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PREVALENCE AND RISK FACTORS OF CLINICALLY SIGNIFICANT DEPRESSION IN CANCER PATIENTS USING THE PHQ-9 AND ESAS-R SCALES: PATIENT-REPORTED OUTCOMES

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Abstract

Background: Depression is a common comorbidity among cancer patients. However, reported prevalence of depression in cancer patients varies widely across studies.The present studyassessed the prevalence and associated factors of clinically significant depression among cancer by using thePHQ-9 and ESAS-r instruments.

Methods: A cross-sectional study was conducted among a convenient sample of cancer patients in a tertiary care cancer center in Riyadh, Saudi Arabia. Depression was assessed using PHQ-9 and ESAS instruments. The prevalence of depression was

assessed by PHQ-9 and ESAS instruments, and then compared in terms of diagnostic accuracy. Risk factors of depression were identified using logistic regression.

Results: A total 301 cancer patients were included in the study. The majority ofparticipants were females 217(72.1%)and with solid tumors 262(87%). The prevalence of clinically significant depression assessed by PHQ-9 and ESAS-r was 35.2% and 27.9%, respectively. In the multivariate regression analysis, Rural residence (OR 3.03; 95% CI 1.37–6.69), Tiredness (OR 1.22; 95% CI 1.04–1.43) Drowsiness (OR 1.22; 95% CI 1.07–1.38), Loss of appetite (OR 1.29; 95% CI 1.13–1.47), anxiety (OR 1.22; 95% CI 1.08–1.39), wellbeing (OR 1.21; 95% CI 1.04–1.41) were identified as a predictors of clinically significant depression. The inter-rate accuracy ofthePHQ-9 andESAS-r showed a significant moderate agreement (κ = 0.480, $p < 0.001$).

Conclusion: The present study finding demonstrate a high prevalence of clinically significant. This warrants the need for a well-structured screening and treatment approachto improve patients' mental wellbeing

Keywords: Cancer, Depression, PHQ-9, ESAS-r, Prevalence, Saudi Arabia

Introduction

Cancers are one of the most challenging diseases for health systems worldwide. Cancer is considered as a serious and life-threatening disease, which has an adverse sequel on the psychological and physiological well-being of patients**[1-3]**. Depression is a common psychological condition observed in cancer patientsdue to cancer disease and treatment, along with other somatic symptoms like pain, nausea/vomiting, anorexia, diarrhea, infertility, cognitive deficits, sleeping disorders, and fatigue**[4]**.

Meta-analyses studies reporteda pooled prevalence of depression in cancer patients between 8% and 25%**[5,6]**.The varied range in the prevalence could be contributed to the difference in the population involved, screening tools used, malignancy type, and disease stage**[5]**.Sometimes depression after cancer diagnosis is adaptive, however, persistent and untreated depression may lead to higher mortality, difficulty in symptoms control, andimpaired health-related quality of life and poor compliance with cancer treatment**[7-10]**.Besides, cancer patients suffering depression may experience hopelessness, worthlessness, and powerless**[10]**.

Depression in cancer patients is often underdiagnosed and undertreated.This could be due to the perception that it is usual or normal for a cancer patient to be depressed, on the other hand, medical staff might confuse depression symptoms with the neurovegetative signs of cancer such as fatigue, sleep disturbance and loss of appetite**[5]**. Nonetheless, clinical advances have been introduced in terms of depression screening systems; improved oncologists communication skills in discussing psychological problems with cancer patients, and effective interventions designed specifically for treatment of depression**[11-14]**. Moreover, accumulating evidence suggested that diagnosis and treatment of depression among cancer patients may reduce disease progression, improves survival rates, reduce in medical costs and improves patients' quality of life**[9]**.

Estimation of disease prevalence have important implications for understanding disease burden and management, making decisions about health care resource utilization, and even in interpreting medical research**[15]**.For these reasons, the American Society of Clinical Oncology (ASCO) recommended that cancer patients should be screened for symptoms of depression throughout the course of

care**[8]**.Although the gold standard and valid approach for depression diagnosis is through interviews conducted by psychologists or psychiatrists, however, this approach is fairlychallenging and time consumingin the clinical settings**[16]**. In clinical practice, using a well-established and validated, self-report instruments in clinical settings becomes widely spread to detect depression disease and severity**[17]**. The advantages of self-report instruments are easy to administer, more practical in settings with limited resources, and inexpensive**[18]**.

