

THE PREVALENCE OF DEPRESSION SYMPTOMS AMONG ADVANCED BREAST CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction. Depression in patients with advanced breast cancer is a serious comorbidity that affects the quality of life of these patients, and their survival rates.

Objective. This study aims at systematically reviewing the current literature with data on the prevalence of depression symptoms in metastatic and recurrent breast cancer patients, examining the pooled mean prevalence of depression symptoms and potential sources of heterogeneity.

Methods. An extensive systematic review of PubMed, Web of Science, Scopus, ScienceDirect, Google Scholar, American Doctoral Dissertations and Open Grey databases, and the following reference list hand-search was performed to retrieve studies from January 2005.

Results. We identified 11 eligible studies that assessed 1223 patients on the presence of depression symptoms, and 465 patients met the criteria. According to the random-effects model, the pooled mean prevalence of depression was 38.23% (95% CI [30.92; 45.83]; I²=

RÉSUMÉ

La prévalence des symptômes de dépression chez les patientes atteintes d'un cancer du sein en stade avancé : revue systématique et méta-analyse

Introduction. La dépression chez les patientes atteintes d'un cancer du sein avancé est une comorbidité grave qui affecte la qualité de vie des patientes et leur taux de survie.

Objectif. Cette étude vise à examiner systématiquement la littérature actuelle avec des données sur la prévalence des symptômes de dépression chez les patientes atteintes d'un cancer du sein métastatique et récurrent, à examiner la prévalence moyenne combinée des symptômes de dépression et les sources potentielles d'hétérogénéité.

Méthodes. Une revue systématique approfondie des bases de données PubMed, Web of Science, Scopus, ScienceDirect, Google Scholar, American Doctoral Dissertations et Open Gray, ainsi que la recherche manuelle de la liste de référence suivante ont été

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87%; Q ($df = 10$) = 77.89, p -value < 0.01). Patients with metastatic stage had a slightly higher prevalence of depression symptoms compared to recurrent breast cancer patients.

Conclusion. Prevalence of depression symptoms among advanced breast cancer patients is high. It is important to improve psychological prevention methods to decrease the occurrence of depression, as breast cancer patients start receiving care from primary diagnosis and offer continuous support and treatment to meet their psychological needs.

Keywords: breast cancer, depression, metastatic, meta-analysis, recurrent, systematic review.

Abbreviations

BDI = Beck Depression Inventory

CES-D = Center for Epidemiologic Studies Depression scale

HADS = Hospital Anxiety and Depression Scale

PECO = population, exposure, comparator, and outcome

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QAC = Quality Assessment Checklist

SDS = Zung Self-Rating Scale for Depression.

INTRODUCTION

Breast cancer is one of the most prevalent cancer types affecting women worldwide, and in 2018, 12.3% of all diagnosed cancer cases globally were attributed to breast cancer¹. According to a meta-analysis of the global survival rates of women with breast cancer, the 5-year pooled survival rate is 73% (95% CI [71-75]), and 10-year global pooled survival rate is 61% (95% CI [54-67])². Colleoni and colleagues (2016) found that 10.4% of patients with local and regional breast cancer are at risk of cancer recurrence after initial treatment during the first five years of being disease-free³. According to several prospective studies, the recurrence rate could go up to 40% in some patients' population, and it could take up to 15 years to return^{4,5,6}. The site of recurrence for breast cancer could be local, regional or distant³. Patients with cancer recurrence, especially with a distant recurrence, experience physical and psychological impairments across multiple domains of quality of life indicators^{7,8}.

Patients with recurrent and de novo metastatic breast cancer are considered advanced cancer patients, with poorer prognosis of survival⁹. According to the American Cancer Society, the 5-year survival of metastatic breast cancer patients is 27%¹⁰. Having

effectuées pour récupérer des études à partir de janvier 2005.

Résultats. Nous avons identifié 11 études éligibles qui évaluaient 1223 patientes sur la présence de symptômes de dépression, et 465 patientes répondaient aux critères. Selon le modèle à effets aléatoires, la prévalence moyenne combinée de la dépression était de 38,23% (IC à 95% [30,92; 45,83]; $I^2 = 87\%$; Q ($df = 10$) = 77,89, p -value $< 0,01$). Les patientes au stade métastatique avaient une prévalence légèrement plus élevée des symptômes de dépression par rapport aux patientes atteintes d'un cancer du sein récurrent.

