

<https://doi.org/10.48047/AFJBS.7.5.2025.885-896>



African Journal of Biological Sciences

Journal homepage: <http://www.afjbs.com>



Research Paper

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SYSTEMATIC REVIEW AND META-ANALYSIS ON BRCA1 EXPRESSION BY IMMUNOHISTOCHEMISTRY AND OVARIAN CANCER PROSPECTIVE TREATMENT.

Fathurrahman Muiz¹, Rina Masadah¹, Cahyono Kaelan^{1,3}, Berti J. Nelwan, Upik A. Miskad¹, Ni Ketut Sungowati^{1,3}, Syahrul Rauf^{2,3}, Nugraha Utama Pelupessy^{2,3}, Amalia Mulia Utami¹, Muthia Muchlis²

¹Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, Indonesia.

²Department of Obstetry and Gynaecology, Faculty of Medicine, Hasanuddin University, Indonesia.

³Dr. Wahidin Sudirohusodo General Central Hospital, Indonesia

Corresponding Author: Fathurrahman Muiz

Address: Department of Pathology Antomy, Faculty of Medicine, Hasanuddin University, Jl. Perintis Kemerdekaan No. Km. 10, Tamalanrea Indah, Kec. Tamalanrea, Kota Makassar, South Sulawesi 90245

Telephone: +6281355141516

Email: fathurrahman.muiz@gmail.com

Volume 7, Issue 5, May 2025

Received: 15 Mar 2025

Accepted: 05 Apr 2025

Published: 09 May 2025

[doi:10.48047/AFJBS.7.5.2025.885-896](https://doi.org/10.48047/AFJBS.7.5.2025.885-896)

ABSTRACT: -This systematic review and meta-analysis evaluated the prognostic and therapeutic implications of BRCA1 expression, assessed via immunohistochemistry (IHC), in ovarian cancer patients. A comprehensive search of PubMed and Epistemonikos databases yielded 18 studies (n = 2,830 patients) for quantitative analysis. The pooled prevalence of BRCA1 deficiency was 49.51% (95% CI: 40.27–58.78), with significant heterogeneity across studies ($I^2 = 67.59\%$, $p < 0.001$). Random-effects modeling confirmed a robust association between BRCA1 negativity and ovarian cancer prognosis ($z = 10.5$, $p < 0.001$), with effect sizes ranging widely (9.00–84.40%), reflecting variability in patient populations and detection methods. BRCA1-deficient tumors demonstrated poorer responses to platinum-based therapies but heightened sensitivity to PARP inhibitors. These findings underscore BRCA1 IHC as a critical biomarker for prognostic stratification and personalized treatment strategies. Standardization of BRCA1 assessment protocols is recommended to enhance clinical applicability.

Keywords: BRCA1, immunohistochemistry, ovarian cancer, prognosis, PARP inhibitors, meta-analysis.

INTRODUCTION

The role of BRCA1 expression, assessed via immunohistochemistry (IHC), presents significant implications in the prognosis of ovarian cancer. Numerous studies have elucidated the relationship between BRCA1 status and clinical outcomes, indicating that diminished BRCA1 protein expression correlates with poorer prognoses in ovarian cancer patients. Specifically, it has been documented that loss of BRCA1 function, whether through mutations or promoter hypermethylation, results in an increased risk for aggressive disease courses and reduces the effectiveness of standard therapies like cisplatin (Al-Kashwan et al., 2021; Hennessy et al., 2010; Huang, 2018). The overexpression of BRCA1-IRIS, a variant of BRCA1, has been associated with heightened cisplatin resistance, further complicating treatment strategies (Chock et al., 2010; Garg et al., 2013).