The ASCO recommended the depression module of the 9-item Patient Health Questionnaire (PHQ-9) for screening the symptoms of depression throughout the trajectory of cancer treatment**[19]**. However, the revisedEdmonton Symptom Assessment System (ESAS-r) is a multidimensional, psychometrically validated tool developed to multiple symptoms**[20]**, and has been used in the clinical settings of our study site. However, depression component particularly of the ESAS-r have not been tested for inter-rater reliability against gold standard in Arabic settings, which might inflate or deflate the burden of depression. Therefore, addressing a concise prevalence and severity of depression among cancer patients and finding the predictors is vital. This study is one of few studies done in Saudi Arabia to find the overall prevalence of depression in cancer patients, with inclusion of adults inpatient and outpatient from different specialities including hematology, oncology radiation oncology, and palliative care patients, regardless of the treatment types/cycles.

Our main objective was to assess the prevalence and associated factors of depression among cancer by using thePHQ-9 and ESAS instruments, with focus on clinically significant depression that might be associated with disability or need additional examination, referral, and management**[1]**. Our secondary objective was to assess the

inter-rater reliability of PHQ against the ESAS to measure the screening performance of depression and degree of agreement between PHQ-9 and ESAS-r instruments.

Materials and Methods

Study Design and Sample

A cross-sectional study was conducted between August 2018 and May 2019 at the comprehensive cancer center of King Fahad Medical City, Saudi Arabia. A convenience sample of participants was recruited from the hematology, oncology, radiation oncology and palliative care departments. Inclusion criteria were: (i) have a confirmed pathological cancer diagnosis, (ii) aged ≥18 years, (iii) provide informed consent, (iv) able to communicate and cooperate with study team. Patients with psychiatric or cognitive disorders, acute or unstable medical condition, and with hearing or visual impairments were excluded from the study.

Measures

Data were collected through face to face interviews and medical chart review using a valid and reliable structured survey by trained research assistants. The survey composed of three sections.The first sectioninvolved thedemographic and clinical data which consisted of questions including: age, gender, marital status, education level, place of residency, type of cancer, disease stage (hematology patients were graded into 4 grades: low,intermediate,intermediate-high and high risks and then included in the 4 stages), and palliative performance scale (PPS) [**21**]. The PPS scores were collected from each patient and graded by the researchers to grade the functional ability of patients. The second section involved a previously validated assessment instrument, the Patient Health Questionnaire (PHQ)-9 [**22**]. The PHQ-9 is a 9-question instrument to screen the presence and severity of depressive symptomatology, and was test among cancer population [**23,24**]. The PHQ-9

instrument ask the patients about the degree of applicability of each question, using a 4-point Likert scale. Patients' responses ranged from 0 to 3 [min-max: 0-27], where 0 means "Not at all" and 3 means "Nearly every day." A total score of (0–4) indicates minimal depression, (5-9) mild depression, (10-14) moderate depression, (15-19) moderately severe depression, and (20-27) severe depression. The third section comprised of a self-administered Edmonton Symptom Assessment Scale (ESAS-r), a 9-item visual analogue tool. The prevalence and severity of the symptom was rated on an 11-point numeric rating scale that ranges from 0 (no symptoms) to 10 (worst possible symptoms) to evaluate patient-reported symptoms among cancer patients [**1**]. The ESAS-r screens depression and other distressing symptoms: pain, tiredness/fatigue, drowsiness, nausea, lack of appetite, shortness of breath (SOB), anxiety, and overall well-being. ESAS-r items were collectively summed and graded as moderate and severe symptoms (≥4).

We recorded depression as clinically significant that warrants active treatment or further referralwhen the patients reported a score of ≥10 by PHQ-9 scale and ≥4 by ESAS-r.

Sample size calculation

The sample size required for this study was 300 patients, it was calculated based on 5% alpha and 95% confidence interval with an estimated prevalence of 25% and 5% precision.

