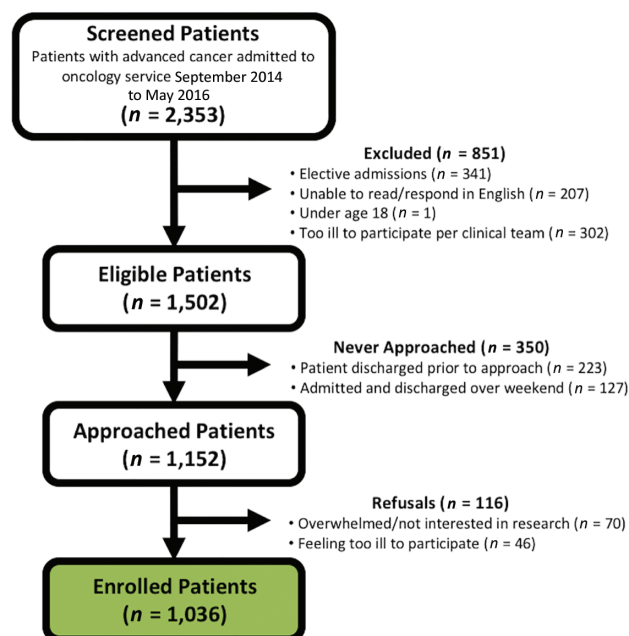


Figure 1. CONSORT diagram.

MATERIALS AND METHODS

Study Procedures

We prospectively enrolled patients with advanced cancer who had an unplanned hospital admission to the oncology service at Massachusetts General Hospital from September 2, 2014, to May 6, 2016, as part of a parent longitudinal cohort study, which was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. We screened the daily inpatient oncology census to identify eligible patients whom we consecutively enrolled (Fig. 1). On the first weekday after admission (within 2–5 days of hospitalization), we obtained written, informed consent from potential participants. Each participant contributed one unique hospitalization, and for the purposes of this study, we did not include repeat hospitalizations that occurred during the study period.

Participants

Eligible patients were 18 years of age or older and had a known diagnosis of advanced cancer prior to admission, which we defined as a cancer not being treated with curative intent. For patients receiving chemotherapy, we identified those not being treated with curative intent based on the chemotherapy order entry treatment intent designation (palliative vs. curative). For patients not receiving chemotherapy, we identified those not being treated with curative intent based on documentation in the oncology clinic notes. We excluded patients with elective or planned hospital admissions, defined as hospitalizations for chemotherapy administration, chemotherapy desensitization, or scheduled procedures. We also excluded patients with leukemia and those who were admitted for stem cell

transplantation. Finally, we only included study participants who could read and respond to study questionnaires in English.

Study Measures

Hospital Length of Stay

We defined hospital LOS as the number of days from hospital admission to hospital discharge.

Depressive Symptoms and Antidepressant Medications

We used the electronic health record (EHR) to assess for documentation of active depressive symptoms in the 3-month period prior to hospital admission. We searched for the terms “depression,” “depressed,” “depressive,” “MDD,” “dysthymia,” “dysthymic,” “dysphoric,” and “mood dysregulation” in participants’ charts and extracted all excerpts containing these terms from outpatient oncology, primary care, palliative care, and psychiatry clinic notes in the 3 months prior to hospital admission. Three physician coders reviewed these excerpts using a two-stage process to reach consensus on whether patients had active depressive symptoms assessed at the time of the visit as described by the documentation. In the first stage, each coder independently reviewed each excerpt to determine whether it described active depressive symptoms, excluding descriptions of prior depressive symptoms that had occurred in the past but had since resolved. In the second stage, all coders together reviewed any discordantly coded excerpts from the first stage to reach final consensus.

In addition, we reviewed participants’ hospital admission notes to determine if their medication lists included one or more antidepressant medications. We defined antidepressant medications using the World Health Organization Anatomical Therapeutic Chemical classification system codes N06A and N06CA (supplemental online Appendix A). For the purposes of this study, we refer to patients having “depressive symptoms” as those who had documented active depressive symptoms in the outpatient setting in the 3 months prior to hospital admission. We refer to patients taking “antidepressant medications” as those who had one or more antidepressant medications on their medication list at the time of hospital admission.

Sociodemographic and Clinical Factors

We reviewed the demographics section of the EHR to obtain participants’ date of birth, sex, race, relationship status, education, and religion. We also reviewed participants’ outpatient oncology clinic notes to determine cancer type, date of advanced cancer diagnosis, and Charlson Comorbidity Index score.