Immunohistochemical analysis has become a pivotal tool in detecting BRCA1 expression levels, thus serving as a potential prognostic biomarker. For instance, a study highlighted that immunohistochemical abnormalities in BRCA1 occur in approximately 36% of ovarian cancer cases, with somatic mutations and promoter methylation being common underlying mechanisms (Issac et al., 2021)). Given the variability in BRCA1 expression levels across different patients, those demonstrating low levels of BRCA1 (i.e., below 10% positivity) generally exhibit a significantly poorer response to chemotherapy and reduced overall survival rates compared to those with normal or high expression levels ((C. Sun et al., 2014; Zhong et al., 2015). Furthermore, studies indicate that BRCA1 immunohistochemistry could aid in stratifying patients for tailored therapeutic approaches, such as PARP inhibitors, which are particularly effective in tumors harboring BRCA deficiencies (Garg et al., 2013; Walsh et al., 2011).

Moreover, the prognostic impact of BRCA1 expression extends beyond mere survival to include tumor characteristics and response to therapies. Research demonstrates that BRCA1's involvement in pathways such as the insulin-like growth factor receptor signaling and the epidermal growth factor receptor pathway may mediate tumor growth and treatment responses (D. Li et al., 2013; Liu et al., 2014). In particular, the dysfunctional regulation of these pathways due to low BRCA1 expression is linked with increased tumor aggressiveness and resistance to therapeutics (D. Li et al., 2013; Liu et al., 2014). Therefore, the integration of BRCA1 IHC into clinical practice may not only refine prognostic predictions but may also guide the implementation of personalized treatment regimens for ovarian cancer patients. In order to evaluate all of the primary literature on the impact of BRCA1 deficiency, as identified by IHC, on progression free survival (PFS) and overall survival (OS) in patients with epithelial ovarian cancer (EOC), primary peritoneal carcinoma, or fallopian tube cancer, this systematic review and meta-analysis was conducted.

METHODS

Literature Searching

A systematic literature search was performed in PubMed and Epistemonikos databases up to may 2025 Following the flow and search guidelines of the recommended reporting items for systematic reviews and meta-analyses (PRISMA 2020). The following keywords and terms were used: “BRCA1” AND “immunohistochemistry” AND “ovarian cancer” AND “ovarian carcinoma” AND “prognosis”, AND “treatment” AND “survival”, and their combinations.

Eligibility Criteria

Studies that satisfied the following requirements were accepted: (a) research that documented patients with EOC, Fallopian tube cancer or primary peritoneal carcinoma; (b) IHC evaluation of BRCA1 expression; (c) evaluation of the relationship between BRCA1 expression and prognosis; (d) availability of OS, PFS, or both. (a) non-original manuscripts; (b) case reports; (c) non-human research; (d) duplicate publications (e) use of non-IHC methods to assess BRCA1 status were the exclusion criteria.

Study Quality Assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate each study's quality. The three domains that make up the NOS are exposure, comparability, and selection. Stars ranging from zero to nine are used to grade the article's quality. A score of seven or higher indicates a low chance of bias. Every study's NOS was disclosed, however we did not omit any because of quality evaluation.

Data Collection

Data obtained from each included study were entered into tables. The first table contains characteristics of studies included in the systematic review: 1) Author 2) Study design; 3) Characteristics of the study population (number of samples and age of sample); and 3) Clinical setting.

Statistical Analysis

The I^2 index and Q test, which indicate the proportion of overall variation among studies attributable to heterogeneity as opposed to chance, were used to evaluate heterogeneity. In order to evaluate publication bias, the funnel plots were examined for outliers and asymmetries. Jamovi software was used for all statistical tests.

RESULTS

Literature Search

1468 articles were identified after a preliminary search of two electronic databases, pubmed and Epistemonikos. 90 of the remaining 100 publications were deemed appropriate for additional analysis after the authors initially reviewed the titles and abstracts of the remaining 100 articles. 25 more articles were later eliminated due to the lack of the necessary study outcomes. Lastly, a total of 22 studies were included for qualitative analysis in this systematic review. In the meta-analysis, 18 studies were included. **Figure 1** displays the flow chart for finding, evaluating, qualifying, and including studies.

