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Clinically Significant Depressive Symptoms are Prevalent in People with Extremely Short Prognoses - A Systematic Review

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ABSTRACT

Context:

Currently, systematic evidence of prevalence of clinically significant depressive symptoms in people with extremely short prognoses is not available to inform its global burden, assessment, and management.

Objectives:

To determine the prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses (range of days to weeks).

Methods:

A systematic review and meta-analysis (random effects model) were performed (PROSPERO: CRD42019125119). MEDLINE, Embase, PsycINFO, CINAHL, and CareSearch were searched for studies (1994-2019). Data were screened for prevalence of clinically significant depressive symptoms (assessed using validated depression-specific screening tools or diagnostic criteria) of adults with advanced life-limiting illnesses and extremely short prognoses (defined by survival or functional status).

Quality assessment was performed using the Joanna Briggs Institute Systematic Reviews Checklist for Prevalence Studies for individual studies, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) across studies.

Results:

Thirteen studies were included. The overall pooled prevalence of clinically significant depressive symptoms in adults with extremely short prognoses (n = 10 studies; extremely short prognoses: N = 905) using depression-specific screening tools was 50% (95%CI: 29%-70%; I^2 = 97.6%). Prevalence of major and minor depression were 10% (95%CI: 4%-16%) and 5% (95%CI: 2%-8%), respectively. Major limitations included high heterogeneity, selection bias and small sample sizes in individual studies.

Conclusions:

Clinically significant depressive symptoms were prevalent in people with advanced life-limiting illnesses and extremely short prognoses. Clinicians need to be proactive in the recognition and assessment of these symptoms to allow for timely intervention.

Keywords:

Palliative Care; Prognoses; Depression; Prevalence; Systematic Review; Meta-analysis

Running Title: Depression in the Dying – A Systematic Review

KEY MESSAGES

Clinically significant depressive symptoms affected half of the people with extremely short prognoses. Results provide clinicians, policy-makers & funders, researchers and general public with new information about the high prevalence of clinically significant depressive symptoms in the last days-to-weeks of life, highlighting the need for pro-active recognition, assessment and management.

INTRODUCTION

Depression is a complex and debilitating condition often seen in the people with advanced life-limiting illnesses. For individuals affected at the end-of-life, clinical depression can amplify suffering, limit capacity for pleasure, meaning, and engagement with their loved ones (1-3). It may also be associated with a desire for hastened death (4).

Assessing and managing depressive symptoms in the setting of advanced life-limiting illnesses can be complex. A key factor in the complexity stems from the amorphous use of the terminologies of 'depression' and 'palliative care population' in the literature. In fact, this term "depression" can imply: 1) a symptom of low-mood state; 2) depressive syndromes consisting of a collection of low-mood related symptoms (e.g. guilt, suicidal ideation, or anorexia) secondary to various mental disorders or; 3) specific depressive disorders (e.g. major depressive disorder) defined by the gold-standard diagnostic criteria (5). These diagnostic criteria include Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases and Related Health Problems for depressive disorders (ICD) (6-9). Meanwhile, the studied 'palliative care population' can differ significantly from one study to another due to the absence of a standardised referral system for palliative care (10). The heterogeneity of definitions and the numerous assessment methods across the literature complicate the assessment and management of depression at the end-of-life. These have contributed to the wide range of depression prevalence (2%-30%) found in the general population with advanced life-limiting illnesses (2, 3, 11-18).

The recognition, assessment and management of depressive symptoms is even more challenging in the subset of the palliative population who are in the last days to weeks of life (19, 20). This period is usually characterised by an increasing dependence on others for care, increasing symptom burden and declining functional scores indicative of one month or less of median survival (19, 21). These include: Karnofsky Performance Scale (KPS) $\leq$ 40, Eastern Cooperative Oncology Group (ECOG) 4, and Palliative Performance Scale $\leq$ 50 (19, 22, 23). Frailty and associated symptoms (such as severe fatigue, hypersomnia, and physical weakness) may make it difficult for clinicians to recognise and assess depressive symptoms, especially in people presenting with depressive disorders for the first time (3). In this setting, treatment can also be challenging. Psychological therapies may require adaptation as the patients' cognition might be impaired with poor concentration or delirium, while their energy levels and motivation are often limited (19, 24, 25). Engagement in therapy may be too tiresome for some individuals and the benefits of the therapy may not manifest in time (25). Typical oral antidepressants might not work soon enough due to the person's extremely short prognosis (26), or cannot be swallowed due to frailty (25). Therefore, some clinicians feel a sense of futility in assessing and managing depressive symptoms of these individuals (20).

As this subset of the palliative population with extremely short prognoses and clinically significant depressive symptoms has specific challenges and needs, it is important to define its prevalence. Previous systematic reviews of the prevalence of depressive symptoms in the palliative care and oncology settings did not explicitly examine prevalence in people with extremely short prognoses (11, 12). Additionally, studies included in these reviews focused on specialist palliative care and oncology cohorts (11, 12). Patients with advanced life-limiting illnesses and extremely short prognoses not known to these services would have been excluded.

For the purpose of this review, consistent with the literature, the term "clinically significant depressive symptoms" has been used. This term embraces various depressive conditions defined by either: 1) diagnostic criteria, such as ICD, or DSM (27); and 2) validated depression-specific screening tool (28-30). It does not include delirium with depressive features. The inclusion of prevalence defined by depression-specific screening tools would ensure subsyndromal depression are accounted for – i.e. clinically significant depressive symptoms that fulfill specific cut-offs of screening tools but not the conventional diagnostic criteria .

Knowledge of the prevalence of clinically significant depressive symptoms in people with extremely short prognoses would quantify its global burden and inform screening, assessment and impetus for developing targeted therapies.

Aim

To determine the prevalence of clinically significant depressive symptoms in people with extremely short prognoses (median survival of ≤ 4 weeks with absolute cut-off of < 2 months) suffering from advanced life-limiting illnesses, as indicated by survival or functional status data (Karnofsky Performance Scale [KPS] ≤40 or equivalent) (22, 23, 31, 32).

METHODS

Design & Protocol Registration

Systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (33). This review focusing on prevalence studies represented the first part of the systematic review protocol prospectively registered in PROSPERO (CRD42019125119).

Search Strategy

A systematic search of the electronic databases of MEDLINE (OVID), PsycINFO, Embase, CINAHL, and CareSearch (CareSearch filter utilised via PubMed) for studies published between January 1994 and February 2019 was performed (last search 27 February 2019). The search was limited to the last 25 years, as 1994 was the year when DSM-IV was assimilated to ICD-10 to ensure congruence (34).

The search strategy included search terms in the domains of [Palliative Care or Advanced Life-Limiting Illnesses] AND [Prevalence] AND [Depression] was used initially in MEDLINE (OVID). The search terms were then adapted for other electronic databases accordingly (see 'Search Strategy' in Supplementary File 1).

Inclusion criteria for studies were: any setting of care or study design; adults (≥ 18 years) with advanced life-limiting illnesses and extremely short prognoses in the range of days to weeks defined by either survival data (absolute survival of <2 months) or functional status indicative of a median survival of 1 month (equivalent of AKPS ≤ 40 or Eastern Cooperative Oncology Group (ECOG) 4) (22,

23, 31, 32); and prevalence of clinically significant depressive symptoms defined by a validated tool (e.g. Hospital Anxiety and Depression Scale [HADS]) or a depressive disorder defined by diagnostic criteria (DSM or ICD or equivalent). In relation to diagnostic criteria, the term "major/minor depression" will be used in this review to encompass: 1) Both "major/minor depressive disorders" and "major/minor depressive episodes" in DSM (6, 7) and; 2) "major/minor depression" in ICD (8, 9).

Excluded studies were those not peer-reviewed (e.g. theses); studies with no validated method of assessing depressive symptoms; studies using measures not specific to depression (e.g. Edmonton Symptom Assessment Scale); as well as systematic reviews and meta-analyses, case studies, opinion papers, editorials, study protocols or guidelines. A manual selection for adult, human and English studies was performed without the use of filters to minimise the risk of missing articles due to delayed coding issues. The reference lists of relevant systematic reviews and meta-analyses were hand-searched for eligible studies.

Study Selection

Search results were imported into Endnote X9.2 for duplicate removal, and subsequently exported to Covidence for title and abstract, and full text screenings (35, 36).

Each study was reviewed by both the primary investigator (WL) and a reviewer from the alternative reviewer group (MP, CS, EL, AH, DP, MA, SK). Fortnightly calibration session was held to maintain inter-rater reliability. Reasons for exclusions at full text review were documented. A third independent reviewer (BD) was involved in resolving conflict.

Data Extraction

Data extracted from individual studies included: country; study design; eligibility of sampled population; settings; diagnoses; participant demographics; sampling method; definition and number of participants with extremely short prognoses; depression definition, assessment timing and method; and number and prevalence of clinically significant depressive symptoms in people with extremely short prognoses. When necessary, the authors of the publications were contacted for clarification of the data.