Conclusion. La prévalence des symptômes de dépression chez les patientes atteintes d'un cancer du sein avancé est élevée. Il est important d'améliorer les méthodes de prévention psychologique pour réduire la survenue de la dépression, car les patientes atteintes d'un cancer du sein commencent à recevoir des soins dès le diagnostic primaire et offrir un soutien et un traitement continu pour répondre à leurs besoins psychologiques.

Mots-clés: cancer du sein, dépression, métastatique, méta-analyse, récurrente, revue systématique.

a progressive illness that could significantly limit the longevity imposes a high psychological burden on patients¹¹. Depression in patients with breast cancer, and especially in metastatic and recurrent breast cancer patients is a serious comorbidity that could not only affect the quality of life for patients but most importantly, further lower their survival rates¹². Furthermore, among hospitalized female cancer patients with metastatic disease higher number of comorbidities were associated with diagnosed depression¹³.

To the authors' best knowledge, a systematic review of the prevalence of depression symptoms among metastatic and recurrent breast cancer patients has not been performed.

THE OBJECTIVE OF THE STUDY was to systematically review current literature with data on the prevalence of depression symptoms in metastatic and recurrent breast cancer patients, examine the pooled mean prevalence of depression symptoms and potential sources of heterogeneity.

MATERIAL AND METHODS

The study protocol is registered with the PROSPERO International prospective register of systematic reviews (Reference: CRD42020153960).

Search strategy

For this review, PubMed, Web of Science, Scopus, ScienceDirect, Google Scholar, American Doctoral Dissertations and Open Grey databases were searched with the last search being done in July 2020. Search terms were based on the population, exposure, comparator, and outcome (PECO) of interest (population: breast cancer, comparator: none, exposure: prevalence numbers, outcome: depression symptoms). The full search strategy is presented as Appendix 1. Initially, eleven studies were selected from the database search, and then we performed hand search based on the list of references of the selected articles. The PROSPERO database was also searched to identify the registration of similar studies.

Eligibility criteria

In this review, we used methods from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The inclusion criteria for the studies: 1) adults (aged ≥ 18); 2) metastatic (stage IV) or recurrent (local, regional, or distant) breast cancer patients with a primary diagnosis of breast cancer; 3) reported either proportion or number of patients with depression symptoms using self-report evaluation tools; 4) were observational 5) published in English since 2005. The exclusion criteria: 1) publications that did not convey study results; 2) publications that duplicated previously reported study results; 3) publications that focused only on young or geriatric patients; 4) had a high risk of bias; 5) lacked required information.

Selection of studies and data extraction

Following the PRISMA guidelines, the database search, and the selection of studies based on their eligibility and data extraction were performed by two independent researches (IK and FB)¹⁴. Up to two contacts via email were made to authors to obtain missing data. The required information list was created and approved by all authors, and included: first author, year of publication, country, study design, sampling, number of eligible and approached patients, number of included patients, age, marital status, depression evaluation scale, evaluation scale cutoff, number of patients with depression symptoms and risk of bias.

Quality assessment

To assess the risk of bias, we used the nine-item Quality Assessment Checklist (QAC) for prevalence studies¹⁵. The QAC evaluates the representativeness of the target population, the representativeness of the sample, the selection bias, the non-response bias, the data collection method, the case definition

acceptability, the assessment tool reliability and validity, the mode of data collection, and the calculation adequateness. Each item is scored "0" if the risk of bias is absent, and "1" if present. The overall risk of bias is calculated as the summation of all points. The risk of bias is low if the sum of points is between 0 and 3. Each researcher evaluated the risk of bias independently for every included article, and disagreements, when present, were resolved through consensus.