Statistical analysis

Descriptive statistics were used to summarize the participants' demographic and clinical information as well as the levels of depression (PHQ-9) and symptoms (ESAS-r).Additionally, we used Cohen's kappa coefficient (κ) to demonstrate

agreement of depression status by PHQ-9 and ESAS-r. A two-tailed a p-value of 0.05 was considered significant. All statistical analyses were performed using SPSS 25.0 software.

Ethical Consideration

The study was approved by the Institutional Review Board of King Fahad Medical City [reference number 16-287]. The identity of the participants was kept confidential. In addition, patients were informed that their agreement to participate in the study implies their consent.

Results

Table 1 displays the demographic and clinical characteristics. A total of 301 patients were included. The majority of the participants were aged 41 years and above, (72.1%) were females, 74% were married. Participants with solid tumors represented 87% of the study sample, 35.5% with stage 4, and 96.7%hade a PPS of >40. **(Table - 1)**

Table1. Sociodemographic and clinical characteristics of study participants

		n (%)
Age (years)	18-30	34(11.3)
	31-40	47(15.6)
	41-50	83(27.6)
	51-60	75(24.9)
	>61-70	62 (20.6)
Gender	Male	84(27.9)
	Female	217(72.1)
Marital status	Not married, divorced, widowed	78(25.9)
	Married	223(74.1)

Education	Secondary school and less	171(56.8)
	Higher education	130(43.2)
Place of residence	Urban	206(68.4)
	Rural	95(31.6)
Type	Solid tumors	262(87)
	Hematological	39(13)
Stage of cancer [a]	1	46(15.3)
	2	72(23.9)
	3	61(20.3)
	4	107(35.5)
PPS**	≤ and less	10(3.3)
	> 40	291(96.7)

[a]for15 patients to complete staging was not available
**PPS palliative performance scale.

Table 2 displays the prevalence and severity of depression using PHQ-9 depression and ESAS-r scales. The prevalence of clinically significant depression among study patientswas 35.2%as measured by PHQ-9, and 27.9% as measured by ESAS-r. There was moderate agreement between the two PHQ-9 and ESAS-r, $\kappa = 0.480$, $p < 0.001$.

Table 2. Prevalence and severity of depression using PHQ-9 depression and ESAS-r scales

PHQ-9 depression	**n(%)**
Minimal depression; Score (0-4)	109 (36.2)
Mild depression; Score (5-9)	86 (28.6)
Moderate depression; Score (10-14)	59 (19.6)
Moderately severe depression; Score (15-19)	32 (10.6)
Severe depression; Score (20-27)	15 (5)
ESAS-r	

No depression; Score (0)	149 (49.5)
Mild Depression; Score (1-3)	68 (22.6)
Moderate depression; Score (4-6)	53 (17.6)
Sever depression; Score (7-10)	31 (10.3)
Clinically significant depression using PHQ-9scale (>10)	106 (35.2)
Clinically significant depression using (≥4)	84 (27.9)

In the univariate analysis,factors associated with clinically significant depression were female gender, rural residence, advanced stages of cancer (stage 3and 4) and the ESAS-r symptoms (pain, tiredness, drowsiness, nausea,loss of appetite, shortness of breath, anxiety,wellbeing).**Table 3**

Table3.Univariate analysis of predictive factors of depression.

Factors	OR*	95% C.I.**	*P* – value***
Female Gender	2.74	(1.51,4.98)	**<0.0001**
Marital Status (married)	1.21	(0.71,2.06)	0.49
Higher Education	1.44	(0.90,2.33)	0.13
Rural residence	1.88	(1.14,3.1)	**0.01**
Age			
31-40 years old	2.01	0.75 - 5.41	0.16
41-50 years old	1.83	0.74 - 4.57	0.18
51-60 years old	1.43	0.56 - 3.65	0.44
61-70 years old	2.54	0.93 - 6.94	0.06
>71 years old	2.43	0.75 - 7.8	0.13
Setting	0.57	(0.32,1.02)	0.06

