

Cancer pain and depression: A systematic review of age-related patterns

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BACKGROUND: Pain is a common and debilitating symptom experienced by cancer patients of all ages. Cancer pain is associated with elevated levels of depression; however, age-related patterns in this relationship remain unclear. This information is important to provide effective palliation of pain and depression to the growing numbers of older cancer patients.

OBJECTIVE: To provide a systematic review of the literature regarding age-related patterns in the intensity or prevalence of depression among cancer patients with pain.

METHODS: Medical and psychological literature databases were searched to identify eligible studies. The methodological quality and outcomes of the studies were compiled and systematically reviewed.

RESULTS: Five articles, describing four studies, met the inclusion and exclusion criteria. Due to high levels of cross-study methodological variability, a qualitative review was undertaken. Three of the four studies did not find evidence for age-related patterns in depression. The fourth study found that depression increased with age.

CONCLUSION: The weight of the evidence suggests that younger and older cancer patients with pain report comparable levels of depression. However, this conclusion remains preliminary due to the methodological limitations of the available studies. Research is needed to more adequately address this important issue.

Key Words: Age differences; Aging; Cancer pain; Depression,

Cancer is predominantly a disease of older persons. Each year, more than 40% of new cancer cases and 60% of cancer-related deaths in Canada occur in people older than 70 years of age (1). The number of older people with cancer will increase as the population ages (1). Although cancer is associated with a broad spectrum of symptoms, pain is one of the most common and the most feared (2). Furthermore, it is the most significant in terms of reducing quality of life (3).

Many older people with cancer experience considerable and persistent pain. Walsh et al (4) found that over 80% of elderly advanced cancer patients reported daily pain. Within the hospice setting, over 40% of older patients reported severe pain (5). Cancer pain has been associated with depression among older people in institutional (6) and outpatient (7) settings. Although cancer pain and depression in older people are significant and growing problems, few studies have assessed age-related patterns in depression among people with ongoing cancer pain. This information may contribute

Douleur cancéreuse et dépression : Analyse systématique des modes de présentation liés à l'âge

HISTORIQUE : La douleur est un symptôme courant et invalidant chez les patients cancéreux de tous âges. La douleur cancéreuse est associée à des taux élevés de dépression. Par contre, certains modes de présentation de la douleur liés à l'âge restent à élucider. Cette information est importante pour offrir un traitement palliatif efficace contre la douleur et la dépression chez un nombre croissant de patients cancéreux âgés.

OBJECTIF : Fournir une analyse systématique de la littérature sur les modes de présentation de l'intensité ou de la prévalence de la dépression liés à l'âge chez les patients souffrant de douleur cancéreuse.

MÉTHODES : Les auteurs ont interrogé des bases de données de littérature médicale et psychologique afin de relever les études pertinentes. La qualité méthodologique et les conclusions des études ont été compilées et analysées de manière systématique.

RÉSULTATS : Cinq articles décrivant quatre études répondaient aux critères d'inclusion et d'exclusion. En raison des taux élevés de variabilité méthodologique entre les études, une analyse qualitative a été entreprise. Trois des quatre études n'ont fait état d'aucun mode particulier de présentation de la dépression liée à l'âge. La quatrième étude a révélé que la dépression augmentait avec l'âge.

CONCLUSION : Le poids de la preuve donne à penser que les patients jeunes et âgés souffrant de douleur cancéreuse font état de taux comparables de dépression. Par contre, cette conclusion reste préliminaire en raison des limites méthodologiques des études disponibles. La recherche doit se poursuivre pour que l'on puisse étudier de manière plus adéquate cette importante question.

to more effective palliation of both pain and distress and to improved quality of life for patients across the adult lifespan.

The relationship between chronic nonmalignant pain and depression has received considerable empirical and clinical attention. Depression is highly prevalent among people with chronic pain (8). Possible mechanisms for this relationship span the biopsychosocial spectrum and include shared neurophysiological, cognitive, environmental and predispositional factors (9). Several studies have shown that the prevalence and intensity of depressive symptoms are not different with age among people with chronic nonmalignant pain (10-13). That is, younger and older people with chronic nonmalignant pain are equally vulnerable to symptoms of depression.