Data analysis

Data analysis was performed using R-studio statistical software with the meta- and metaphor- packages. To account for some level of between-study variability and identify potential influential studies for the meta-analysis results we performed a leave-one-out analysis. The outcome of interest was the number of patients with depression symptoms, according to the results of a self-report depression questionnaire. Data were combined using a forest plot. The pooled average prevalence of depression symptoms was calculated with Freeman-Tukey double arcsine transformation using random-effects restricted maximum likelihood estimator to handle small sample sizes and extreme proportions. To examine whether clinical and socio-demographic factors account for the heterogeneity in the prevalence of depression symptoms among metastatic and recurrent breast cancer patients, we performed the univariable meta-regression analysis. To further explore the sources of heterogeneity, several subgroup analyses were performed. For the subgroup analysis, because of the different sample sizes, we assumed a common between-study variance component and pooled within-group estimates of between-study variance.

Assessment of risk of bias across studies

To detect the risk of publication bias that may affect the cumulative evidence, we plotted the proportion of patients with depression symptoms in each included study by the inverse of its standard error, and then visually examined the funnel plot on the presence of the asymmetry. To examine, if the method of funnel plot construction can induce the asymmetry, we plotted the proportion of patients with depression symptoms by the inverse of the sample size in each study. As a next step of assessment, we performed the Egger's unweighted regression test for funnel plot asymmetry.

RESULTS

The extensive search of PubMed, Web of Science, Scopus, ScienceDirect, Google Scholar, American Doctoral Dissertations and Open Grey