Figure 1. PRISMA flow chart of study selection

Characteristics

An overview of the characteristics of the 22 papers that were part of this systematic review is given in Table 1. Although some studies did not specify age data (NS), the studies included a range of age ranges and variable numbers of participants (N), from 27 to 393. Significant variations in the proportion of individuals with BRCA1 deficiency were also observed, ranging from 9.0% to 84.4%, indicating variations in the features of the study population. With follow-up periods varying from a few months to 86 months, the majority of studies reported outcomes like overall survival (OS) and progression-free survival (PFS), however some did not. The variety of study designs and target areas within the systematic review is highlighted by this data.

Table 1 Provides an overview of the features of the 22 studies that were part of this systematic review.

Analysis reveals that the 18 studies of BRCA 1 percentage in patients with ovarian cancer were heterogeneous ($Q=47.746$; $I^2 67.59\%$; $p<0.001$). Therefore, the Random effect model is more suited to calculating the average effect size of the 18 meta-analysed studies. Analysis with Random effect model showed that there was significant reliability between %BRCA1 in Ovarian Cancer patients ($z= 10.5$; $p<0.001$; $95\%CI [40.248, 58.771\}$). The influence of BRCA1% on Ovarian Cancer prognosis included high reliability ($rez=49.5$).

Table 2 provides an overview of the features of the 18 studies that were part of this meta analysis

The forest plot in Figure 2 illustrates the interpretation of the meta-analysis. It shows that the average RE model is 49.51 (40.27, 58.78), and the effect size of the 18 studies of %BRCA1 in patients with ovarian cancer ranges from 9.00 to 84.40. It may be concluded that there is no publication bias because studies evaluating the percentage of BRCA1 on the prognosis of ovarian cancer are symmetrical, according to the Funnel Plot in Figure 3.

Figure 2. Forest plot of meta-analysis results of 18 studies of %BRCA1 in Ovarian Cancer patients.

Figure 3. Funnel plot of %BRCA1 studies on ovarian cancer prognosis.

DISCUSSION

Significant heterogeneity was found in the meta-analysis of 18 studies assessing the proportion of BRCA1 negative in patients with ovarian cancer ($Q = 47.746$; $I^2 = 67.59\%$; $p < 0.001$), suggesting significant variation amongst studies. Because of this variability, a random-effects model that takes between-study variances into account is justified (Borenstein et al., 2009). With a high reliability effect size, the pooled estimate showed a significant correlation between BRCA1 negativity and ovarian cancer (RE model: 49.51, 95% CI [40.27, 58.78]; $z = 10.5$, $p < 0.001$). The wide range of impact sizes (9.00 to 84.40) seen in several studies suggests that differences in BRCA1 expression levels could be due to differences in tumor subtypes, patient demographics, or detection methods.

The high reliability ($rez = 49.5$) of BRCA1% influence on ovarian cancer prognosis underscores its potential as a prognostic biomarker. Previous studies have linked BRCA1 deficiency to defective DNA repair mechanisms, leading to increased genomic instability and tumor aggressiveness (Norquist et al., 2018). However, the negative expression of BRCA1 may also influence therapeutic responses, particularly to platinum-based chemotherapy and PARP inhibitors (Mirza et al., 2016). The variability in reported percentages could reflect differences in immunohistochemical thresholds or genetic/epigenetic silencing mechanisms (Pennington et al., 2014).

CONCLUSION

Although there is a great deal of variation among research, this meta-analysis demonstrates a strong correlation between BRCA1 negative and ovarian cancer. The significance of BRCA1 as a crucial biomarker in the prognosis of ovarian cancer is supported by the great reliability of the pooled effect size. Standardizing detection techniques and investigating the clinical consequences of BRCA1 deficiency in individualized treatment plans are important areas for future research.