Quality and risk of bias assessments were performed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for use in JBI Systematic Reviews - Checklist for Prevalence Studies (for individual studies) (37, 38) and the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (across studies) (39, 40).

The primary investigator (WL) extracted data from all included studies. Alternative reviewers (MP and AH) checked the validity of extracted data and independently performed quality/bias assessment of studies by randomly selecting studies using a random number generator. Given that 100% consensus was reached on discussion after randomly reviewing five of the 13 studies, remaining studies were only reviewed by the primary investigator (WL).

Data Synthesis

Prevalence rates were calculated from the number of cases with clinically significantly depressive symptoms and extremely short prognoses over total number of cases with extremely short prognoses in each included study. Random effects models were used in accordance with the method of Nyaga et al (2014) to produce pooled prevalence estimates for clinically significant depressive symptoms defined by specific screening tools and diagnostic criteria (41, 42). The I^2 statistics were used to estimate heterogeneity and risk of bias. Potential sources of heterogeneity were further investigated by use of visual inspection of the data, forest plots and through meta-regression analysis. Inverted funnel plots and Egger's tests were performed to assess for small study effects or publication bias. Analyses were carried out with the function for proportion meta-analysis in STATA Version 16.0

RESULTS

As outlined in the PRISMA diagram (Figure 1), 7957 studies were identified through the electronic databases. After removal of duplicates, 5531 studies underwent title and abstract screening, leaving 500 studies for full-text screening. Following this, 13 studies (Table 1) were included for data extraction, with 57.1% (278 out of 487) full-text screening studies not having data on the sub-group of interest (people with extremely short prognoses). Hand-searching did not identify any eligible studies.

Study demographics are illustrated in Table 2. All 13 included studies had a prospective design, with five studies (43-47) being longitudinal and eight being cross-sectional only (4, 48-54). Two studies had a combination of malignant and non-malignant diseases (e.g. cardiovascular, respiratory and other diseases) (52, 54). Ten studies focused on malignant disease only (4, 43, 44, 46-51, 53). Out of these, one study focused on advanced gynecological cancer (53) and another on lung cancer (46). Other eight malignant studies involved a combination of various types of cancers (4, 43, 44, 47-51). Extraction of data of interest from specific malignant or non-malignant conditions in studies involving combination of conditions was not possible. Only one study focused exclusively on a non-malignant disease (late stage amyotrophic lateral sclerosis) (45).

Six studies involved inpatients only (4, 43, 47, 48, 53, 54), of which three were palliative care specific (4, 47, 53). One study was home care only (palliative care specific) (52). Four studies were mixed settings (44, 49-51), one of which was palliative care specific (49). Two studies did not specify the setting of care (45, 46).

Mean age reported in eight studies ranged from 58.0 to 70.9 years old. Five studies did not report mean age. The percentage of males ranged from 36.5% – 69.8% in 11 studies. One study did not report participant gender (44), and one study only recruited females with advanced gynaecological cancers (53).

For the definition of extremely short prognoses, seven studies reported functional status equivalent of AKPS ≤ 40 (median survival of one month) (46-51, 53), and eight studies reported directly on survival data (4, 43-45, 47, 49, 52, 54). Two studies reported both survival and functional status data (47, 49).

Ten studies defined clinically significant depressive symptoms using a specific tool: Patient Health Questionnaire 8 or 9 [PHQ-8 or 9] (n = 5) (44, 45, 50, 51, 54), HADS (n = 4) (43, 46, 49, 53), and Depression Rating Scale [DRS] (n = 1) (52). Four studies used diagnostic criteria (DSMIIIR, IV or V) (4, 47, 48, 54), while one study used both PHQ-9 and DSMV (54).

Prevalence of Clinically Significant Depressive Symptoms

The prevalence of clinically significant depressive symptoms in people with life-limiting illnesses and extremely short prognoses was analysed with reference to tools, diagnostic criteria and risk of bias.

Tools

1. ≥Mild or Minor Severity (PHQ8/9≥5, HADS≥8, DRS≥3)

Overall pooled prevalence of clinically significant depressive symptoms of mild/minor severity or greater (defined as: PHQ8/9≥5, HADS≥8, DRS≥3 (55-57); n = 10) (43-46, 49-54) in people with extremely short prognoses (N = 905) was 50% (95%CI: 29%-70%) (Figure 2). There was high heterogeneity (I^2 = 97.6%).

Meta-regression found no significant differences between prevalence of depressive symptoms measured by different tools (p = 0.774). Differences in tools also did not account for the high heterogeneity among studies (Adjusted R^2 = -12.40%). Interestingly, DRS≥3 appeared to yield lower prevalence of depressive symptoms of 21% (95%CI: 17%-25%; n = 1). Removal of the prevalence data from DRS≥3 raised overall pooled prevalence to 53% (95%CI: 37%-70%) and reduced heterogeneity slightly (I^2 of 93.1%) (extremely short prognoses sample: N = 547).

2. ≥Moderate or Major Severity (PHQ8/9≥10, HADS≥11)

When performing sub-group analyses on depressive symptoms with the severity cut-off of moderate or more (PHQ8/9≥10 or HADS≥11 (56, 57); n = 7), pooled prevalence of clinically significant depressive symptoms in people with extremely short prognoses (N = 476) was 55% (95%CI: 37% - 74%) (43, 44, 49-51, 53, 54). Heterogeneity was still high (I^2 = 93.4%). (Prevalence data from DRS≥3 was not included in subgroup analysis as DRS≥3 contained both major and minor depressive symptoms) (55).

There was no statistically significant difference (p = 0.36) between pooled prevalence measured by PHQ8/9≥10 (47% [95%CI: 23%-71%]) and that by HADS≥11 (64% [95%CI: 40%-89%]), accounting for only 4.2% of the study heterogeneity in the greater or equal to moderate severity sub-group (meta-regression adjusted R^2 = 4.2%).

Common Disorders by DSM Diagnostic Criteria

Prevalence of depressive symptoms defined by common disorders through diagnostic criteria (DSMIIIR/IV/V) included:

- Major depression (Major depressive disorder / episode; n = 3) (4, 47, 54):

  - On meta-analysis, the pooled prevalence of major depression in people with extremely short prognoses (N = 308) was 10% (95%CI: 4%-16%; extremely short prognoses sample size: N = 308; Figure 3).
  - Heterogeneity among studies was only moderate (I^2 = 57.5%).
- Minor depression (n = 1) (47): 5% (95%CI: 2%-8%; extremely short prognoses: N = 200)

Longitudinal Changes

In five longitudinal studies, data for longitudinal changes in prevalence of clinically significant depressive symptoms over the 3-6 months before death could be extracted in two studies (43, 44). Tang et al (2016) reported increasing prevalence of clinically significant depressive symptoms (defined by HADS ≥11) in Chinese cancer patients as days to death approached from 44.58 % (181–365 days), 49.91 % (91–180 days), 69.44 % (31–90 days), to 82.64 % (1–30 days) (43). Rabkin et al (2009), also in the cancer population but in United States, reported a prevalence of major depression (using PHQ-9) of 0% at 3 months before death, rising to 29% in the last month of life (44).

Two studies informed the proportion of new onset symptoms in those cases with clinically significant depressive symptoms and extremely short prognoses, which were 36.3% [four out of 11 – Rabkin et al (2005)] and 57.1% [four out of seven – Rabkin et al (2009)] (44, 45).

Quality /Risk-of-Bias Assessment

Quality of Individual Studies

Seven of 13 studies did not fulfil at least 1 item of the JBI checklist (Figure 4). The leading source of bias (not fulfilling specified item criteria) was selection bias (Item 1-5: 21.5%), followed by attrition bias (Item 9: 15.4%), and detection/measurement bias (Item 6-7: 3.8%). No analysis bias was identified.

Prevalence by Low Risk-of-Bias Studies

There were only two studies found to have low risk of bias, fulfilling all nine criteria in the JBI checklist of prevalence studies. These differed in country of study and method of depression identification (48, 49).

Despite these differences, they both had the same depression prevalence of 47%: Stromgren et al (2002) – study from Denmark using the tool HADS≥11 yielded 47% (95%CI: 39%-55%) (49); and Zhao et al (2014) – study from China using DSMIV criteria for Depressive Disorders (major & minor depression, dysthymia and mood disorders due to general medical conditions with depressive features) found 47% (95%CI: 34%-60%) (48).

Quality across Studies

Each domain of Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess quality across studies (described below). However, the overall quality score could

not be generated using the online platform for GRADE (GRADEPro), as it was not configured for systematic reviews of prevalence studies (40, 58, 59).

For risk-of-bias across studies, there were serious limitations due to the general selection bias intrinsic to researching populations with life-limiting illnesses. Participants were often excluded if they had significant cognitive impairment or frailty.

For the domain of indirectness, all studies directly addressed their research questions on the prevalence of depressive symptoms.