Statistical Analysis

We used descriptive statistics to evaluate frequencies, means, and standard deviations (SD) of study variables. We assessed differences by depressive symptoms and use of antidepressant medications in sociodemographic and clinical factors using χ^2 tests for categorical variables and

independent sample Student’s *t* tests for continuous variables. We used Student’s *t* test to compare hospital LOS between those with and without depressive symptoms. To determine if use of antidepressant medications moderated the relationship between depressive symptoms and hospital LOS, we computed an interaction term between presence of depressive symptoms and use of antidepressant medications. We then included this interaction term along with both of its components in a linear regression model with hospital LOS as the outcome. The interaction term had a *p* value of $< .15$ in this model, indicating a potential moderation effect worth exploring through subsequent subgroup analyses [35, 36]. We then performed subgroup analyses for participants with and without use of antidepressant medications, conducting linear regression models within each subgroup adjusted for potential confounders including age, sex, marital status, education level, comorbidities (Charlson Comorbidity Index), time since advanced cancer diagnosis, and cancer type [23–25, 37–43]. All reported *p* values are two-sided, with $p < .05$ considered statistically significant. We used SPSS version 22.0 (IBM, Armonk, NY) for statistical analysis.

RESULTS

Of 1,152 patients approached, we enrolled 1,036 (89.9% of approached; Fig. 1). Participants had a mean (SD) age of 63.86 (12.84) years, and approximately half were female (49.4%; Table 1). Mean (SD) Charlson Comorbidity Index score was 0.89 (1.29). The most common cancer types were advanced gastrointestinal (32.0%), lung (18.3%), and genitourinary (10.9%) malignancies, with a mean (SD) time since diagnosis of 16.76 (23.74) months. Mean (SD) hospital LOS was 6.26 (4.82) days. The median hospital LOS was 5.0 (range, 1–34) days.

Overall, 126 patients (12.2%) had documented depressive symptoms in the 3 months prior to admission, and 288 (27.8%) had antidepressant medications on their medication list at the time of admission. Patients with documented depressive symptoms were more likely to be on antidepressant medications compared with those who did not have documented depressive symptoms ($n = 61/126$, 48.4% vs. $n = 227/910$, 24.9%; $p < .001$; Fig. 2). We found no significant differences in patient characteristics between those with and without documented depressive symptoms (supplemental online Appendix B). However, compared with those not taking antidepressant medications, patients taking antidepressant medications were younger (mean [SD], 62.43 [12.76] vs. 64.41 [12.84] years; $p = .026$) and more likely to be female ($n = 159/288$, 55.2% vs. $n = 353/748$, 47.2%; $p = .021$; supplemental online Appendix C). Patients with depressive symptoms and patients using antidepressant medications were more likely to receive palliative care consultation during their hospital stay ($n = 65/126$, 51.6% vs. $n = 276/910$, 30.3%; $p < .001$; $n = 117/288$, 40.6% vs. $n = 224/748$, 29.9%; $p = .001$). Patients with depressive symptoms experienced longer hospital LOS than those without depressive symptoms (mean [SD], 7.25 [5.69] vs. 6.13 [4.67] days; $p = .036$). This finding remained significant in a