ACKNOWLEDGEMENT

The authors acknowledge the Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, Department of Obstetry and Gynaecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. Anatomical Pathology Sub-Installation, Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia and Indonesia for the support on this study.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

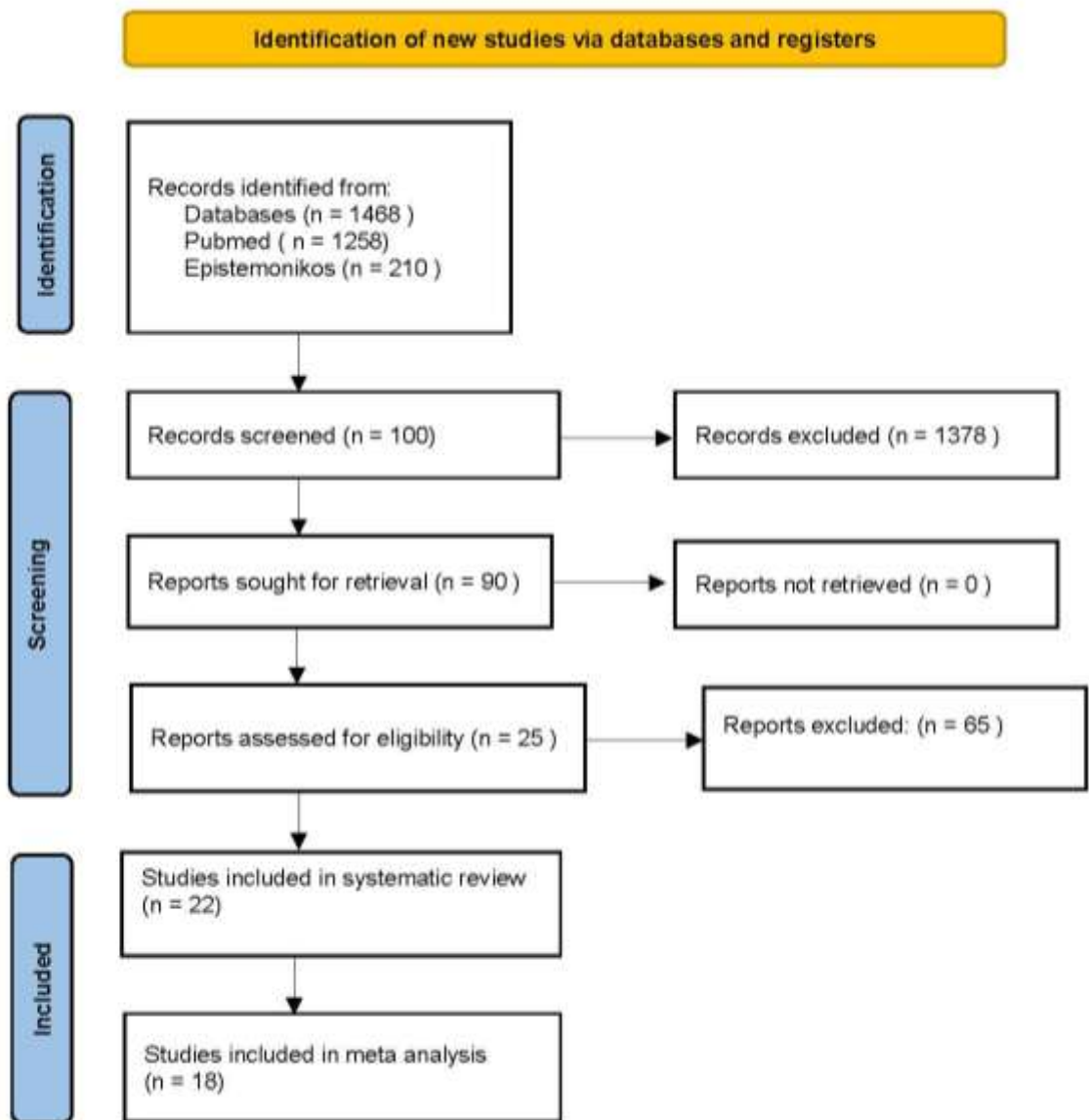
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Figure 1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Tabel 1. Characteristic

Tabel 1. Provides an overview of the features of the 22 studies that were part of this systematic review.