Depression is a common symptom in cancer, with clinically significant symptoms reported by up to 30% of cancer patients (14). These symptoms are more common in those who have more advanced disease, are hospitalized, or have greater disability (15) or physical distress (16). Concomitant

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psychological distress contributes to the worsening of suffering (17) and quality of life, and shortened survival (18,19). Attention to depressive symptoms is clinically important because both psychological and pharmacological interventions have been shown to be effective in the treatment of symptoms that meet criteria for the diagnosis of major depressive disorder (20). Interestingly, several studies have suggested that older cancer patients are less likely than younger patients to report depression (21-23). However, these studies have not always considered the role of pain in the relationship between age and depression. Therefore, it is difficult to predict whether depression will differ among younger and older cancer patients with pain. Evidence from chronic noncancer pain patients suggests that depression is not related to age, but evidence from cancer patients suggests that increasing age is associated with lower levels of depression.

A systematic review was undertaken to critically evaluate the available data regarding age-related patterns in depression among people with cancer pain. It has been noted that such systematic reviews serve a number of important functions. They synthesize the volume of information published on a given topic and distinguish higher quality, methodologically sound publications from those that are less rigorous (24). They can also identify gaps in the literature and highlight directions for future research.

METHODS

Study identification and selection

The protocol adopted to carry out the present systematic review was adapted from the method guidelines of the Cochrane Collaboration Back Review (25) and Musculoskeletal Review Groups (26). Electronic searches using MEDLINE, EMBASE, Web of Science, CINAHL, PsycINFO and abstracts of the Cochrane Library Issue 3, 2006, were conducted. The search was limited to English language publications between the years 1965 and 2006. The following search terms were used, as applicable: cancer, oncology, neoplasm, malignant, pain, depress, depression, distress, ageing/aging, aged, age difference and elderly. In addition to electronic database searches, hand-searches of relevant textbooks, journal indices and reference lists from relevant review articles were conducted.

Inclusion criteria were publications that compared levels of depressive symptoms in younger and older groups of cancer patients with pain, or included age as a variable in statistical analyses designed to identify correlates of depression in cancer patients with pain. Exclusion criteria were studies that reported only qualitative findings, case studies, dissertations, and studies that did not include specific measures of pain and depression but assessed these symptoms only as part of a composite symptom burden score. Abstracts were reviewed for relevance and discarded if the methodology did not meet these criteria. Abstracts and manuscripts were also reviewed to determine the age distribution of the study sample. Because there is no established criterion for distinguishing younger from older groups, an age cutoff of 50 years or older was chosen to maximize findings in the older adult population. An effort was made to avoid the inclusion of multiple publications of the same study or to identify such studies if different data were presented across publications. Only findings relevant to the primary research question were included in this review. Two reviewers (LG and LRG) independently confirmed the eligibility of studies.

Data abstraction

All studies that reported data relevant to our research question were included, regardless of their methodological quality. The characteristics of each study were evaluated, based on a modification of existing methodological quality checklists (27,28). Data were extracted using a modified version of the data extraction form of the Cochrane Back Review Group (www.cochrane.iwh.on.ca/forms.htm; current at October 7, 2006). Data abstraction and evaluation were carried out independently by two reviewers (LG and LRG) and any disagreements were resolved through discussion.

RESULTS

Following an extensive electronic and manual search of the literature, five articles were identified that reported studies that met the inclusion criteria (Table 1). Two of these (29,30) reported different data from the same group of patients and were included as one study in the present review. Therefore, we refer to four studies but include five citations in the remainder of the present review. Due to the heterogeneity of the studies' populations and measures, it was not feasible to make direct quantitative comparisons of findings. As such, a qualitative, descriptive analysis was performed.

Data for the four studies included in the review were extracted according to a modified version of the data extraction form of the Cochrane Back Review Group (www.cochrane.iwh.on.ca) and are presented in Table 1. Studies were largely cross-sectional ($n=3$), with only one presenting longitudinal data. Sample size ranged from 70 (31) to 268 (32). Patients were predominantly Caucasian, with the exception of the Chinese palliative care inpatients studied by Kai-hoi Sze et al (31). The remaining studies were conducted in Greece (29,30), the Czech Republic (33) and the United States (32). Three studies (29-32) had equivalent percentages of male and female patients, while in the remaining study, the majority of the sample was female (33). Three of the studies included samples with a variety of disease sites and stages (29-32), whereas the fourth was limited to people with gastrointestinal cancer (33). Two studies reported disease stage and/or presence of metastases (29-31). Two of the studies (31,32) compared depressive symptoms between groups of older and younger adults with cancer pain, whereas the other two studies (29,30,33) included age as a continuous variable in the analysis of depressive symptoms among cancer patients with pain.