Regarding imprecision, there was a lack of established guidance in assessing precision for meta-analyses of prevalence studies. Assuming the use of the width of confidence intervention in the GRADE approach to assess precision, there was a relatively low precision for prevalence of depressive symptoms identified by tools (50% [95%CI: 29%-70%]). However, precision was modest for that identified by diagnostic criteria, with major depression having the widest confidence interval (10% [95%CI: 4%-16%]). If precision was defined as the sensitivity and specificity of tools used, then it was relatively high across the studies. All the tools used (PHQ, HADS and DRS) have been psychometrically tested in the palliative care or oncology settings (55, 60-62).

For inconsistency, there was high heterogeneity across studies for the prevalence of depressive symptoms by tools (I^2 = 93.4%-97.6%), but only modest heterogeneity (I^2 = 57.5%) for prevalence of depressive symptoms by diagnostic criteria for major depression.

To assess for small study effects and publication bias, studies with sample sizes of 100 or less were removed from meta-analyses. The final pooled prevalence estimates of clinically significant depressive symptoms by tools (≥ mild severity) (50% [95% CI: 8% – 92%]; I^2 = 99.4; n = 3 (43, 49, 52)) and diagnostic criteria for major depression (8% [95%CI: 5.0% - 12.6%]; n = 1 (47)) have not changed significantly from the estimates that included all studies. Regression (Egger's) tests of the corresponding inverted funnel plots again showed no evidence of small study effects or publication bias for the meta-analyses that included all selected studies: using depression-specific screening tools (⩾mild or minor severity; Egger's Coefficient: 0.87 [95%CI: -7.45 to 9.19); p = 0.815); and diagnostic criteria for major depression (Egger's Coefficient: 1.04 [95%CI: -36.12 to 38.21]; p = 0.782).

DISCUSSION

High Prevalence of Clinically Significant Depressive Symptoms in Extremely Short Prognoses Setting

This evidence synthesis found high prevalence (one in two individuals) of clinically significant depressive symptoms in people with extremely short prognoses.

The duration of a median survival of one month (indicated by the functional scores of KPS ⩽ 40 or ECOG 4) with the upper limit of two months was used to differentiate individuals with extremely short prognoses from others with advanced life-limiting illnesses. This is an important distinction as this time period is the time during which frailty and symptomatology of the terminal illnesses (e.g. fatigue, delirium and inability to swallow) significantly escalates, hindering effective depression

assessment and management (19, 24, 25). This extremely short life-expectancy period makes the conventional depression interventions unlikely to be successful due to their slow onset-of-actions, and supports the consideration for alternative rapid-onset interventions such as methylphenidate or ketamine (26, 63, 64).

The prevalence of clinically significant depressive symptoms in advanced life-limiting illnesses using HADS score ≥11 have been reported in a systematic review to be around 29% (11). This review adds to the data by finding a higher pooled prevalence of 50% in the sub-group with extremely short prognoses using depression-specific tools. If only studies with HADS score ≥11 were considered, an even higher overall pooled prevalence of 64% resulted, including the 47% from the low risk-of-bias study (49).

Meanwhile, the prevalence of combined depressive disorders in the general advanced illness population using diagnostic criteria has been reported to be 25% in another systematic review (12). This is lower than the corresponding prevalence of 47% found using diagnostic criteria in people with extremely short prognoses in the current review (48). The higher prevalence of clinically significant depressive symptoms in those with extremely short prognoses is further supported by the findings of longitudinal studies by Tang et al (2016) (included in this review) and Seow et al (2011), where both studies reported increases of 33% and approximately 10% respectively in prevalence of clinically significant depressive symptoms in the last six months of life (19, 43).

Reasons for high prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses are likely multi-faceted. In addition to individuals having the stressors of advanced life-limiting illnesses and associated adjustment issues, inadequacy of recognition, assessment and management of these symptoms during life-limiting illnesses at earlier stages may be a factor. Studies reveal around 40% of clinicians treating people with advanced life-limiting illnesses do not regularly screen or assess for depressive symptoms, with as low as 7% of the depressed cases being recognised and up to 70% of affected individuals receiving inadequate interventions (20, 48, 65-68). There is intrinsic difficulty in assessing depressive symptoms in individuals whose advanced life-limiting illnesses might mimic depressive symptoms, as well as challenges in providing interventions likely to be effective in time (1, 26). Further barriers to suboptimal recognition, assessment and management include: clinicians' fear of distressing patients, especially given the stigma associated with psychiatric diagnoses (3, 69); lack of awareness and skills to detect and manage depression (20, 68, 70-75); perceived lack of resources such as time (20, 68, 76), acceptable assessment tools and access to mental health services (20, 69, 77-82); beliefs that depression is 'normal' (69, 76); and that screening & interventions are likely to be futile in this context (70, 71, 73, 83). It is possible that addressing these barriers might lead to an earlier detection and management of depressive symptoms in people with advanced life-limiting illnesses. This may subsequently lower the prevalence of such when prognoses are extremely short.

Meanwhile, evidence suggests a significant proportion of individuals with advanced life-limiting illnesses and extremely poor prognose were experiencing clinically significant depressive symptoms for the first time (36%-57% from Rabkin et al (2005) and Rabkin et al (2009) in this review (44, 45)). This is also supported by the findings of a trend for building prevalence as death approaches (43, 44). Given the limitation of having only small number of studies with small sample sizes, these findings need to be interpreted with caution. The findings should not be perceived as definitive but

hypothesis generating. The exact prevalence of new-onset cases needs to be further studied. Nonetheless, one might also ponder on the underlying drivers for having a substantial proportion of new cases of depressive symptoms in the last weeks to days of life. It may be possible that the pathological processes of the advanced life-limiting illnesses themselves such as brain metastases or hypercalcemia cause depressive symptoms (84). Other potential drivers for new-onset depressive symptoms may be: the associated distressing symptoms and functional limitations that are often more marked towards the end-of-life due to disease progression (19, 43, 46, 85); the associated grief & hopelessness (86); loss of dignity (87, 88); concerns about social relationship (e.g. perceived lack of support or fear of being a burden to others) (43, 47, 85); and existential distress (88). It would be instructive to see whether targeting these issues decreases incidence of depressive symptoms in people with extremely short prognoses in future studies.

Methods of Defining Clinically Significant Depressive Symptoms

The construct of "clinically significant depressive symptoms" in the literature is an interesting one. It encompasses depressive disorders diagnosed by the conventional diagnostic criteria (27). It also includes subsyndromal depression where depressive symptoms are severe enough to fulfil certain thresholds set by various depression-specific screening tool but cannot be diagnosed as specific depressive disorders using diagnostic criteria (27-30). In fact, the sole use of diagnostic criteria in assessing for depressive symptoms in the extremely short prognoses setting might underestimate the true prevalence of these symptoms. Firstly, there may not be enough time for specific depressive disorder (e.g. two weeks for major depression (9)) to be established due to the short life expectancies (89). Secondly, up to three-quarters of patients with extremely short prognoses might to excluded from studies, as the assessment of diagnostic criteria using psychiatric interviews could be too burdensome, considering their cognitive impairment or frailty (4, 11, 47)). The addition of using validated depression-specific screening tools in the palliative care setting to identify individuals with clinically significant depressive symptoms may overcome the issue of missing individuals with subsyndromal depression by diagnostic criteria. Nonetheless, the use of depression-specific tools does come with the intrinsic shortfall of "false-positivity". When used as indirect measurements of specific depressive disorders, normal anticipatory grief may not be entirely excluded, leading to an over-estimation of the prevalence of specific depressive disorders (90, 91). Perhaps, a better way to perceive the use of depression-specific screening tools is not to use them to predict for certain depressive disorders in this context. Rather, these tools have the value in identifying people who have clinically significant depressive symptoms at a certain time point that requires clinician attention and interventions, including those with subsyndromal depression.

There are a myriad of depression specific screening tools . Among these, relatively few have been validated for use in the palliative care setting. These include: HADS, Single and Two Items Questions ("Are you depressed?" +/- "Have you lost interest in activities?"), Visual Analogue Scale, Edinburgh Postnatal Depression Scale, and Beck Depression Inventory-Short Form (91). The current study identified three tools that were used in people with life-limiting illnesses and extremely short prognoses: Patient Health Questionnaire 8/9 (PHQ 8/9), HADS and Depression Rating Scale (DRS - InterRAI PC). This review and meta-analysis did not observe any statistical differences between them. This is consistent with the findings by Cameron (2008) and Hansson et al (2009) that demonstrated

similar prevalence of depressive symptoms generated by HADS and PHQ-9 with overall convergent validity between the two tools, though there was a lack of convergence between the severity cut-offs (56, 57). However, it is possible that, with only a modest number of studies using tools (n = 10), this study was insufficiently powered to detect the differences between them. Particularly, the one study that used DRS seemed to have yielded a low prevalence estimate (52). The underlying reason might be due to the construct of DRS. The DRS was originally designed to detect depressive symptoms in nursing home residents, for whom assessing patients face-to-face using psychiatric interviews or self-reported depression-specific tools might be impractical (55). Its scoring depends on the daily observed standardized mood and behavioural item data collected in the Resident Assessment Instrument, the Minimum Data Set (55). Different from PHQ-8/9 or HADS, it only contains three depression-specific items (sad facial expression, tearfulness, and observed negative statements by residents [passive suicidal ideation]). Four other items are less depression-specific (anger & irritability, expressions of fears, repetitive health complaints; and repetitive anxious concerns) (55). Therefore, there is a possibility that DRS under-recognized depressive symptoms in patients who had other depressive symptom items included in PHQ-8/9 or HADS but did not have depressed or teary affect, leading to a lower prevalence estimate. The comparison and feasibility of these tools for the use of detecting clinically significant depressive symptoms in people with extremely short prognoses warrant further investigation.