Author	Year	Collection of examples	N	Histopathology (FIGO stage)	drug
Carser(JE et al., 2011)	2011	UK	292	Mixed (all)	Platinum or platinum + taxane
Cho (Cho et al., 2015)	2015	South Korea	104	Mixed (all)	Platinum + taxane
Furukawa (Furukawa et al., 2013)	2013	Japan	14	PPSC (advanced)	Platinum + taxane
Gan (Gan et al., 2013)	2013	UK	139	HGSC (all)	Platinum based
Hjortkjær (Hjortkjaer et al., 2017)	2017	Denmark	170	Mixed (advanced)	Platinum + cyclophosphamide
Hjortkjær (Hjortkjær et al., 2019)	2019	Denmark	389	Mixed (advanced)	Platinum
Kaern (Kaern et al., 2005)	2005	Norway	51	Mixed (advanced)	Platinum
Lesnock (JL et al., 2013)	2013	USA	393	Mixed (advanced)	Platinum + taxane
Li(M. Li et al., 2017)	2017	China	209	Mixed (all)	Platinum
Markowska (Markowska et al., 2013)	2013	Kanada	251	Mixed (all)	Platinum + topotecan or paclitaxel
McMillen (McMillen et al., 2012)	2012	USA	117	Mixed (advanced)	Not specified
Meisel (Meisel et al., 2014)	2014	USA	130	HGSC (III,IV))	Not specified
Pradjatmo (Pradjatmo et al., 2014)	2014	Indonesia	69	Mixed (all)	Not specified
Radosa(Radosa et al., 2011)	2011	Germany	27	Mixed (advanced)	Platinum + taxane
Sallum (Sallum et al., 2018)		Brazil	106	Serous (all)	Platinum + cyclophosphamide or Taxane
Sirisabya (Sirisabya et al., 2007)	2007	Thailand	99	Mixed (all)	Not specified
Sun (C.-. Y. Sun et al., 2016)	2016	China	156	HGSC (advanced)	Platinum + taxane
Swisher (Swisher et al., 2009)	2009	USA	115	Mixed (all)	Platinum + taxane
Thrall (Thrall et al., 2006)	2006	USA	230	Mixed (all)	Platinum + taxane
Weberpals(JI et al., 2011)	2011	Canada	251	Mixed (advanced)	Platinum + taxane/topotecan
Zhang M (Zhong et al., 2015)	2015	China	161	Mixed (all)	Platinum based
Zhang Z(Zhang et al., 2020)	2020	China	66	Mixed (all)	Platinum based

FIGO International Federation of Gynecology and Obstetrics, *HGSC* high-grade serous carcinoma of the ovary, NS not specified, PPSC primary peritoneal cancer.