PPS [a]	0.53	(0.15,1.88)	0.33
Cancer Type[b]	0.69	(0.33,1.45)	0.33
Stage of cancer			
Stage of cancer (2nd)	1.48	(0.62,3.52)	0.37
Stage of cancer (3rd)	2.67	(1.13,6.35)	**0.03**
Stage of cancer (4th)	2.61	(1.18,5.81)	**0.02**
ESAS-r			
Pain	1.3	(1.19,1.42)	**<0.0001**
Tiredness	1.6	(1.42,1.81)	**<0.0001**
Drowsiness	1.45	(1.32,1.6)	**<0.0001**
Nausea	1.25	(1.15,1.36)	**<0.0001**
Loss of appetite	1.45	(1.32,1.6)	**<0.0001**
Shortness of breath	1.38	(1.22,1.55)	**<0.0001**
Anxiety	1.37	(1.26,1.5)	**<0.0001**
Wellbeing	1.38	(1.24,1.54)	**<0.0001**

[*]OR: odds ratio, **C. I: Confidence interval, *** *p* value< 0.05 considered significant, [a]PPS: palliative performance scale, [b]cancer type: hematological compared to others,
The significant p-value is in bold.

The multivariate logistic regression analysis showedthe following groups as being at a higher risk of clinically significant depression: Rural residence (OR 3.03; 95% CI 1.37–6.69), Tiredness (OR 1.22; 95% CI 1.04–1.43) Drowsiness (OR 1.22; 95% CI 1.07–1.38), Loss of appetite (OR 1.29; 95% CI 1.13–1.47), anxiety (OR 1.22; 95% CI 1.08–1.39), wellbeing (OR 1.21; 95% CI 1.04–1.41).**Table 4**

Table4. Multivariate logistic regression analysis of factors predictive of depression.

Factors	OR[*]	95% C.I.**	p-value***
Female gender	1.36	(0.58-3.18)	0.48
Rural residence	3.03	(1.37-6.69)	**0.01**
Stage of cancer			
Stage of cancer (2nd)	1.03	(0.33-3.22)	0.96
Stage of cancer (3rd)	1.61	(0.50-5.17)	0.43
Stage of cancer (4th)	1.19	(0.39-3.61)	0.76
ESAS-r			
Pain	0.99	(0.85-1.15)	0.89
Tiredness	1.22	(1.04-1.43)	**0.02**
Drowsiness	1.22	(1.07-1.38)	**<0.01**
Nausea	1.00	(0.88-1.14)	0.99
Loss of appetite	1.29	(1.13-1.47)	**<0.001**
SOB	1.07	(0.91-1.26)	0.43
Anxiety	1.22	(1.08-1.39)	**<0.001**

Wellbeing	1.21	(1.04-1.41)	**0.01**

*OR: odds ratio, ** C. I: confidence interval, ***p value< 0.05 considered significant

Discussion

The aim of this study was to identify the prevalence and associated factors of depression in cancer patients.Additionally, we assessed the interrater agreement between the PHQ-9 and the used tool (ESAS-r) for assessing the depression at the study setting.Our results showed that the prevalence of clinically significant depression among cancer patients assessed by PHQ-9 and ESAS-r was 35.2% and 27.9%, respectively. Increased likelihood of clinically significant depression was associated with resident patients of rural areas, tiredness, drowsiness, anorexia, anxiety, and poor feeling wellbeing. Additionally, our study employed two valid and reliable tools (PHQ-9 and ESAS-r) to assess the prevalence of depression among cancer patients. The Cohen's kappa test showed a significant moderate level of agreement betweenthe PHQ-9 and ESAS-r scales.

Evaluation of depression prevalence in cancer patients was a subject of many studies worldwide. However, the prevalence of depression remains varied. Compared with some previous literature, the reported prevalence rates of clinically significant depression in our study werehigher than the pooled prevalence among cancer patients reported by Krebber et al meta-analysis study (8%-24%) [5]. Another systematic review conducted by Riedl et al concluded that the prevalence rate of clinical depression mean was 21.2 % among patients with different cancer diagnosis [17].