In contrast, when exploring the prevalence of depressive symptoms using diagnostic criteria (gold-standard) for specific depressive disorders, the prevalence of major and minor depression represented a relative minority. Major and minor depressions accounted for only 10% and 5% respectively of those with extremely short prognoses and clinically significant depressive symptoms. This reflects the observations that clinically significant mood disturbances are prevalent (around 40%) but major depression is relatively uncommon in the general cancer or terminal settings (89, 92). In fact, the prevalence of major depression and other associated mental disorders might not increase as death approaches (92). Nonetheless, the pooled prevalence of combined depressive disorders (major & minor depression, dysthymia and mood disorders due to general medical conditions with depressive features) found in this review was high, at 47% by Zhao et al (2014) (48). This raises the possibility that much of the clinically significantly depressed individuals with extremely short prognoses may not be diagnosed with major or minor depression, but rather, be labelled as other disorders with depressive features (e.g. adjustment disorder) (84). Interestingly, the composite prevalence of various depressive disorders for people with extremely short prognoses of 47% seemed to equate to the prevalence of depressive symptoms defined using screening tools (as seen in the results of the low-risk-of-bias studies and the pooled prevalence of 50%-55% in meta-analyses using tools) (48, 49). This raises the possibility that, in those with extremely short prognoses, one can use depression screening tools such as HADS or PHQ to estimate the combined prevalence of various depressive disorders (and therefore the burden of depression). This would avoid the need to undergo extensive psychiatric interviews as required by the diagnostic criteria for patients for whom these interviews might be too burdensome and thus not be feasible. This too warrants future study. In contrast, for diagnostic purposes, these screening tools should not replace diagnostic criteria in diagnosing depressive disorders (63). Rather, these screening tools are means to help clinicians identify individuals with clinically significant symptoms needing interventions.

Limitations: Quality Assessment/Risk-of-Bias

The predominant types of risk of bias across studies in this review, consistent with the other similar systematic reviews exploring the prevalence of depressive symptoms in advanced life-limiting illnesses, were selection and attrition (non-responder) biases (11, 12). The findings of this review need to be interpreted considering these biases. In the included studies, a significant proportion of participants with extremely short prognoses were excluded due to their being significantly cognitively impaired or too frail to undergo study assessment (even up to 75% in one study) (47). Given the assessment of depressive disorder is contentious for those with significant cognitive impairment or dementia, marked by a wide range of prevalence of depressive symptoms, prevalence studies in the setting of significant cognitive impairment or dementia were excluded in this systematic review (93-95). More than half of the full texts screened (57%) could not have data for those with extremely short prognoses extracted with a lack of the functional status or survival data of interests. There is, therefore, a need for future research involving advanced life-limiting illnesses to include prognostic or survival measures such as those used in this review. Feasible alternative methods of assessing for depressive symptoms in this context also need further investigation.

Another limitation of this review is that studies that used general symptom measurement scales with non-specific depression measurement such as the Edmonton Symptom Assessment System Depression Score (ESAS) were excluded (19, 21). This was to ensure measurement accuracy. However, prevalence of depressive symptoms in people with extremely short prognoses captured by ESAS in Seow et al, 2011 (36%) and Liu et al, 2013 (41.7%) were consistent with results of this systematic review (19, 21). This raises the possibility that ESAS may be a feasible screening tool for depressive symptoms in people with extremely short prognoses.

Similar to other systematic reviews reporting prevalence of depressive symptoms in palliative care, this systematic review is limited by the high heterogeneity of the included studies (11, 12). Due to the small number of studies included (n = 13) and many studies having a combination of variables (e.g. a combination of malignant and non-malignant diseases or mixed recruitment settings), extensive investigation of potential moderators that account for heterogeneity using meta-regression cannot be performed with statistical validity. Nonetheless, one can postulates that the majority of heterogeneity is contributed by the same factors listed in other similar systematic reviews: the various populations studied, assessment methods and depression definitions (11, 12).

Strengths and Other Limitations

Firstly, the results reported by this review represents possibly the largest number of people with extremely short prognoses (N = 1245) in the current literature. This review utilised inclusive search strategies to include the broader population of advance life-limiting illnesses that would not necessarily have been referred to palliative care, as well as both malignant and non-malignant disease. However, there is a relative lack of representation of studies focusing on non-malignant disease. This is because many screened non-malignant studies did not include a measure of functional status, especially later in people's disease trajectory. Additionally, there was a lack of studies that reported the prevalence findings of malignant or non-malignant diseases separately. Therefore, comparison of prevalence estimates between studies with malignant versus non-malignant disease has not been possible.

An important limitation of this review is the inclusion of studies with small sample sizes into the meta-analysis, introducing the risk of small study effects and publication bias (96-98). Nonetheless,

inverted funnel plots and Egger's regression tests have demonstrated the lack of small study effects. The removal of studies with sample sizes of 100 or less from meta-analyses have demonstrated comparable findings (96). Perhaps, in this context, a robust estimation of prevalence would be achieved through including all available evidence, as limiting studies due to small study size may introduce subjectivity to the final result (99). However, the lack of sample size in individual studies have contributed to the overall limited precision of the prevalence estimates. This is indicated by the wide confidence intervals of the prevalence data.

A strength of this review is that the prevalence of clinically significant depressive symptoms has been explored by considering various methods of detection (utilising depression-specific screening tools and different diagnostic criteria through psychiatric interview). This ensures that the pooled prevalence better reflects the overall global burden of depressive symptoms experienced by this sub-population.

Another major strength of this study is that this is one of the few reviews with meta-analysis of prevalence that uses formal guideline to critically appraise individual studies (JBI Systematic Reviews Checklist for Prevalence Studies) and across studies (GRADE approach), for the first guideline established to appraise individual prevalence studies was only published in 2017 (37-40). For quality assessment across studies, GRADE approach has been frequently utilised for meta-analysis of cause-and-effect and diagnostic tools (40, 58, 100). However, it has yet to be adapted for the use of assessing prevalence studies (59). Therefore, this systematic review has used the general principles of the GRADE approach to perform quality assessment across studies. The overall GRADE score has not been generated in this review to allow the opportunity for objective judgments by the readers.

Implications

The findings of the increase in prevalence as death approaches with up to half of the people with extremely short prognoses having clinically significant depressive symptoms have major implications for clinical practice, policy makers & funders, and future research.

Implication for clinical practice

There is a need for some forms of systematic processes (e.g. screening for depressed mood on first contact with palliative care services) to increase clinicians' awareness of potentially depressed individuals, as the affected individuals might be reluctant to report symptoms of depression due to social stigma (3, 11, 20). Patients and families may need to be encouraged to talk about their mood by clinicians, and certain components of the depression screening tools might be helpful to act as prompts (e.g. using PHQ-9 to ask about anhedonia).

Emphasis must be placed on clinicians to not neglect patients' concerns of depressed mood in the context of having extremely short prognoses as 'normal reactions' to the dying process. Clinicians need to be aware that there is a high likelihood of these patients suffering from depressive symptoms that significantly impair their quality-of-life without meeting the diagnostic criteria of various depressive disorders (subsyndromal depression). The disclosures of these symptoms from patients, therefore, need to be thoroughly explored and addressed, with the expression of depressive symptoms encouraged and de-stigmatised (3). Individuals with subsyndromal depression

may still benefit from various psychological support interventions to prevent more severe depressive symptoms and disorders from developing (63). In fact, given the high prevalence of these symptoms, there is an argument that all patients with extremely short prognoses should be offered empathic non-pharmacological supportive services (e.g. counselling / supportive psychotherapy) as primary prevention for possible depressive symptoms, and have the escalation of treatments as deemed appropriate.

Implication for policy makers and funders

The high prevalence of clinically significant depressive symptoms in this subgroup of extremely short prognoses necessitate the treating clinicians to be trained and empowered for timely assessment and management of depressive symptoms. The clinical culture needs to be one that offers supportive environment to staffs engaging with depressed patients (e.g. allowing extra time in clinic for depression assessment, offering de-briefing sessions for staffs). Integration between palliative care and psychiatry may improve the tendency of under-recognition of depressive symptoms, leading to better depression care (101-103). Public health interventions aiming at improving public awareness of mood health at the end-of-life, de-stigmatising depressive symptoms and encouraging open discussion are also required (3).