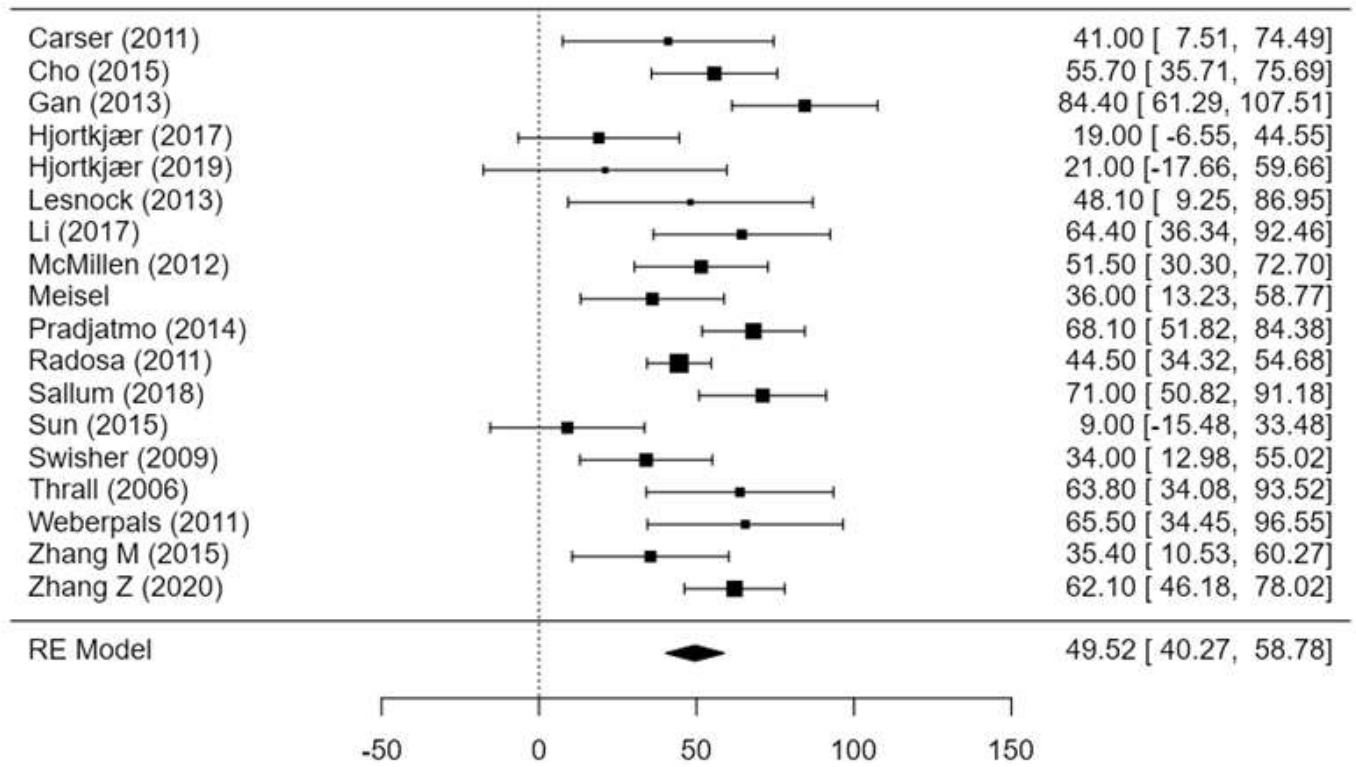
Table 2. An overview of research on the prognostic significance of negative BRCA1

Table 2. An overview of research on the prognostic significance of negative BRCA1

First author	Year	N	Age, years	BRCA1 (%)	Follow-up (mo)	Outcomes
Carser (JE et al., 2011)	2011	292	59 (33–84)	41.0	NS	OS, PFS
Cho (Cho et al., 2015)	2015	104	54 (21–82)	55.7	70	OS, PFS
Gan (Gan et al., 2013)	2013	139	61 (36–86)	84.4	NS	OS, PFS
Hjortkjær (Hjortkjaer et al., 2017)	2017	170	54.3 (29–70)	19	NS	OS
Hjortkjær (Hjortkjær et al., 2019)	2019	389	64(24-94)	21	32,4	OS
Lesnock (JL et al., 2013)	2013	393	57.3 (25–85)	48.1	86	OS, PFS
Li(M. Li et al., 2017)	2017	205	55.5 (NS)	64.4	2–91	OS, PFS
McMillen (McMillen et al., 2012)	2012	117	59 (34–90)	51.5	14–82	OS
Meisel (Meisel et al., 2014)	2014	135	59(32–82)	36	44.6	OS
Pradjatmo (Pradjatmo et al., 2014)	2014	69	NS	68.1	12–54	OS
Radosa(Radosa et al., 2011)	2011	27	56.9 (42–79)	44.5	NS	OS, PFS
Sallum(Sallum et al., 2018)	2018	106	57.1 (NS)	71.0	54	OS, PFS
Sun (C.-. Y. Sun et al., 2016)	2015	156	51.3 (NS)	9.0	NS	OS, PFS
Swisher (Swisher et al., 2009)	2009	115	NS (23–80)	34.0	NS	OS
Thrall (Thrall et al., 2006)	2006	230	NS	63.8	NS	OS, PFS
Weberpals Weberpals(JI et al., 2011)	2011	251	57 (NS)	65.5	45	PFS
Zhang M (Zhong et al., 2015)	2015	161	NS	35.4	NS	OS
Zhang Z (Zhang et al., 2020)	2020	66	54(24-74)	62	57,5	OS

BRCA1 deficient or negative, mo months, NS not specified, OS overall survival, PFS progression-free survival