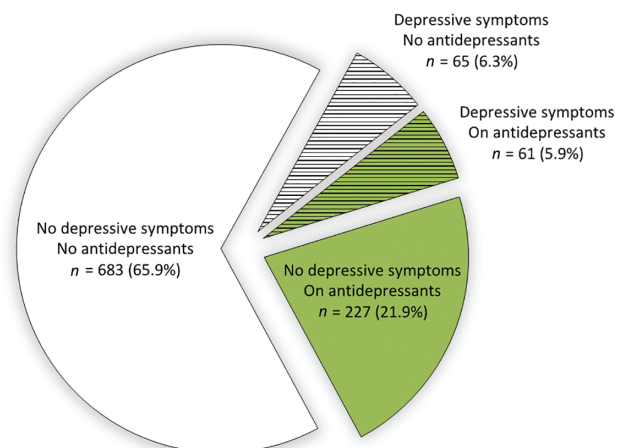
Table 1. Patient characteristics

Characteristics	All patients (<i>n</i> = 1,036), <i>n</i> (%)
Age in years mean (SD)	63.86 (12.84)
Sex	
Female	512 (49.4)
Male	524 (50.6)
Race	
White	957 (92.4)
African American	35 (3.4)
Asian	21 (2.0)
Hispanic	21 (2.0)
Other	2 (0.2)
Relationship status	
Married	686 (66.2)
Single	154 (14.9)
Divorced	115 (11.1)
Widowed	81 (7.8)
Education	
High school and below	326 (31.5)
Beyond high school	625 (60.3)
Missing	85 (8.2)
Religion	
Catholic	515 (49.7)
Christian, non-Catholic	322 (31.1)
None	130 (12.5)
Other	69 (6.7)
Charlson Comorbidity Index, mean (SD)	0.89 (1.29)
Cancer type	
Gastrointestinal	332 (32.0)
Lung	190 (18.3)
Genitourinary	113 (10.9)
Melanoma	90 (8.7)
Breast	75 (7.2)
Lymphoma	64 (6.2)
Head and neck	56 (5.4)
Gynecologic	52 (5.0)
Sarcoma	50 (4.8)
Cancer of unknown primary	14 (1.4)

Abbreviation: SD, standard deviation.

linear regression model adjusted for age, sex, marital status, education level, comorbidities, time since advanced cancer diagnosis, and cancer type (unstandardized coefficient [B], 1.16; standard error [SE], 0.47; 95% confidence interval [CI], 0.24–2.09; $p = .014$).

Using linear regression, we found that use of antidepressant medications moderated the association between depressive symptoms and hospital LOS (depressive symptoms \times antidepressant medications, B, -1.36 ; SE, 0.93 ; 95% CI, -3.19 – 0.47 ; $p = .146$), thus prompting further analysis of the association between depressive symptoms and hospital LOS within subgroups based on presence or absence

**Figure 2.** Percentage of patients with depressive symptoms and/or taking antidepressant medications.

of antidepressant medications. In subgroup analyses, among patients not on antidepressant medications, depressive symptoms were associated with longer hospital LOS (mean [SD], 7.88 [6.05] vs. 6.11 [4.56] days; $p = .025$). However, among those using antidepressant medications, depressive symptoms were not associated with hospital LOS (mean [SD], 6.57 [5.23] vs. 6.17 [5.01] days; $p = .578$; Fig. 3). We found similar results in linear regression models adjusted for age, sex, marital status, education level, comorbidities, time since advanced cancer diagnosis, and cancer type. In these models, depressive symptoms were an independent predictor of longer hospital LOS for patients not on antidepressant medications (B, 1.71; SE, 0.63; 95% CI, 0.47–2.95; $p = .007$), but this association was not significant for patients with depressive symptoms who were using antidepressant medications (B, 0.57; SE, 0.76; 95% CI, -0.92 – 2.07 ; $p = .453$).

DISCUSSION

In this study, over one tenth of hospitalized patients with advanced cancer had active depressive symptoms documented in the EHR in the 3 months prior to admission, and more than one quarter had antidepressant medications on their medication list at the time of hospital admission. Notably, we found that patients with depressive symptoms experienced longer hospital LOS, yet the use of antidepressant medications moderated this relationship. Specifically, among patients not taking antidepressant medications, average hospital LOS was over 1 day longer for those with documented depressive symptoms, a clinically meaningful finding as patients with cancer prefer to spend fewer days in the hospital [33, 34]. However, among patients taking antidepressant medications, hospital LOS did not differ between those with and without depressive symptoms. Collectively, these data support the association between untreated depressive symptoms and poor outcomes in patients with cancer.

To our knowledge, this is the first study to observe that depressive symptoms documented in the medical record are