Implication for future research

This review highlights the needs for further research in people with advanced life-limiting illnesses and extremely short prognoses as studies focusing on this subpopulation as their primary objectives are lacking. The wide confidence intervals of prevalence estimates found in this study reflects the lack of any agreed nation or international criteria for referral to hospice / palliative care services, and the relatively poor estimation of people's prognosis by many clinicians (10). Importantly, this systematic review and meta-analysis forms an important first step to create a platform for more uniform population eligibility definitions for future, larger studies. The validity and acceptability of using functional scores as prognostic indicators for extremely short prognosis in non-malignant diseases needs to be further explored.

For depression research in this subpopulation, more prospective longitudinal studies are required to estimate the new occurrences of depressive symptoms better in individuals with extremely short prognoses. Identifying a feasible and acceptable screening tool and assessing the benefits of implementing screening is vital. The optimal method of assessing depressive symptoms, accounting for the possibility of patients not fulfilling certain components of the conventional diagnostic criteria due to the short life expectancy, and the feasibility and acceptability of the substitute approach of diagnosis (i.e. Endicott Criteria) need further exploration (104). Clinicians' perspectives on assessing and managing depression in this context, as well as the corresponding views from patient and their families also require study.

CONCLUSION

Clinically significant depressive symptoms (including subsyndromal depression) are common in people with advanced life-limiting illnesses and extremely short prognoses (approximately 50%).

Clinicians caring for people with extremely short prognoses need to be proactive in the recognition and assessment of these symptoms to allow for timely interventions. Much research is required to establish effective assessment and management strategies in this field.

AUTHOR CONTRIBUTIONS

Under the supervision of DC, MA, and BD, WL designed the systematic review protocol, search strategies (with assistance of the librarians of the University of Technology Sydney) and registered it to PROSPERO. The alternative reviewer group (MP, CS, SK, AH, EL, DP, and MA) reviewed the draft PROSPERO registration, screened title & abstracts and full-texts, and BD independently resolved conflicts. Data extraction and quality assessments were performed by WL and independently checked by MP and AH on random selections of five included studies. WL with the assistance of SC performed statistical analysis. WL with the assistance of the whole alternative reviewer group (MP, CS, SK, AH, EL, DP, and MA) and SC under the supervision of DC, MA, and BD prepared, edited and finalised the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

The authors report no conflict of interests.

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Table 1.

Characteristics of included studies

Author Year	Location, Country	Study Design	Source Population Eligibility / Recruitment Setting	Diagnoses	Demographics of Source Population (Total number [N], Age, Gender)	Sampling Method	Definition of Extremely Short Prognoses / Number from Source Population	Depression Definition / Assessment Timing & Method	Number (n) and Prevalence (%) of Clinically Significant Depressive Symptoms in People with Extremely Short Prognoses
Alamri et al 2017 (54)	Jeddah, Saudi Arabia	Prospective Cross-sectional Prevalence Study	Elderly patients aged 60 years and older admitted to the medical (51%) and surgical wards (49%) of a single university hospital. Exclusion: severe cognitive dysfunction, acute psychosis, bipolar disorder, schizophrenia, language barrier, aphasia, hearing impairment, reduced level of consciousness, or unstable medical illnesses	Cancer (not otherwise specified) and mixed non-malignant diseases (Cardiovascular, gastrointestinal, genitourinary, infectious, metabolic-endocrine, musculoskeletal, neurological, respiratory, and other)	N = 200 Mean age: 70.2 (SD: 8.1) Male = 41.0%	Consecutive	Hospital mortality /Survival (Author responded in email stating all those with hospital mortality had survival <60 days) N = 19	1. Self-administered PHQ-9: • ≥10: "major depression" • ≥ 5-9: "other depressive disorders" 2. Structured clinical interview with DSMV for "major depressive disorder" Within 48 hours of hospital admission by a trained research team member.	PHQ-9 ≥10: n = 6 (31.6%) PHQ-9 ≥ 5-9: n = 2 (10.5%) DSMV Major Depressive Disorder: n = 1 (5.3%)
Breitbart et al 2000 (4)	New York, United States	Prospective Cross-sectional Prevalence study	Hospitalized, terminally ill cancer patients recruited after admission to a 200-bed palliative care hospital with life expectancy of less than 6 months. Inclusion: English speaking; sufficiently cognitively intact to provide informed consent and valid data; and were not considered likely (by their physician) to suffer psychological harm from participation. Exclusion: Mini-Mental State Examination score below 20.	Cancer (not otherwise specified)	N = 92 Mean age: 65.9 (SD: 15.6) Male = 40.0%	Unclear	Survival with average time until death was 28 days N = 89 (interviews could not be completed for 3 subjects)	DSMIV for "major depressive episode" After admission jointly by two investigators via structured clinical interview (interrater reliability coefficients 0.55).	DSMIV major depressive episode: n = 15 (16.9%)
Chan et al 2012 (53)	Hong Kong, China	Prospective Cross-sectional study	Adult patients (≥18 years) with advanced (Stage III-IV) gynaecological malignancy in the palliative phase admitted to the palliative care unit of Grantham Hospital, Hong Kong. Inclusion: Chinese descent; fluent in the Cantonese dialect; and being capable of giving informed consent to participate in the study. Exclusion: Unable to complete the questionnaires due to either physical or cognitive limitation; and	Gynecological cancers (ovary, cervix, uterus)	N = 53 Mean age: 62.1 (SD: 15.5) Male = 0%	Consecutive	Functional status: median PPS = 40 N= 53	HADS (Chinese Cantonese version – Cronbach's α=0.77): • 8 to 10: "doubtful case" • 11 or higher: "definite case" • 15 or higher: "severe depression" Within 3 days of admission interviewed by principal investigator	HADS score: • 11 or higher "definite case": n = 33 (62.2%) • 15 or higher "severe depression": n = 10 (19%)

			being unable to communicate either verbally or in writing.						
Chochinov et al 1995 (47)	Winnipeg, Canada	Prospective longitudinal prevalence study	Terminal cancer adult patients from palliative care units of two hospitals in Winnipeg, Canada. Exclusion: Cognitively impaired and unable to give informed consent or were too gravely ill to take part in a detailed interview.	Mix cancer types (lung, gastrointestinal, genitourinary breast, hematological and other)	N = 200 Mean age: 70.9 (SD: 10.6) Male = 48.5%	Unclear	Survival: Median of 43 days Functional status: mean KPS 40 N = 200	DSMIIIR: Major and Minor Depressive Episodes One week or more after admission using semi-structured diagnostic interview administered by a trained psychiatric nurse, clinical psychologist or a psychiatrist. Two-week follow-up interview conducted only for those with desire to die at the initial interview. Inter-rater reliability measured by having second rater attend 13.5% of random sample interview (kappa 0.76).	DSMIIIR: • Major depressive episode: n = 16 (8%) • Minor depressive episode: n = 9 (4.5%) *Cannot extract prevalence data of extremely short prognosis on the two week follow-up time point (as only those with desire for death were re-assessed and reported).
Fisher et al 2014 (52)	Ontario, Canada	Prospective Cross-sectional Prevalence Study	Home care palliative care adult patients in 6 of 14 sites in Ontario involved in pilot implementation of new palliative care need assessment tool (InterRAI Palliative Care) with a mix of malignant and non-malignant diseases. *"Participants were classified as palliative by the home care case manager if they were no longer responsive to curative treatment, considered to be dying, and the goal of care was to alleviate distressing symptoms in the last stage of their illness" Exclusion: Significant cognitive impairment (i.e., Cognitive Performance Score [CPS] < 4); Unable to give informed consent	Cancer (not otherwise specified) and non-malignant diseases (Cardiovascular, Chronic Obstructive Pulmonary Disease, and other)	N = 5144 Average age of 70.0 (range: 19.6 – 107.2; two-thirds of the sample > age 65) Male = 49.1%	Unclear	Survival: Estimated prognosis <6 weeks N = 358	Depression Rating Scale (DRS) (InterRAI Palliative Care) ≥ 3 for "Depressive Symptoms" Assessor rating at time of assessment not otherwise specified	Table 1: "Depressive Symptoms" by Depression Rating Scale (DRS) (InterRAI Palliative Care) ≥3: n = 74 (20.7%)
Hartung et al 2017 (51)	5 regions across Germany	Prospective Cross-sectional Prevalence study	Adults (age 18 through 75), proficient in German, with cancer from a mixture of clinical settings - total of 84 inpatient oncology wards, outpatient clinics, cancer rehabilitation centres in five distinct regions across Germany (Freiburg, Hamburg, Heidelberg, Leipzig and Würzburg). Exclusion: Cognitive and verbal impairments that interfered with ability to give informed consent.	Mix cancer types (thyroid, brain, pancreas, hematological, female genital organs, bladder, lung, stomach/esophagus, head and neck, soft tissue, breast, testis, kidney/urinary tract, colon/rectum, hepatobiliary, melanoma, prostate,	N = 4020 Mean age: 58 (SD: 11) Male = 48.6%	Consecutive	Functional status: ECOG4 N = 13	PHQ-9 ≥10 for "depressed" (German version of the self-report measure) Timing of assessment not specified	"Depressed" by PHQ-9 ≥ 10: n = 6 (46.2%)