PRISMA 2009 Flow Diagram

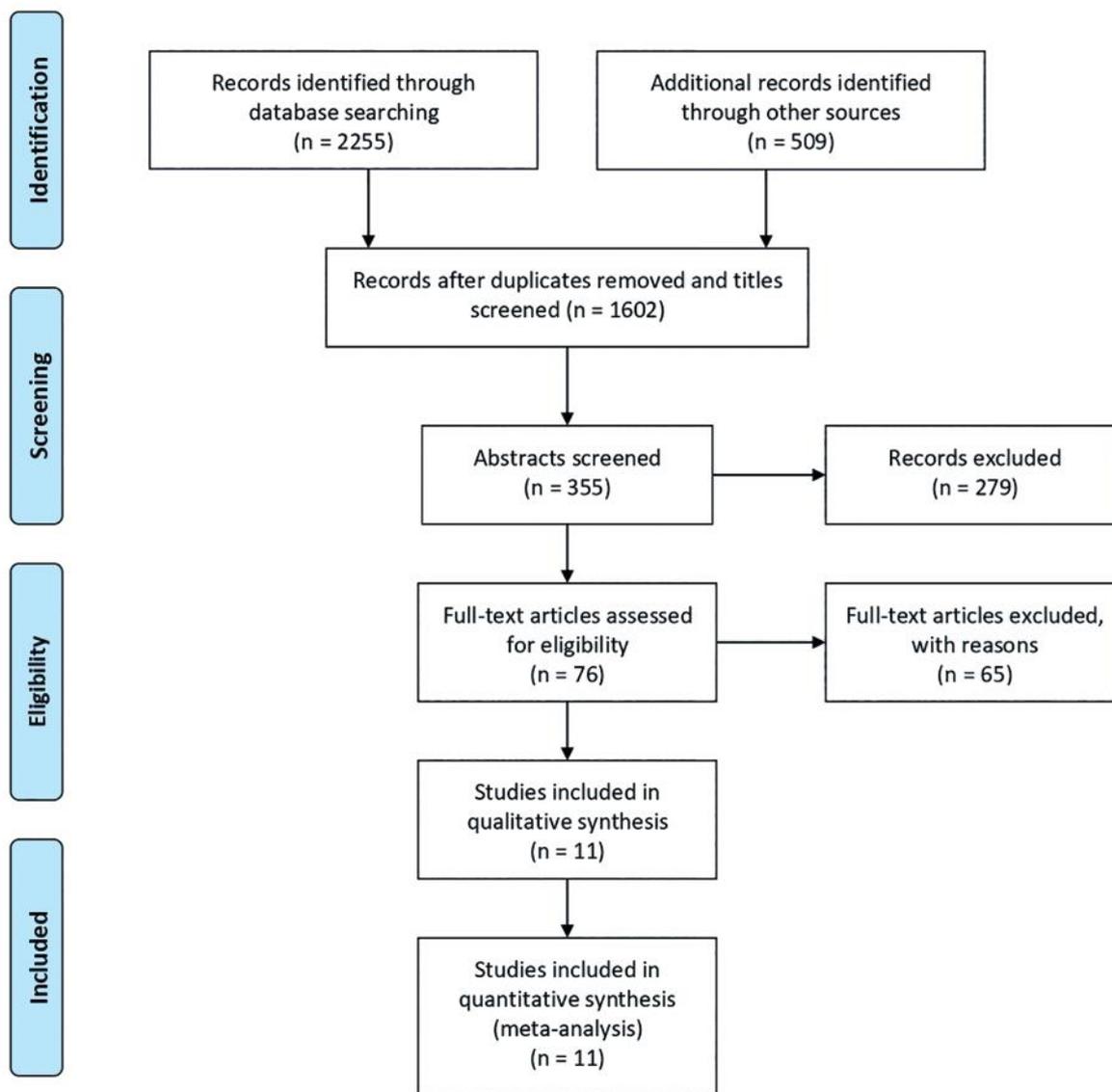


Fig. 1. The PRISMA flowchart of study selection.

databases retrieved 1602 non-duplicative articles. 76 papers were screened for their eligibility, and eleven studies met the criteria. The initial reference search included 509 references of those eleven articles, where no additional articles met the inclusion criteria (Fig. 1).

Characteristics of included studies

The proportion or number of patients with depression symptoms were reported in eleven studies, that were conducted in seven countries using

four different diagnostic methods, such as Beck Depression Inventory (BDI), Center for Epidemiologic Studies Depression scale (CES-D), Hospital Anxiety and Depression Scale (HADS) and Zung Self-Rating Scale for Depression (SDS). The sample size ranged from 41 to 201 participants, with a mean sample size of 111. The mean age of participants was 56.83 years (range: 51-65 years). Most of the studies had cross-sectional design, and consecutive sampling method. All included studies had a low risk of bias and scored three or below on the QAC scale.

Table 1. Characteristics of the included studies.

| # | First author | Year | Country | Income level | Hoy score | Design | Sam-pling | Sample size | Depressed pts n (%) | Depression scale | Age, years mean (SD) | Married n (%) |
|----|-------------------------------------|------|---------|------------------------|-----------|----------------------|------------------|-------------|---------------------|------------------|----------------------|---------------|
| 1 | Alfano A.C. ³⁶ | 2013 | Brazil | up- per-mid- dle | 3 | cross-sec- tional | consecu- tive | 126 | 47 (37.3) | HADS (8) | 51,4 (10.9) | 74 (58.7) |
| 2 | Brothers B.M. ³⁷ | 2009 | USA | high | | cohort | consecu- tive | 67 | 24 (35.8) | CES-D (16) | 54 (11) | |
| 3 | Guo X. ¹⁷ | 2017 | China | up- per-mid- dle | 3 | cohort | consecu- tive | 176 | 104 (59.1) | SDS (50) | | |
| 4 | Jehn C.F. ³⁷ | 2012 | Germany | high | 3 | cross-sec- tional | consecu- tive | 70 | 29 (41.4) | HADS (8) | 59,9 (10.2) | |
| 5 | Keurogh- lian A.S. ³⁸ | 2010 | USA | high | 3 | cross-sec- tional | consecu- tive | 124 | 32 (25.8) | CES-D (16) | 53,1 (10.6) | 70 (56.45) |
| 6 | Kokkonen K. ³⁹ | 2017 | Finland | high | 3 | cross- sectional | consecu- tive | 119 | 44 (37.0) | BDI (5) | | |
| 7 | Low C.A. ⁴⁰ | 2015 | USA | high | 4 | cohort | consecu- tive | 103 | 40 (38.8) | CES-D (16) | 57,2 (10.84) | 69 (67) |
| 8 | Milbury K. ⁴¹ | 2013 | USA | high | 3 | cross- sectional | consecu- tive | 201 | 74 (36.8) | CES-D (16) | 52,2 (10.5) | 199 (99) |
| 9 | Sarenmalm E.K. ⁴² | 2007 | Sweden | high | 3 | descrip- tive | consecu- tive | 56 | 21 (37.5) | HADS (8) | 65 | 35 (62.5) |
| 10 | Shin J.A. ¹⁶ | 2016 | USA | high | | cross-sec- tional | consecu- tive | 140 | 25 (17.9) | HADS (7) | 60,71 (12.8) | 83 (59.29) |
| 11 | Slovacek L. ⁴³ | 2009 | Czech | high | 3 | cross- sectional | consecu- tive | 41 | 25 (61) | SDS (50) | 58 | |

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; n, number; pts, patients; SD, standard deviation; SDS, Zung Self-Rating Scale for Depression; USA, the United States of America.