In the only longitudinal study available, Williamson and Schulz (32) compared younger and older patients with cancer pain attending an outpatient palliative radiation clinic. At baseline and at an eight-month follow-up assessment, participants completed a pain index created by the authors (a composite of verbal descriptor ratings of pain intensity, severity, pattern and presence in the last month), the Center for Epidemiologic Studies Depression Scale (CES-D), which has been validated for use with medically ill (34), pain (35) and older (36) populations, and a measure of activity restriction due to pain. Reliability for the pain index for the whole sample was excellent (Cronbach's $\alpha = 0.91$) but reliability and validity across age groups were not reported. Age differences in pain scores were not found and in both age groups, pain decreased significantly over time. Depression scores were in the moderate range and did not differ between the age groups. At baseline, 21% of patients scored above the cutoff associated with clinical depression (CES-D 16 or greater), and 14%

TABLE 1
Studies assessing age-related patterns in depression among patients with cancer pain

Study	Age and sample size	Female, %	Population	Design	Pain scale	Depression scale	Primary results
Williamson and Schulz, 1995 (32)	Young (n=136): 30 to 64 years (mean not reported); Older (n=132): 65 to 90 years (mean not reported)	51.0	Outpatient palliative radiation clinic	Longitudinal	4-item index	CES-D	No difference in proportion of younger and older patients scoring above CES-D cutoff No age differences in intensity of pain or depression at baseline or follow-up Age-related role of activity restriction and comorbidities in relationship between pain and depression
Kai-hoi Sze et al, 2000 (31)	Young (n=31), <65 years; Older (n=39), ≥65 years; mean age by group not reported	51.0	Inpatient palliative care unit	Cross-sectional	VAS	HADS-D	No differences in proportion of younger and older patients scoring above HADS-D cutoff
Mystakidou et al 2005, 2006 (29,30)	n=120; mean age 61.4 years (range 24 to 83 years)	49.2	Inpatient and outpatient palliative care unit	Cross-sectional	BPI, EORTC QLC-30	HADS-D	Increasing age was an independent predictor of increased depression
Knotkova et al, 2004 (33)	n=71; mean age 68.2 years (range 48 to 91 years)	64.8	GI cancer inpatients	Cross-sectional	NRS, MAPS	NRS	Age was not related to depression levels

BPI Brief Pain Inventory; *CES-D* Centre for Epidemiological Studies Depression Scale; *EORTC QLC-30* European Organization for Research in the Treatment of Cancer Quality of Life Questionnaire; *GI* Gastrointestinal; *HADS-D* Hospital Anxiety and Depression Scale – Depression subscale; *MAPS* Multidimensional Affect and Pain Survey; *NRS* Numeric Rating Scale; *VAS* Visual analogue scale

scored above this cutoff at follow-up. Importantly, the proportion of younger and older people scoring above cutoff at each time point did not differ ($P=0.50$).

Sixty-two per cent of the younger and 58% of the older participants completed the follow-up assessment. The majority of the attrition was due to patient death. Patients who died had reported more pain, depression and activity restriction at the first assessment than those who completed both assessments. The authors did not report attrition patterns separately for each age group. For patients participating in both assessments, the difference on the CES-D between the age groups was less than one point at each assessment ($P=0.94$). We compared the magnitude of the correlation of pain and depression between the age groups using a Fisher's Z transformation and found a trend for the correlation to be stronger in the older ($r=0.42$) than the younger group ($r=0.28$; $P\leq 0.09$). Preliminary analyses suggested that sex, income, primary cancer site and treatment factors were not related to pain or depression, and these variables were not included in subsequent analyses. Activity restriction fully mediated the relationship between pain and distress in younger patients but only partially mediated it in older patients. In addition, younger patients without comorbid conditions reported higher levels of depression than younger patients with comorbid chronic illness and older patients with and without comorbid illness. Analysis of the predictors of depression scores at follow-up revealed important age-related patterns. Among younger patients, depression at the eight-month follow-up was predicted by both baseline depression and activity restriction. However, among the older patients, baseline depression, but not activity restriction, predicted subsequent levels of depression. Interestingly, pain was not a

significant predictor of depression in either age group. These results may be due to the small sample size ($n=84$ younger and $n=77$ older) retained for the follow-up assessment or age-related variations in attrition or the psychometric properties of the pain index, which are unknown.