Regional studies from Jordan and Egypt reported a varied depression prevalence from 23.4% to 51.9% among cancer patients among breast cancer patients [23,25,26]. In Saudi Arabia, a study done on 70 colon cancer patients showed that 30% of the study participants had depressive disorder and 12.9% has major depression depending on

Structured Clinical Interview for DSM-IV [27]. Zuhoor et al used NCCN (National Comprehensive Cancer Network) distress thermometer screening tool found that 40% of the patients had depression [28]. However, NCCN thermometer is primarily used to assess the level of distress rather than depression. A study done recently by Almutairi etal [29], showed prevalence of depression in outpatient cancer setting center in Saudi Arabia to be 29%, this study was done in an outpatient setting, they focused on the quality-of-life assessment in cancer patients and used HADS (Hospital Anxiety and Depression scale) for their assessment.

It is conceivable that the differences between our study and previous reports is wide. Therefore, it is comparative to bear considerable responsibilities from clinicians, families and society to support cancer patients to compact the depression through a well-structured psychosocial supportive program, early screening for depression, with appropriate management in an interdisciplinary approach. Further research is needed to find a quick but yet sensitive way to detect depressed patients in a busy cancer clinic setting. Moreover, a more personalised approach to supporting the psychological health of people with cancer is needed. The self-management of psychological distress among people with cancer may be beneficial and could help prevent distress becoming clinical depression or anxiety. Self-management refers to "*the ability of the individual, in conjunction with family, community, and healthcare professionals, to manage symptoms, treatments, lifestyle changes, and psychosocial, cultural, and spiritual consequences of health conditions*". Thus, a dynamic and continuous process of self-regulation is established" [30].

Several factors may impact the development of depression and anxiety among cancer patients, including the cancer type, stage, grade, and treatment option [31]. Interestingly, our results reported several symptomologies that can lead to depression

like tiredness, drowsiness, anorexia, anxiety, and poor feeling of wellbeing. These symptoms are part of ESAS items and constitute common symptoms in cancer patients but they actually at the same time related to a depression diagnosis, this calls for more focus on creating assessment tools for physically ill patients that will be more specific for depression diagnosis [32]. Place of residence was significantly associated with more depression OR 3.03 it might be due to difficulty in accessing medical treatment adding more burden on patients and families [33]. This result is important and needs more elaboration, and it emphasizes that demographic variation plays an important role in psychosocial wellbeing of cancer patients, maybe as or even more important than cancer characteristics.On the other side, our results didn't find an association between cancer type and stage with depression.

The study results revealed that ESAS-D score has a sensitivity of 0.57 (95% C.I: 0.47 to 0.67) and a specificity of 0.88 (95% C.I: 0.82 to 0.92) of, as compared to PHQ-9 questionnaire, and with positive predictive value of 0.72 (95% C.I: 0.63to 0.80) and negative predictive value of 0.79 (95% C.I: 0.75 to 0.82). Indicating that ESAS –D is not sensitive enough to be used as a screening tool for depression. This result correlates with a recent Systematic Review and Meta-Analysis about depression in patients with a malignant diagnosis that showed ESAS-D $\geq$ 4 is 53% sensitive and 90% specific [34].

Strengths and Limitations

Strengths of our study include a relatively large representative sample from the largest governmental tertiary care cancer center. Reliable data collected by a valid and reliable questionnaire. However, this study has limitations. The cross-sectional study design limited our ability to identify causal relations between the prevalence of

depression and variables cannot be determined. The use of convenience sampling techniques considered as a selection bias which might affect the generalizability of our findings Therefore, our findings should be interpreted with cautions.

Conclusion

Our study demonstrated a higher prevalence of depression among the study sample of cancer patients. As depression is proven to be associated with other symptomologies, it is important to to consider a holistic approach in the diagnosis and treatment of depression. Early detection via a valid diagnostic assessment criterion and proper referral can contribute in addressing depression and improve quality of life in cancer patients.The findings of this study can support policymakers and cliniciansin determining the importance of timely detection and treatment of depression.

Declarations

Conflict of interest: The authors declare no competing interests.

Data availability: All data generated or analyzed during this study are available upon reasonable request to the corresponding author.

Abbreviations:PHQ-9:Health Questionnaire depression scale; ESAS-r: revised Edmonton Symptom Assessment System; PPS:Palliative Performance Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders ,4th edition; HADS (Hospital Anxiety and Depression scale).

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