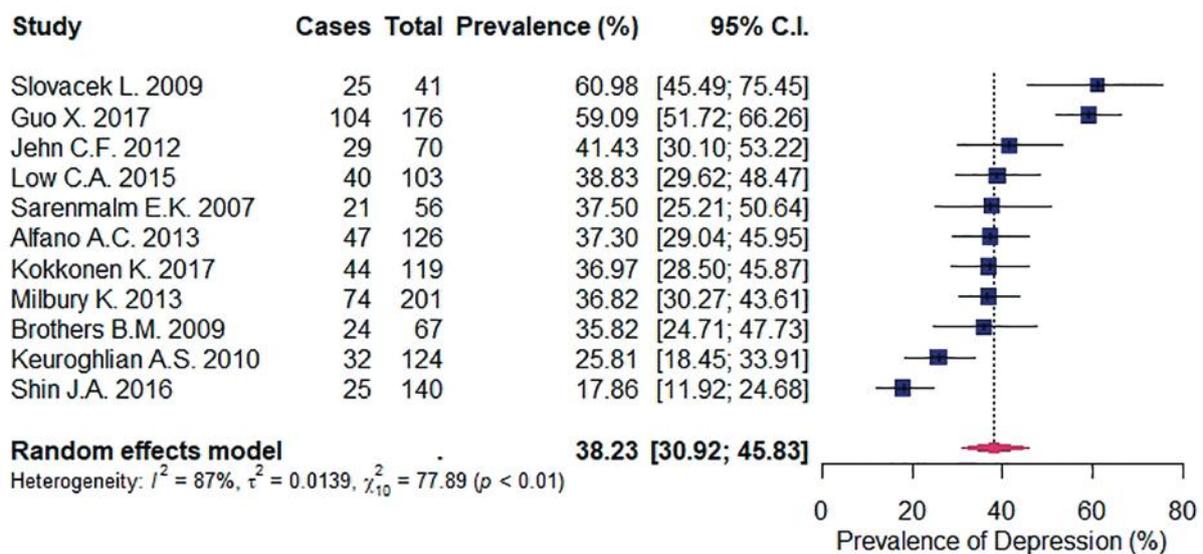


Fig. 2. Prevalence of depression symptoms based on the random-effects model among advanced breast cancer patients. Abbreviations: C.I., confidence interval; P, percentage of variability in the effect sizes which is not caused by sampling error; τ^2 , between-study variance in the meta-analysis; χ^2 , (Q-statistic) difference between the observed effect sizes and the fixed-effect model estimate of the effect size.

1 403 patients were eligible and approached, and 1 223 (87.17%) patients agreed to participate in eleven prevalence studies. In total, symptoms of clinically

significant depression were diagnosed in 465 out of 1223 patients (Table 1).