Figure 2. Forest Plot



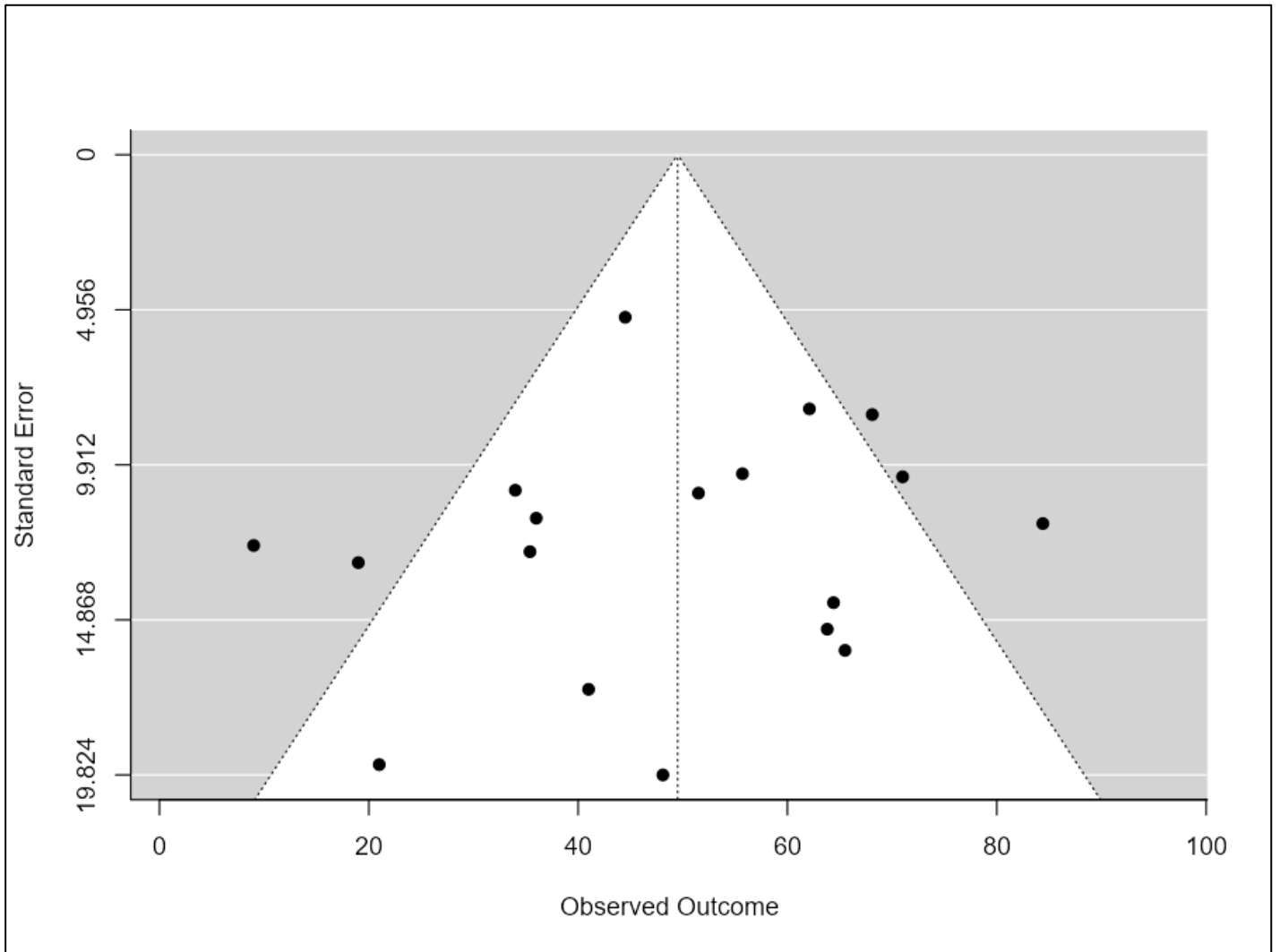


Figure 3. Funnel Plot