Kai-hoi Sze et al (31) assessed pain, using a visual analogue scale (VAS), and depression, using the Hospital Anxiety and Depression Scale – Depression subscale (HADS-D), in a small study of palliative care inpatients with pain due to advanced, terminal cancer. The VAS is a single-item measure of pain intensity consisting of a line with the end points labelled with the extremes of no pain and worst pain. Patients indicate the length of line that corresponds to their current pain intensity (37). The HADS is a 14-item measure of anxiety and depression that was developed for use with medically ill populations (38) and has been validated for older persons (39) and people with chronic pain (40). In this sample, 35% (11 of 31) of younger (younger than 65 years of age) and 23% (nine of 39) of older (65 years of age or older) patients obtained HADS-D scores indicative of probable depression (HADS-D 11 or greater). These rates were not significantly different ($P\leq 0.25$), although the small sample size and the limited data provided regarding each age group make these results difficult to interpret. For instance, the mean age of the patients in each age group is not reported. Given that the mean age for the full sample is 62 ± 14.2 years, with a median of 64 years, it is possible that younger patients were not adequately represented in this study. Interpretation is further limited by the use of the VAS, which has been shown to be of questionable validity in older people (41-43) and in some cancer patients (44). Consistent with this, the authors report that 13 (18.5%)

patients were unable to complete the measures. Taken together, these two studies suggest that depression is highly prevalent among both younger and older palliative care patients with pain due to advanced cancer.

Mystakidou et al (29,30) assessed depression (HADS-D) and pain, using the Brief Pain Inventory (BPI) and the European Organization for Research in the Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), in both outpatients and inpatients referred to a palliative care unit. The BPI is an extensively validated and commonly used measure of pain severity and interference of pain in desired activities, physical function and emotional well-being (45). It is made up of numeric rating scales, which have been validated across the adult lifespan (43). The EORTC QLQ-C30 assesses pain frequency and interference in the past week using verbal descriptor scales (46). It has been validated for use with older cancer patients (47). All measures were completed in Greek, using validated translations. Patients ranged from 24 to 83 years of age (mean age 61.4 years; measure of dispersion not reported). Because age was not of primary interest in this study, age-related patterns are not reported. Pain was rated as the most distressing symptom of cancer, followed by fatigue and sleep disturbance. BPI pain severity and interference scores were in the moderate range, with interference of pain in mood and general activity rated as most severe. The authors reported slightly different regression analyses in each manuscript. In Mystakidou et al (29) (2005), multiple regression analyses revealed that depression was associated with increasing age, EORTC QLQ-C30 pain scores, female sex, quality of life (physical, role, emotional and social), nausea and vomiting, sleep disturbance, constipation, cancer treatment and functional status. This model explained 60% of the variance. In Mystakidou et al (30) (2006), depression scores were associated with older age, female sex and pain interference in enjoyment of life. This model explained 22% of the variance. When the BPI was entered as a scale score rather than item scores, only older age and female sex were associated with depression. This model explained 14% of the variance. This is the only study to suggest that the intensity of depression increases with age among people with cancer pain. Importantly, it is the only study that assessed this relationship concurrently with sociodemographic, medical and physical function variables using multivariate statistics. However, the results may be compromised due to over-fitting of the regression model (ie, $n=120$ but up to 22 predictors are included in one of the models) and therefore are difficult to interpret.

Knotkova et al (33) assessed the relationship of pain to depression in a small ($n=71$) sample of inpatients with stages II to IV gastrointestinal cancer ranging in age from 48 to 91 years. Pain intensity was rated on a numeric rating scale and pain qualities with the Multidimensional Affect and Pain Survey (48), which has been validated for use in oncology populations (49) but remains to be validated for older patients. Unfortunately, this study relied on a single numeric rating of depression. They found that among patients with gastrointestinal cancer, age was not correlated with pain or depression measures ($P=0.21$).