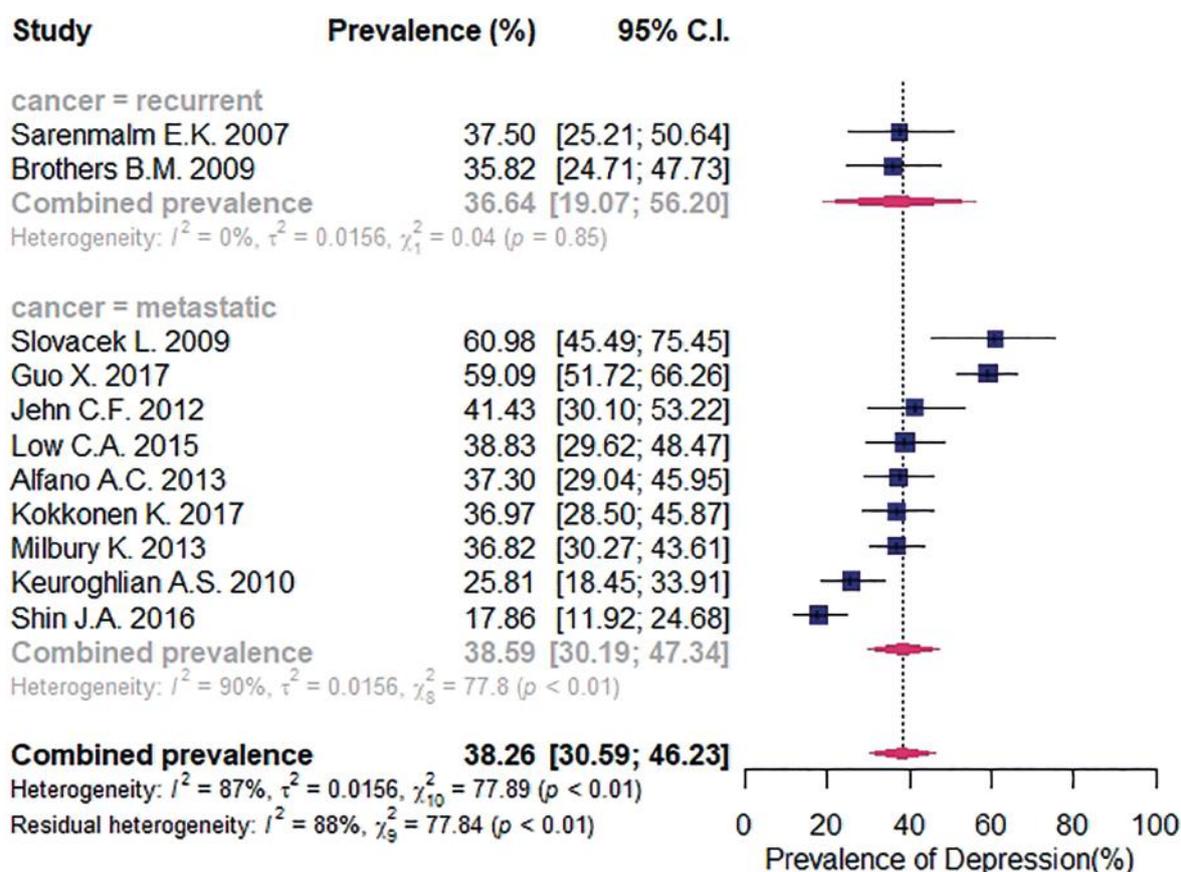


Fig. 3. Subgroup analysis of the depression prevalence based on the random-effects model among advanced breast cancer patients by cancer type. Abbreviations: C.I., confidence interval; P, percentage of variability in the effect sizes which is not caused by sampling error; τ^2 , between-study variance in the meta-analysis; χ^2 , (Q-statistic) difference between the observed effect sizes and the fixed-effect model estimate of the effect size.

Pooled mean prevalence of mild, moderate and severe depression symptoms

Based on the random-effects model, the pooled mean prevalence of mild, moderate, and severe depression symptoms was 38.23% (95% CI [30.92; 45.83]). Test for heterogeneity suggests the presence of high heterogeneity: $I^2 = 87\%$; Q (df =10)=77.89, p-value < 0.01 (Fig. 2).

According to the analysis that identifies the most influential studies, studentized residuals that are larger than “2” were identified in two studies, one with the lowest prevalence of depression symptoms of 17.86%¹⁶, and one with high 59% prevalence of depression symptoms among 176 breast cancer patients¹⁷. When those studies were removed, the pooled mean prevalence of depression symptoms based on the random-effects model was slightly lower at 37.70% (95% CI [32.97; 42.54]).

Assessment of risk of bias across studies

On the first funnel plot, four studies were located outside of the 95% CI limit lines, which is indicative of the high heterogeneity of the included

studies. Visually we did not find clear evidence of the funnel plot asymmetry. The second plot also did not have clear evidence of the asymmetry. The Egger’s unweighted regression tests for both plots were not statistically significant, and returned $z=1.01$, $p=0.31$, and $z=-0.44$, $p = 0.66$ respectively. Our findings suggest that the risk of publication bias across included studies was low.