				other)					
Hopwood & Stephens 2000 (46)	United Kingdom	Prospective – Longitudinal Prevalence Study using data from 3 RCTs	Adults with lung cancer (non-small-cell and small-cell lung cancers) from three multicentred RCTs by United Kingdom Medical Research Council Lung Cancer Working Party: two chemotherapy trials (LU12 and LU16) and one radiotherapy trial (LU13).	Non-small-cell and small-cell lung cancers	N = 1189 (Male = 69.8%), consisted of the below: LU12 (Chemotherapy trial for small-cell lung cancer): N = 310 Median age: 65 (Range 39-90) Male = 63% LU 16 (Chemotherapy trial for small cell lung cancer) N = 370 Median age: 67 (Range 35-83) Male = 63% LU13 (Radiotherapy trial for Non-small-cell-lung cancer) N = 509 Median age: 66 (Range: 33-89) Male = 79%	Random	Functional status: WHO PS 4 N = 11	HADS for "Depression" ("Borderline" or "Case"): • 8-10: "Borderline" • ≥11: "Case" HADS assessed at baseline and at first follow-up	"Depression" (case or borderline score) by HADS ≥8 at baseline: n = 6 (55.0%) *Cannot extract data of extremely short prognosis on the first follow-up time point (High attrition rate with WHO PS 4 prevalence data not reported)
Que et al 2013 (50)	Manila, Philippines	Prospective Cross-sectional Prevalence Study	Adults oncology inpatients and outpatients presented for cancer treatment at a single non-profit tertiary hospital in Manila, Philippines.	Mixed Cancer Types (breast, head and neck, lung, brain, lymphoma, leukemia)	N = 271	Unclear	Functional status: ECOG 4	"Depression" by PHQ-8 (excludes the item on suicidal ideation) ≥10 (Cronbach's α = 0.84)	"Depression" by PHQ-8 ≥10: n = 6 (86%)

					*Age ≥ 53 = 53.5% *Male = 36.5% (*Age & Gender data extrapolated from table 2 of article)		N = 7	Timing of assessment (survey) not specified	
Rabkin et al 2005 (45)	New York, US	Prospective Longitudinal Prevalence Study	Hospice eligible adult patients with late stage amyotrophic lateral sclerosis (ALS) indicated by FVC <50% ("a value related to the risk of hospice admission and death or the need for mechanical ventilation within 6 months") from multiple sites (though 94% enrolled from a single ALS Research Centre) (setting not otherwise specified). Exclusion: dementia; inability to speak English; absence of nonpaid caregiver who agreed to participate; use of mechanical ventilation at baseline; inability to communicate at least "yes" and "no,"; lived outside 3-hour drive from medical centre.	Late-stage amyotrophic lateral sclerosis	N = 80 Age ranged from 27 to 85, 20% were under age 50, and one-third were over 70 Male = 56%	Unclear	Survival: Median interval between time of last monthly interview and death = 30 days N = 53	Major and Minor Depression by PHQ-9*: • Major Depression: ≥5 items with score ≥2 with ≥ 1 item being depressed mood or anhedonia • Minor Depression: ≥3 items with score ≥2 with ≥ 1 item being depressed mood or anhedonia *Authors departed from the standard scoring on three items of PHQ-9 that were sometimes directly caused by ALS: sleep problems, poor appetite, and psychomotor retardation when considered inappropriate, and prorated the remaining items to generate a total score. Scheduled monthly interviews almost always at home until patients met a study endpoint of tracheostomy or death	Depression (Both major and minor Depression) by PHQ-9≥6: n = 17 (32.1%)
Rabkin et al 2009 (44)	New York/San Francisco, United States	Prospective Longitudinal Prevalence Study	Cancer patients with prognosis of 6-12months from oncology services of multiple sites and home care service of a community hospital. Exclusion: Non-English speaking; insufficient cognitive capacity to consent to study; had no a family member or close friend who served as a non-paid caregiver and who agreed to participate; not lived at home within an hour drive from the respective medical centre at study entry	Mixed cancer types (breast, lymphomas, colorectal, lung, pancreas and other)	N = 58 Age and gender of the cohort not reported	Convenience	Survival: Median interval between final assessment and death = 28 days N = 24	"Major depressive disorder" by PHQ-9 ≥10: (≥ five items including depressed mood or loss of interest must be scored 2 or 3) (Cronbach α = 0.79) Assessment by interviews almost always at home scheduled at approximately 1-month intervals until death or the study ended	Major depressive disorder by PHQ-9 ≥10: n = 7 (29.2%)
Stromgren et al 2002 (49)	Copenhagen, Denmark	Prospective Feasibility /Cross-sectional Prevalence study	Danish speaking adult patients with advanced cancer for which no curative or life-prolonging treatment could be offered and referred/admitted to the palliative care services of a Copenhagen hospital (Mixture of inpatient, outpatient and home care palliative care services).	Mixed cancer types (brain, head and neck, gastrointestinal tract, respiratory, breast, genitourinary, gynecological, sarcoma, melanoma/skin,	N = 176 Age: mean 62.9 (No SD reported); median 63	Consecutive	Survival from first contact with department: Median 35 days Functional status: Median KPS 40	"Depression (Definite case)" by HADS ≥ 11 Assessed via self-assessment questionnaire at first contact with the palliative care department.	Depression (Definite case) by HADS ≥ 11: n = 63 (47.0%)

			Exclusion: No informed consent; staff judged the patient too ill to participate	hematologic, unknown)	(Range: 37-91) Gender: Male = 43.8%		N = 134		
Tang et al 2016 (43)	Taiwan	Prospective Longitudinal prevalence study	Adult (≥20 years old) oncology patients with terminal stage cancer and palliative intent treatment (unresponsive to curative cancer treatment and continuing to progress) from medical inpatient units of a medical centre in Taiwan Exclusion: Cognitively incompetent as evaluated by their primary physicians; ability to communicate coherently with data collectors.	Mixed cancer types (lung, liver-pancreas, head and neck, other)	N = 325 Age over 56 years old = 58.5% Male = 57.5%	Convenience	Survival - Time before death of 1-30 days N = 233	"Severe Depressive Symptoms" by HADS scores ≥11 Participants were interviewed while hospitalized or waiting for outpatient visits approximately every 2 weeks until they declined to participate or died.	"Severe Depressive Symptoms" by HADS scores ≥11: n = 192 (82%)
Zhao et al 2014 (48)	Beijing, China	Prospective Cross-sectional Study	Consented adult (≥18 years) cancer patients from the inpatient oncology ward of a hospital in Beijing Exclusion: Too frail or unwell to be interviewed; obvious cognitive impairment based on a brief clinical interview performed immediately before the administration of the Mini International Neuropsychiatric Interview (MINI) 5.0; severe hearing/speech impairment that would make the interview infeasible; being unaware of cancer diagnoses	Mixed cancer types (lung, digestive tract, breast, liver, ovarian, uterine and other)	N = 460 Mean age: 59.4 (SD: 12.0); Range: 20-99 Male = 49.1%	Consecutive	Functional status: ECOG 4 N = 51	"Depressive Disorders*" by DSMIV ascertained by Chinese version of the Mini International Neuropsychiatric Interview (MINI) 5.0 by eight trained psychiatrists (coefficients of interrater and test–retest reliability were 0.92 and 0.98 respectively). *Depressive disorders included: major depressive disorder (MDD), dysthymia, minor depressive disorder, mood disorder due to a general medical condition with major depressive-like episode or with depressive features; and mood disorder due to substances with depressive features. Time of assessment by psychiatrists while as inpatients was not otherwise specified.	"Depressive Disorders*" by DSMIV (MINI): n = 24 (47.1%) *Depressive disorders included: major depressive disorder (MDD), dysthymia, minor depressive disorder, mood disorder due to a general medical condition with major depressive-like episode or with depressive features; and mood disorder due to substances with depressive features.

ABBREVIATIONS: ALS: Amyotrophic Lateral Sclerosis; CPS: Cognitive Performance Score; DRS: Depression Rating Scale (InterRAI Palliative Care); DSM: Diagnostic and Statistical Manual of Mental Disorders; ECOG: Eastern Cooperative Oncology Group Performance Status; FVC: Forced Vital Capacity; HADS: Hospital Anxiety and Depression Scale; KPS: Karnofsky Functional Performance Status Scale; MDD: Major Depressive Disorder; MINI: Mini International Neuropsychiatric Interview; PHQ: Patient Health Questionnaire; PPS: Palliative Performance Scale; PHQ: Patient Health Questionnaire; RCT: Randomized Controlled Trial; SD: Standard Deviation; WHO PS: World Health Organization Performance Status

Table 2.