DISCUSSION

Pain is one of the most common symptoms experienced by cancer patients (2) and has been associated with increased levels of depression (16). However, little attention has been

paid to age-related variations in this relationship. Given the rapid aging of our population (50), the large proportion of older cancer patients (1) and the high prevalence of pain they report (4), it is important that our understanding of cancer pain and aging increase. The objective of the present review was to critically evaluate the data regarding age-related patterns in depression among people with cancer pain. Four studies were identified that assessed this relationship and that met our eligibility criteria. Together, they included 529 patients ranging in age from 24 (29) to 91 years (32) (range not reported by [31]). Most of the patients had advanced cancer and were receiving palliative care, either in the hospital or as outpatients.

All but one of the studies found that age was not related to the prevalence of probable depression or to the intensity of depressive symptoms. In the only study not to support this conclusion (29,30), older age was associated with higher depression scores. Importantly, these studies demonstrated that depression is highly prevalent among advanced cancer patients with pain, with over 20% scoring above cutoffs for probable clinical depression.

The conclusion that depression does not differ with age among people with cancer pain must be tempered by the usual caveats involved in the interpretation of nonsignificant differences (51,52). For instance, because of small sample sizes, the studies simply may not have had the power to detect differences that may exist. However, the P values associated with the results were all greater than 0.20, with the largest value associated with the largest sample ($n=268$, $P<0.94$). This suggests that extremely large sample sizes would be required to find statistically significant age differences and that such differences would likely be small and of questionable clinical significance. Consistent with this, the only study to report mean depression scores found less than a one-point difference between the younger and older patients (32). Although preliminary, we conclude that among advanced cancer patients with pain there is little evidence for age differences in the prevalence or intensity of depression.

This conclusion is consistent with studies of patients with chronic nonmalignant pain but not with studies among the larger population of cancer patients, which suggest that younger cancer patients report more distress than older cancer patients. Unfortunately, these studies did not compare those with and without pain across age groups. Comparisons of older and younger people with cancer and noncancer pain are not currently available. In the few studies comparing individuals with chronic cancer pain and noncancer pain, similar levels of depression have been reported (53,54). Taken together, these results suggest that within the context of pain, older cancer patients are just as likely as younger cancer patients to experience depression. This implies that the factors that protect older people, or conversely that put younger people at risk for depression, may not operate in the same way when cancer pain is present or is an overriding factor.

The studies included in the present review provide some evidence for different models and correlates of pain and depression in younger and older patients. Unfortunately, given the paucity of available data, our consideration of the factors that are important to the experience of depression among people with cancer pain across the adult lifespan must remain highly speculative. For example, Williamson and Schulz (32) found that activity restriction played a greater role in the relationship in younger than older people. This is consistent

with findings from other studies of younger and older patients with chronic noncancer pain. Turk et al (11) reported that the relationship between pain intensity and depression was mediated by perceived life control and pain interference across age groups, but the mediation was greater in younger than older people. Williamson and Schulz (32) suggest that activity restriction is more distressing to younger patients because older patients are habituated to and expect physical impairment and pain with age. However, they did not measure habituation or expectations. Importantly, habituation would lead to the prediction of less depression with increasing age, which the available studies do not support. Further research is needed to test the contribution of important variables such as life control (11) and activity replacement (55) to the activity restriction model of age differences in depression.

One of the studies included in the present review considered the role of comorbid conditions. Specifically, in younger, but not older patients, lack of comorbid conditions was associated with increased depression (32). Interestingly, younger cancer patients with comorbid conditions did not differ from older people. Unfortunately, the other studies included in this review either did not report comorbidities or did not assess their role in the relationship between depression and pain. Although these results require replication, they suggest that younger people with pain may be especially vulnerable to depression if the cancer is their first diagnosis of illness. This may be related to life stage theory, in particular the violation of self-perception as a 'healthy young person' and its implications for the attainment of life goals. This is consistent with evidence regarding stress response symptoms in the context of chronic illnesses. In that regard, younger people experience more distress associated with the diagnosis of cancer than older people; this may be especially true in the context of advanced terminal disease (56). The potential mediating effects of comorbid conditions, life stage and pain have not been considered. It is possible that in younger people a premorbid chronic condition serves as a buffer against the traumatic stress associated with the subsequent cancer diagnosis and related pain. A similar process may not be operative in older people for a variety of reasons, including their having had more experience with and prior expectations of illness, physical symptoms and mortality (57). Although preliminary, these results suggest that the correlates of depression may differ among cancer pain patients of different ages. However, further research using larger samples, longitudinal designs and the exploration of a broad spectrum of potential mediating and moderating effects is required to begin to elucidate these possibilities.