Sub-group analysis of studies that reported the number of patients with depression

Sub-group analyses based on the cancer type showed that the combined prevalence of depression symptoms was almost the same between studies that focused on metastatic and recurrent breast cancer patients. The pooled prevalence of depression symptoms in recurrent (local, regional or distant) breast cancer patients was 36.64% (95% CI [19.07; 56.20]; $I^2=0\%$; Q (df=1)=0.04; $p=0.85$) and 38.59% (95% CI [30.19; 47.34]; $I^2=90\%$; Q (df=8)=77.8; $p<0.01$) in metastatic breast cancer patients (Fig. 3).

Sub-group analysis based on the income level of the country where a study was conducted, showed that the pooled prevalence of depression symptoms in upper-middle income countries was higher than in high-income countries at 48.39% (95% CI [32.31; 64.63]; $I^2=93\%$; $Q(df=1)=14.04$; $p<0.01$) and 35.79% (95% CI [28.20; 43.74]; $I^2=80\%$; $Q(df=8)=39.36$; $p<0.01$) respectively.

Sub-group analysis based on the depression evaluation method showed that the pooled prevalence of depression symptoms among advanced breast cancer patients was the highest when reported with SDS scale at 59.56% (95% CI [51.92; 66.99], $I^2=0\%$; $Q(df=1)=0.04$; $p=0.84$). Different cutoff points were used for the depression symptoms presence with the HADS questionnaire, three studies used "≥8" and one study used "≥7".

Meta-regression finding

According to the meta-regression findings, the publication year, mean age of participants, marital status, and sample size did not significantly account for the heterogeneity in the effect sizes between studies.

DISCUSSION

Depression is a common psychological comorbidity among advanced breast cancer patients, and the prevalence of depression symptoms varies from 17% to 61% according to the studies included in the present analysis. Advanced breast cancer patients have to deal with cancer recurrence or cancer progression beyond the primary location, which puts more pressure on their mental health. According to a meta-analysis of depression prevalence among breast cancer patients which included 44,075 patients, the global prevalence of depression was 32.2% (95% CI [28.9, 35.4]; $I^2 = 99.1\%$)¹⁸. Based on the results of our meta-analysis, the prevalence of depression symptoms among 1223 advanced breast cancer patients was higher (38.23%). This difference could be attributable to the specific focus of the present analysis on the advanced stage, methodological variations, and a smaller number of studies analyzed.

Among clinical factors that were explored as the potential sources of heterogeneity, the metastatic group had a higher prevalence of depression symptoms than the recurrent group, at 38.59% and 36.64%, respectively. One of the factors that could contribute to this difference: recurrent breast cancer patients group included patients with local and regional recurrence, who generally has a more favorable 5-year survival rate.

The methodology of depression diagnosis has been a significant factor that could influence the number of diagnosed patients. Some studies show that the depression diagnosis rate was higher when

self-assessment inventories were used compared to the structured interview results^{19,20,21}, and the results of the present meta-analysis confirm those findings. Generally, most of the self-report depression scales were reported to be not designed to identify major depression or to be used as a diagnostic tool, but as a screening instrument^{22,23,24,25}. Earlier findings suggest that HADS performance in detecting major depression was average but better than other conventional depression inventories²², which could justify our findings on its broad use in different countries.

Among sociodemographic factors that were explored as the potential sources of heterogeneity, we found that the upper-middle income countries had a higher prevalence of depression symptoms compared to the high-income countries, which is also in line with previously reported results¹⁸.

The limitations of the present systematic review and meta-analysis are the following: 1) Although formal tests to investigate possible bias across studies were not statistically significant, we acknowledge that we could not eliminate the publication bias, as we only included published studies in English. We attempted to lower the publication bias by following guidelines on the adequate literature review; 2) This is a meta-analysis of observational studies with their methodological limitations; 3) Studies from African, Eastern Mediterranean and South-East Asia regions did not meet the inclusion criteria of the present meta-analysis; 4) We did not have enough data on the time between diagnosis of breast cancer to the time of the depression evaluation. 5) The heterogeneity of the included studies was high, although we excluded studies with stage III and stage IV breast cancer patients, if they did not define their stage III patients as recurrent^{26,27,28,29} or reported depression before recurrence³⁰. We also excluded studies that reported results on the same group of patients as already included studies^{31,32,33,34}.