Study demographics of included studies (n=13)

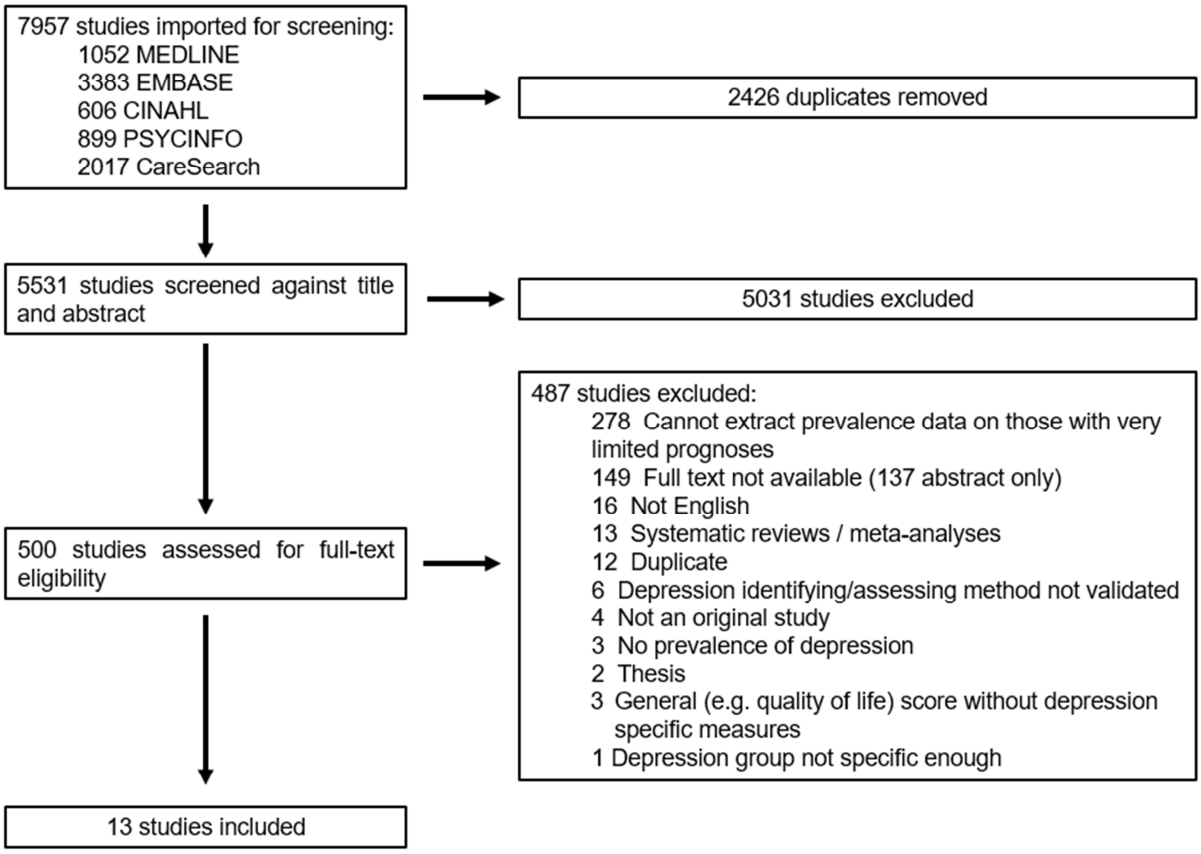
Study Characteristics	**Number of Studies (n out of 13) / Study Descriptions**
Study Design	
Prospective	13
Longitudinal (43-47)	5
Cross-sectional (4, 48-54)	8
Country	
Saudi Arabia (54)	1
Philippine (50)	1
China (Beijing/ Hong Kong/Taiwan) (43, 48, 53)	3
United States (4, 44, 45)	3
Canada (47, 52)	2
United Kingdom (46)	1
Germany (51)	1
Denmark (49)	1
Recruitment Settings	
Inpatient only	6
General (43, 48, 54)	3
Palliative care specific (4, 47, 53)	3
Outpatient only	0
Home care only	1
General	0
Palliative care specific (52)	1
Mixed settings	4
General (44, 50, 51)	3
Palliative care specific (49)	1
Others	2
Setting not otherwise specified (45, 46)	2
Diagnoses	
Combination of malignant and non-malignant conditions (52, 54)	2
Malignant only (4, 43, 44, 46-51, 53)	10
Combination of early and advanced cancer types (50, 51)	2
Advanced / terminal cancer (mix types) (4, 43, 44, 47, 49, 84)	6
Advanced gynecological cancer (palliative phase) (53)	1
Lung cancer (small cell & non-small cell) on palliative chemo /radiotherapy (46)	1
Non-malignant	1
Late stage amyotrophic lateral sclerosis (45)	1
Age	
Mean age	58-70.9 among nine studies (4, 47-49, 51-54) (Five studies did not report mean age)
Gender	

Male %	36.5% – 69.8% (11 studies) (One study has 0% male (gynaecological cancer study (53); and one study did not report gender (44))
Definition of Extremely short prognoses	
1. Functional status (46-51, 53)*	7
ECOG4 (48, 50, 51)	3
WHOPS4 (46)	1
PPS≤50 (53)	1
KPS≤40 (47, 49)	2
AKPS≤40	0
2. Survival (4, 43-45, 47, 49, 52, 54)*	8
Days prior to death (43, 52, 54)	3 (Range: 1-60 days)
Average survival (days) (4, 44, 45, 47, 49)	5 (Range: 28 to 43 days - medians used apart from one study where average is reported but the type not specified (4))
Definition of Clinically Significant Depressive Symptoms	
1. Tools (43-46, 49-54)[Δ]	10
PHQ (44, 45, 50, 51, 54)	5
PHQ9(44, 45, 51, 54)	4
Score≥10 as major depression (44, 45, 51, 54)	4
Score 5-9 as other depressive disorders (45, 54)[†]	2
PHQ8≥10 (no suicide item) (50)	1
HADS (43, 46, 49, 53)	4
HADS≥11 as depression (43, 46, 49, 53)	4
HADS≥8 as borderline depression (46)	1
DRS≥3 (InterRAI PC) (52)	1
2. Criteria (4, 47, 48, 54)[Δ]	4
DSM (4, 47, 48, 54)	4
DSMV (54)	1
DSMIV (4, 48)	2
DSMIIIR (47)	1
ICD	0
Endicott	0
3. Conditions by DSM (4, 47, 48, 54)	4
Major depressive disorder/episode (4, 47, 48, 54)	4
Minor depressive disorder/episode (47, 48)	2
Dysthymic disorder (48)	1
Mood disorder due to general medical condition with depressive features (48)	1

Footnotes: *2 studies had both functional status / survival (47, 49); [†]Rabkin et al, 2005 uses 3 or more PHQ9 items with score ≥2 as minor depression (45);[Δ]1 study had both DSMV + PHQ9 (54)

Figure 1.