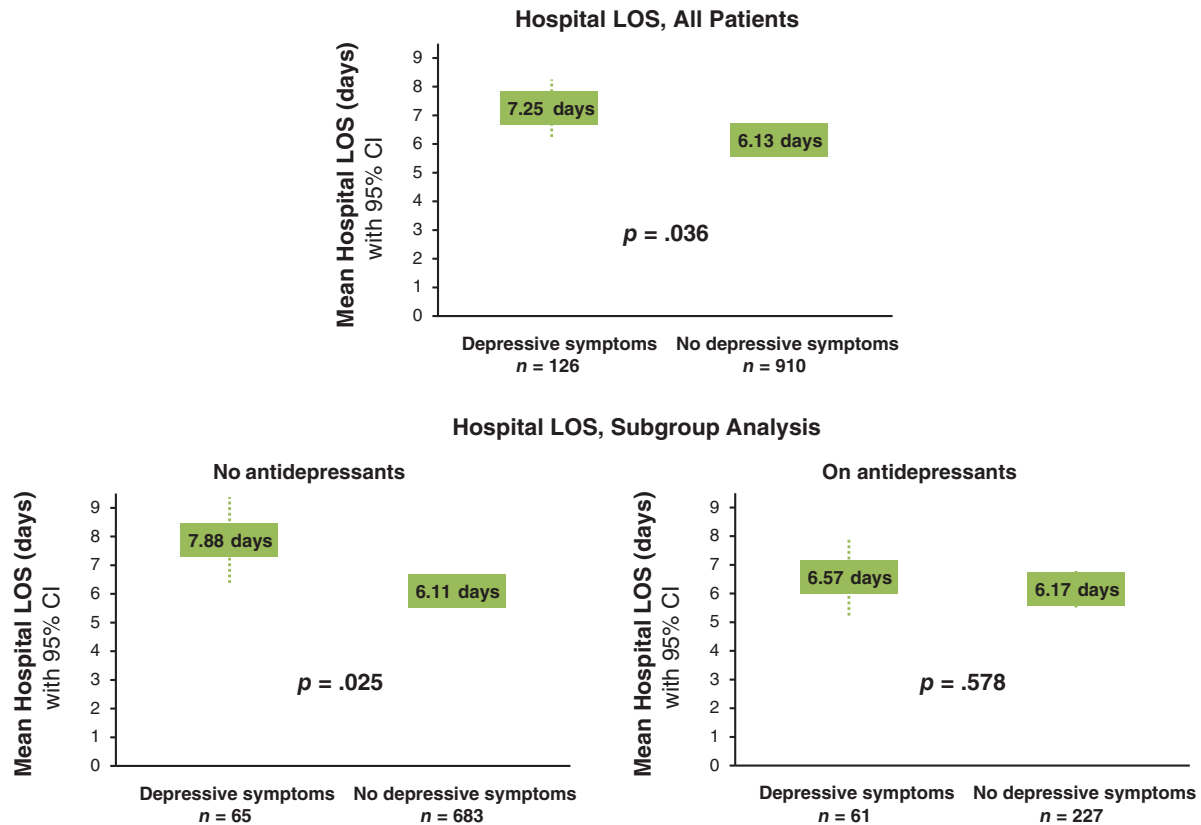


Figure 3. Hospital length of stay by depressive symptoms, with subgroup analysis by use of antidepressant medications. Abbreviations: CI, confidence interval; LOS, length of stay.

associated with longer hospital LOS in patients with advanced cancer. Prior studies in the general medicine literature and among patients with cardiovascular and pulmonary disease have shown associations between psychological distress and increased use of health care services [44–48], yet relatively few studies from the oncology setting have linked depression with increased health care utilization [25–27]. Explanations for the association between depressive symptoms and prolonged hospital LOS include the potential effects of patients' psychological symptoms on their treatment adherence, health-seeking behaviors, and physical symptoms such as pain or fatigue [49–51]. Prior data suggest that patients with cancer wish to avoid time in the hospital [33, 34]; therefore, in order to enhance care delivery and outcomes for these patients, additional work is needed to further clarify potential mechanisms linking depressive symptoms and hospital LOS among patients with advanced cancer.

Additionally, we demonstrated novel findings that use of antidepressant medications moderated the relationship between patients' depressive symptoms and hospital LOS. Specifically, we showed that patients' depressive symptoms were associated with longer hospital LOS among those not receiving antidepressant medications, whereas we found no relationship between depressive symptoms and hospital LOS among those receiving antidepressant medications. Clinically, this supports the need to address patients' depressive symptoms in order to mitigate downstream effects, including those linked to health care utilization and hospital LOS.

Notably, patients' median hospital LOS in our study was 5 days, which is slightly longer than prior studies that have reported a median hospital LOS ranging from 3 to 4 days in hospitalized patients with cancer [52, 53]. This is potentially related to the fact that our study focused on patients with advanced cancer and further highlights the need to investigate ways to decrease health care utilization in this population. Thus, although additional prospective research is essential to confirm our findings, these results provide evidence supporting the need to identify and treat depressive symptoms among patients with advanced cancer.