Unfortunately, there are several aspects of these studies that limit their methodological quality and the conclusions we can draw. The most fundamental of these is that only one study (32) was designed a priori to assess age-related patterns. As a result, the samples may not adequately represent patients across the adult lifespan. In one study, age distribution was not reported, while in the others insufficient detail was provided to assess the representativeness of the sample. Further, the results of the studies may not generalize to the oldest-old, frail elderly people or to those with cognitive or communication impairments. Another probable consequence of the post hoc consideration of age is that the studies did not include age-related variables that could impact on the outcomes such as comorbidities, including chronic nonmalignant pain, polypharmacy and psychosocial factors.

Another limitation arises from the design of the studies. As mentioned, sample sizes were small, thereby limiting the power of the studies to detect differences. In addition, variables that could have impacted on the outcomes were not controlled, including treatments received for pain or depression, pain characteristics (ie, duration, location, quality) or cancer characteristics. Consideration of metastases, treatment factors, and disease site and stage are crucial because these may influence the experience of pain and psychological distress (58,59). Surprisingly, none of the studies reported on the prevalence of premorbid clinical depression. Finally, the studies did not consider which symptoms of depression the younger and older people were endorsing. This analysis might yield important information regarding the nature of depression and the possibility of inflation of scores by normal age-related changes (60).

Measurement issues also limit the interpretation of the results. These include wide cross-study variability in the pain assessment tool used. More problematic was the use of the VAS, which is difficult for older (36,41) and cancer patients (44) to complete, or of nonstandardized measures constructed by the authors (32). A similar problem is evident in the assessment of depression. Several different standardized scales were used, and one study assessed depression with only a single item (33). In two studies, validated cutoffs were used to identify patients whose scores were indicative of probable clinical depression (31,32). However, these studies did not include systematic clinical interviews to validate diagnoses.

There are also limitations that arise due to the methods adopted for this systematic review. We reviewed only English language publications, although the evidence that this is a source of potential bias remains equivocal (25). Although we carried out an extensive search for articles, we may have inadvertently omitted studies that met our eligibility criteria. While we cannot rule out this possibility, we endeavored to minimize it by having two researchers independently conduct the exhaustive searches.

CONCLUSIONS AND FUTURE DIRECTIONS

Pain is one of the most common symptoms experienced by people with cancer (61). It is often associated with depression and impaired quality of life, consistent with a biopsychosocial model of pain (54,62,63). Similar to the literature regarding chronic nonmalignant pain, the present review did not find evidence for age differences in the prevalence or intensity of depression among advanced cancer patients with pain. Although studies of cancer patients have suggested that older age is associated with less depression, the results of the present review suggest that these age-related patterns are obscured by the impact of ongoing pain. However, the conclusions of this review are based on a small number of studies that, for the most part, were not designed to adequately assess age-related patterns. Research is urgently needed to systematically assess depression among people with cancer pain across the adult lifespan. These studies should employ well-validated measures of both pain and depression, ensure adequate representation across the adult lifespan and examine the role of factors such as comorbidity, activity interference and disease characteristics. Prospective designs are needed to elucidate not only age differences in rates and intensity of depression and pain but also age-related patterns in symptom profiles, prognostic and risk factors, the trajectory of symptoms over time,

and responses to therapeutic interventions. Until such data are available, there is no reason to believe that older cancer patients with pain are less vulnerable than younger patients to depression. Therefore, the assessment and management of pain and depression should be a priority in the supportive care of cancer patients of all ages.

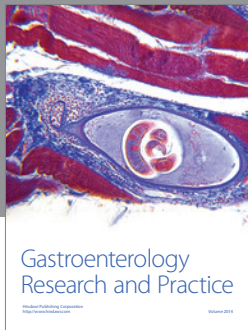
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