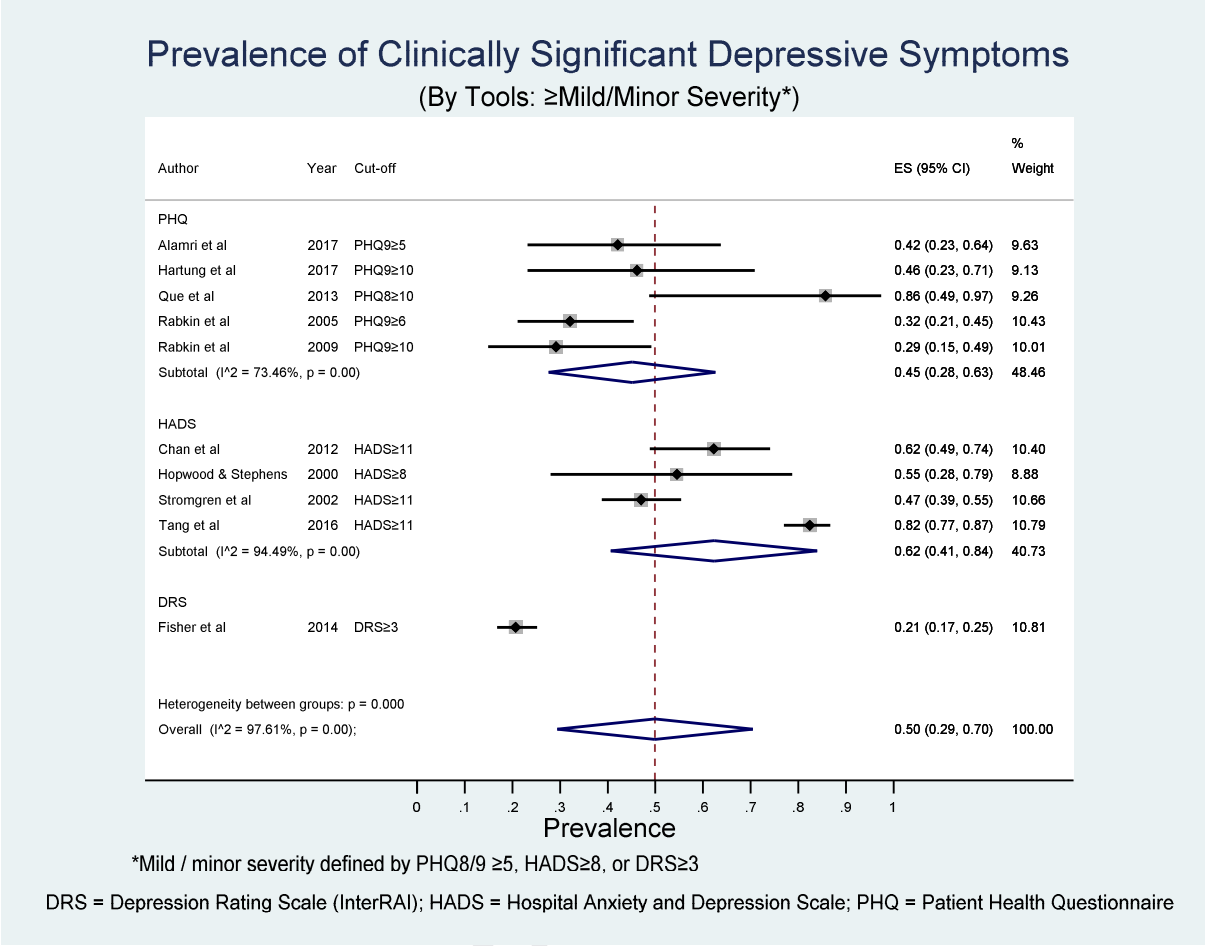
PRISMA Flow Diagram (33)



Caption: PRISMA diagram: 7957 studies were identified through the electronic databases. After removal of duplicates, 5531 studies underwent title and abstract screening, leaving 500 studies for full-text screening. Following this, only 13 studies were included for data extraction. Out of the 478 articles excluded: 57.1% (278 out of 487) of full-text screening studies did not have data on the sub-group of interest (people with extremely short prognoses); 149 articles had no full text (majority were abstracts or posters only); 16 were not English; 13 were systematic reviews/ meta-analyses; 12 were further duplicate identified; 4 were not an original study; 3 had no prevalence of depression; 2 were thesis; 3 were general score without depression specific measures; and 1 study had depression group not specified well enough.

Figure 2.

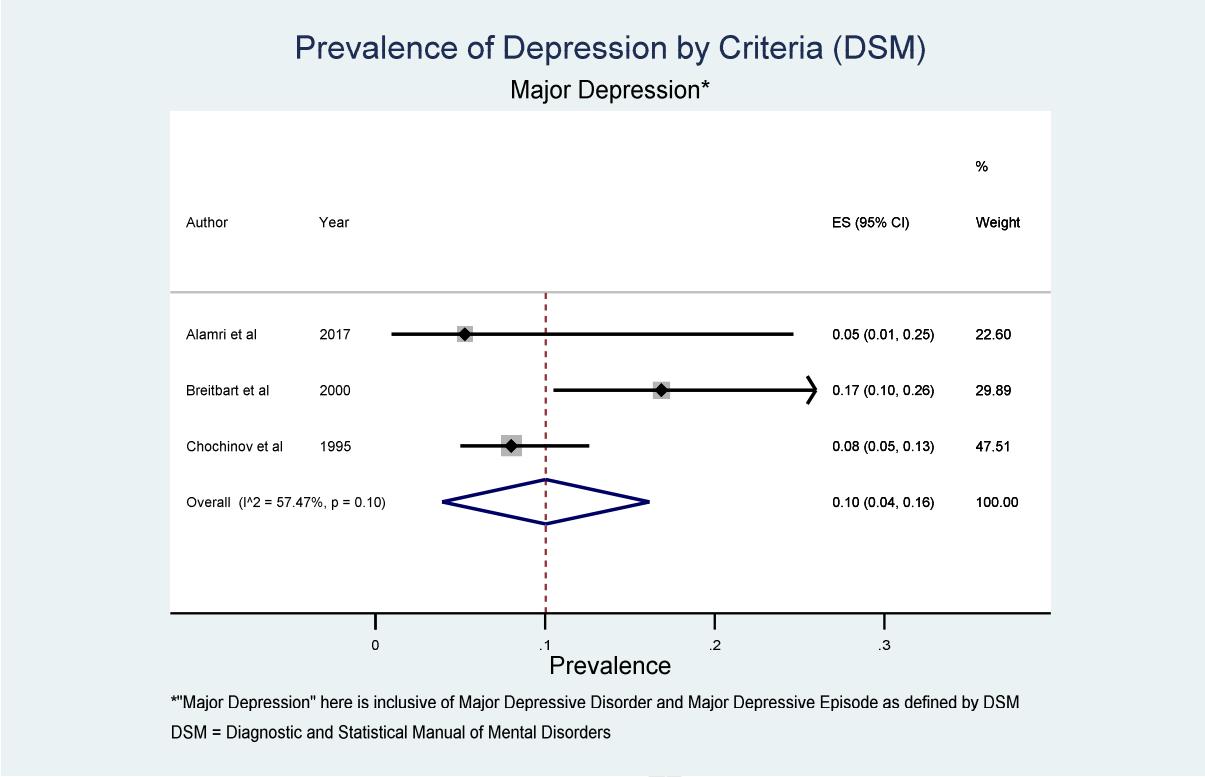
Prevalence of clinically significant depressive symptoms in people with advanced life-limiting illnesses and extremely short prognoses identified by depression-specific screening tools.



Caption: Overall pooled prevalence of clinically significant depressive symptoms of mild/minor severity or greater (defined as: PHQ8/9≥5, HADS≥8, DRS≥3(55-57); n = 10) (43-46, 49-54) in people with extremely short prognoses (N = 905) was 50% (95%CI: 29%-70%). Heterogeneity was high (I^2 = 97.6%). For the subgroup with moderate severity or more (PHQ8/9≥10 or HADS≥11(56, 57); n = 7): Pooled prevalence was 55% (95%CI: 37% - 74%; N = 476) (43, 44, 49-51, 53, 54). Heterogeneity was high (I^2 = 93.4%).

Figure 3.

Pooled prevalence of major depression in people with advanced life-limiting illnesses and extremely short prognoses (n = 3; extremely short prognoses N = 308).



Caption: On meta-analysis, the pooled prevalence of major depression in people with extremely short prognoses (N = 308) was 10% (95%CI: 4%-16%; extremely short prognoses sample size: N = 308) (4, 47, 54).

Figure 4.

Risk of bias assessment using Joanna Briggs Institute (JBI) Systematic Review Checklist for Prevalence Studies (37, 38).

		JBI Checklist for Prevalence Studies (Items 1-9)*								
Study	Authors / Year	1	2	3	4	5	6	7	8	9
1	Alamri et al 2017	Y	Y	?	Y	N	Y	?	Y	?
2	Breitbart et al 2000	N	?	N	?	?	Y	N	Y	N
3	Chan et al 2012	Y	Y	?	Y	Y	Y	Y	Y	?
4	Chochinov et al 1995	N	?	Y	Y	N	Y	Y	Y	N
5	Fisher et al 2014	?	?	Y	Y	Y	Y	?	Y	?
6	Hartung et al 2017	?	Y	Y	?	?	Y	Y	Y	Y
7	Hopwood & Stephens 2000	N	Y	Y	N	N	Y	Y	Y	Y
8	Que et al 2013	?	?	Y	N	N	Y	?	Y	Y
9	Rabkin et al 2005	Y	?	Y	Y	Y	Y	Y	Y	Y
10	Rabkin et al 2009	N	N	N	Y	Y	Y	Y	Y	?
11	Stromgren et al 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Tang et al 2016	Y	N	Y	Y	Y	Y	Y	Y	Y
13	Zhao et al 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y

*Joanna Briggs Institute Systematic Review Checklist for Prevalence Studies Items 1-9 (Options: 'Yes'; 'No'; 'Unclear'; and 'Not Applicable'):

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Overall appraisal: Include; Exclude; Seek further info (All 13 studies were included)

CAPTION: Seven out of 13 studies did not fulfil at least 1 item of the checklist. Only two studies were found to have low risk of bias, fulfilling all nine criteria. The leading source of bias (not fulfilling specified item criteria) was selection bias (Item 1-5: 21.5%), followed by attrition bias (Item 9: 15.4%), and detection/measurement bias (Item 6-7: 3.8%). No analysis bias was identified.