Clinical implications of our findings: the health-care providers have to be prepared to have more than one-third of patients with breast cancer with psychological needs of various degrees not only at primary diagnosis but also afterward at recurrence and progression and beyond. According to a systematic review by Zainal and colleagues (2013), even among long-term breast cancer survivors the prevalence of depression goes up to 56%³⁵. It is important to improve psychological prevention methods to decrease the occurrence of depression, as breast cancer patients start receiving treatment from primary diagnosis and offer necessary evidence-based support and treatment to meet their psychological needs. For future research, our findings imply that there is a need to access what kind of psychological correction methods might be the most effective specifically among advanced breast

cancer patients group to prevent the depression development and to help them manage their psychological burden through the entire treatment course.

CONCLUSIONS

Our results suggest that more than one-third of patients with metastatic and recurrent breast cancer are at risk of having various degrees of depression, which is consistent with previously reported results on the global depression prevalence among breast cancer patients. The high pooled prevalence of depression in this group indicates that those patients require adequate psychological support not only at the time of diagnosis, but throughout the entire course of their treatment.

Author Contributions:

I.K. conceived the original draft preparation. I.K., B.T., and F.B. were responsible for conception and design of the review. I.K., B.T., and F.B. were responsible for the data acquisition. I.K. and N.Z.Z. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. I.K., B.T., N.Z.Z. and F.B. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law.“

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Appendix 1. The prevalence of depression symptoms among advanced breast cancer patients: a systematic review and meta-analysis. Search strategy.

| PubMed | Web of Science | Scopus | Science direct | Google Scholar | American Doctoral Dissertations | Open Grey |
|---|---|---|---|--|--|--|
| depression advanced breast cancer 184 depression metastatic breast cancer 347 depression recurrent breast cancer 242 Date: July 13, 2020 Filters: Species: Human; Languages: English Year: 2005 – 2020 | depres* advanced breast cancer 455 depres* metastatic breast cancer 346 depres* recurrent breast cancer 97 depres* advanced breast neoplasm 19 depres* metastatic breast neoplasm 14 depres* recurrent breast neoplasm 1 depres* advanced breast tumor 67 depres* metastatic breast tumor 77 depres* recurrent breast tumor 12 Date: July 13, 2020 Search in TOPIC (Searches title, abstract, author keywords, and Keywords Plus.) Filters: Year: 2005 – 2020 Document type: Article | “advanced breast cancer” AND “depression” 349 “metastatic breast cancer” AND “depression” 297 “recurrent breast cancer” AND “depression” 104 “advanced breast tumor” AND “depression” 161 “metastatic breast tumor” AND “depression” 165 “recurrent breast tumor” AND “depression” 0 Date: July 14, 2020 Search in TITLE ABSTRACT KEYWORD Filters: Article Types: Research Articles Year: 2005 – 2020 | “advanced breast cancer” AND “depression” 13 “metastatic breast cancer” AND “depression” 22 “recurrent breast cancer” AND “depression” 1 “advanced breast cancer” AND “depression” 3 “metastatic breast cancer” AND “depressive” 10 “recurrent breast cancer” AND “depressive” 0 Date: July 13, 2020 Advanced Search: In the Title Filters: Exclude citations Exclude patents Languages: English Year: 2005 – 2020 | “advanced breast cancer” “depression” 3 “advanced breast cancer” “depressive” 1 “metastatic breast cancer” “depression” 23 “metastatic breast cancer” “depressive” 11 “recurrence” “breast cancer” “depression” 2 “recurrence” “breast cancer” “depressive” 2 Date: July 13, 2020 Advanced Search: In the Title Filters: Exclude citations Exclude patents Languages: English Year: 2005 – 2020 | Breast cancer depress* 23 Date: July 07, 2020 | depression breast cancer 15 Date: July 14, 2020 |