Notably, over 12% of patients in our study had documented depressive symptoms in the 3 months prior to hospital admission, and over 27% had one or more antidepressant medications on their home medication list at time of admission. Although these findings corroborate much prior oncologic literature [19–24, 54–56], to our knowledge, this study is the first to describe rates of both depressive symptoms and use of antidepressant medications in such a large population of hospitalized patients with advanced cancer. The large discrepancy between rates of documented depressive symptoms and of use of antidepressant medications in our sample aligns with prior literature, which has demonstrated that most adults who screen positive for depression are not receiving treatment for depression, and conversely, most who receive depression treatment do not necessarily screen positive for depressive symptoms [57]. Difficulties assessing depressive symptoms among patients with cancer could also

contribute to this discrepancy, as oncology clinicians may struggle to distinguish between pathological mood symptoms and normal reactions to severe illness [24, 28, 29, 58]. Despite these challenges, our study suggests that active depressive symptoms documented by outpatient clinicians can help identify a high-risk group of patients with advanced cancer. Future work should focus on enhancing clinicians' ability to assess and treat depressive symptoms in patients with cancer [21, 22, 28, 29].

Several limitations of this study warrant discussion. First, we enrolled participants able to provide informed consent in English receiving outpatient oncology care from a single tertiary care site with limited socioeconomic or racial/ethnic diversity, limiting the generalizability of our results. Second, we relied on chart review for documentation of depressive symptoms and use of antidepressant medications. Future work should incorporate a standardized clinical interview of all participants, as this could provide important information about patients' depressive symptoms and their treatment. For documented depressive symptoms, we lacked information on their duration and severity and could not differentiate between those attributable to a major depressive disorder versus those attributable to other conditions such as complicated grief and/or an adjustment disorder with depressed mood. For antidepressant medications, we lacked data regarding their date of initiation, patient adherence, and whether they had been prescribed for indications other than depressive symptoms such as anxiety, neuropathic pain, or hot flashes. We did not factor into our analyses which specific antidepressant medications were prescribed, doses of antidepressant medications, or whether patients were taking a combination of antidepressant and antipsychotic medications. Moreover, we lacked data on nonpharmacologic treatment for patients' depressive symptoms. Finally, differences in illness severity, unmeasured comorbid conditions (e.g., anxiety or other symptoms), and other factors could have confounded the relationship among depressive symptoms, use of antidepressant medications, and hospital LOS. Furthermore, it is possible that clinicians may not prescribe antidepressant medications as readily for patients with shorter life expectancy because of the delayed onset of benefit and possibility of side effects. Thus, we cannot comment on causality or determine the actual mechanisms of the associations we found among depressive symptoms, use of antidepressant medications, and longer hospital LOS. Future efforts would ideally incorporate prospective collection of validated measures of depressive symptoms and current antidepressant use to identify associations with subsequent health care utilization.

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CONCLUSION

We found that a substantial proportion of hospitalized patients with advanced cancer have documented depressive symptoms and are prescribed antidepressant medications. We demonstrated that patients with documented depressive symptoms experience a longer hospital LOS compared with those without documented depressive symptoms, and we observed an important new finding that the use of antidepressant medications moderates the relationship between depressive symptoms and prolonged hospitalizations. These findings provide additional evidence supporting the need to recognize and address depressive symptoms among patients with advanced cancer.

ACKNOWLEDGMENTS

This study was funded by NCI K24 Award CA181253 (J.S. Temel), Massachusetts General Hospital Cancer Center Funds (J.S. Temel), and the Scullen Center for Cancer Data Analysis (E.P. Hochberg).

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DISCLOSURES

The authors indicated no financial relationships.

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For Further Reading:

Ryan D. Nipp, Georg Fuchs, Areej El-Jawahri et al. Sarcopenia Is Associated with Quality of Life and Depression in Patients with Advanced Cancer. *The Oncologist* 2018;23:97–104.

Implications for Practice:

This study found that sarcopenia, assessed using computed tomography scans acquired as part of routine clinical care, is highly prevalent in patients with newly diagnosed, incurable cancer. Notably, patients with sarcopenia reported worse quality of life and greater depression symptoms than those without sarcopenia. These findings highlight the importance of addressing muscle loss early in the course of illness among patients with incurable cancer. In the future, investigators should expand upon these findings to develop strategies for assessing and treating sarcopenia while striving to enhance the quality of life and mood outcomes of patients with advanced cancer.