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The underreporting of phase III chemo-therapeutic clinical trial data of older patients with cancer: A systematic review

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Abstract

Purpose—Inspired by the American Society of Clinical Oncology's recommendations to strengthen the evidence base for older adults with cancer, the purpose of this systematic review is to identify the reporting of treatment efficacy and adverse events specific to older adults with cancer in Phase III chemo-therapeutic clinical trials. This review also investigates the frequency with which these data points were reported in the literature to identify gaps inreporting and opportunities to expandthe knowledge base on clinica loutcomes for older adults with cancer.

Methods—Chemo-therapeutic clinical trial data published from July 1, 2016 to June 30, 2017 was reviewed. Manuscripts (n = 929) were identified based on keyword searches of EMBASE and

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Conception and design of study: KB, JLKS, BC, IP, AS.

Acquisition of data: KB, ES.

Data analysis or interpretation:KB, JLKS, BC, IP, ARM, TK,RV, CDH, BJ, KP, JLL, AS.

Drafting of manuscript or critical revision: KB, JLKS, BC, IP, ARM, TK, RV, CDH, BJ, KP, JLL, AS.

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Declaration of Competing Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

PubMed. After removal of duplicates (n = 116) and articles that did not meet this study's inclusion criteria (n = 654), 159 articles were identified for review.

Results—Reviewed papers were published in 36 different scientific journals and included twenty-five different cancer types. Of the 159 articles, 117 (73.6%) reported age-specific medians and 75 (47.2%) included stratifications of data by age. Treatment efficacy was reported in 96.2% of the articles with 39.9% reporting effectiveness of treatment by age. Reporting of adverse events was included in 84.9% of the articles with only 8.9% reporting these events stratified by age.

Conclusion—Results suggest inadequate reporting of treatment efficacy and adverse events as well as basic descriptive statistics about the age distribution of study subjects. Conscious efforts are needed to address these deficiencies at every level of planning and conducting clinical trials as wells as reporting outcomes stratified by age. Ultimately, standardized reporting could lead to improved treatment decisions and outcomes for older adults with cancer.

Keywords

Geriatric oncology; Older adults; Phase III clinical trials; Systematic review

1. Introduction

Older adults, defined as those aged 65 years and older, constitute the largest percentage of the cancer patient and survivor population [1–22]. However, this growing group is not adequately represented in clinical trials [2]. The 2013 Institute of Medicine report, *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*, highlighted this important and ongoing issue, concluding that lack of an evidence base for this special population is detrimental to the quality of cancer care in older adults [3]. Recommendations from this report can be summarized as follows: first, more patients reflecting the population and actual disease experience need to be enrolled in clinical trials and second, more data need to be collected, analyzed, and reported regarding this underrepresented population.

In 2015, the American Society of Clinical Oncology (ASCO) published recommendations to strengthen the literature regarding care for older adults with cancer, *Improving the Evidence Base for Treating Older Adults with Cancer* [4]. This white paper included several suggestions to expand the body of data used to treat older adults with cancer. Journal editors were urged to develop policies to improve the inclusion and reporting of clinical trial data specific to older adults. An important action step from this recommendation was:

> "Require authors to submit and report the detailed age distribution (by decade) of the population included in the study, not just the age ranges of the population, and data analyses that could potentially yield valuable age-related information, including age-based analyses of response, and toxicity." (p. 3831) [4]

In November 2017, ASCO and the US Food and Drug Administration convened a conference to discuss this issue. From this joint workshop came action items to shift the landscape of clinical trial enrollment and reporting. This meeting reiterated the charge to

move the 2015 ASCO recommendations into practice, including the directive to change data reporting practices for older adult study participants.

Our research group conducted a systematic review to identify the reporting status of Phase III chemo-therapeutic clinical trial treatment efficacy and adverse events in older adults with cancer. We sought to investigate the frequency with which these data points were reported in the literature as a means to identify gaps in reporting and opportunities to expand evidence about outcomes in older adults with cancer.

2. Methods

The data used in this systematic review were from articles published online or only in print between July 1, 2016 and June 30, 2017, based on PubMed and EMBASE searches. This time interval was selected to capture articles that would have been unlikely to be affected by the 2015 ASCO statement. Inclusion criteria were articles that reported findings from chemo-therapeutic Phase III cancer clinical trials in adults. This included articles that were secondary analyses of data pertaining to health-related quality of life as well as long-term follow-up of select patients from the original Phase III cancer clinical trials. The exclusion criteria were: 1) all Phase I, Phase II, and aggregated data from Phase II/III studies; 2) Phase III studies that focused upon radiation and/or surgical treatment interventions; 3) case studies; 4) cross-sectional studies; and 5) qualitative studies.

A keyword search strategy was developed by medical librarians (See Box 1). The initial search, conducted in early January 2017, covered journals published from July 1, 2016. Subsequent searches were performed automatically every Monday to cover publications through July 31, 2017. All results were entered into RefWorks, a reference management system. The title and abstract of all articles entered into RefWorks were reviewed by research group member KBS to determine if the inclusion criteria were met.

2.1. Sample

There were 929 articles captured by the keyword searches, 178 articles through PubMed and 751 through EMBASE. There were 116 duplicares. Six-hundred and thirty-three (68.1%) articles were excluded due to not meeting the inclusion criteria in terms of disease, being a phase III treatment study, and/or not having a publishing date in the designated time frame. An additional 21 (2.2%) of the articles were found not to meet the inclusion criteria after full article review by members of the research group. The final sample included 159 articles (See Fig. 1).

2.2. Data Collection

A data extraction survey was developed through an iterative process by five members of the Cancer and Aging Research Group (CARG) Advocacy Group. At two points in the survey development process, other members of CARG reviewed and provided comments during regularly scheduled conference calls. The data extraction survey was built in REDCap [5] and pilot tested using 10 articles,after which modifications were made and the final survey established (See Appendix 1). The data extraction survey included DOI, journal title, article

title, cancer type, and specific questions focusing on the data in the methods, results, and discussion sections.

To evaluate interrater reliability, 15 articles were reviewed by three to six reviewers duringthe early stage of the investigation. The resulting agreement rate was 85%, ranging from 71% to 100%. The remaining articles were evaluated independently by at least two reviewers. Responses were downloaded from REDCap into SPSS version 23 [6] and evaluated for inter-reviewer differences. If extracted data differed between reviewers of the same article, a research assistant reviewed the article and resolved discrepancies. These revisions were reviewed for accuracy by the first author. The data was then corrected in the dataset resulting in 159 articles (Appendix 2) with extracted data that was congruent across reviewers.

3. Results

The 159 articles were published in 36 different scientific journals. One-third of the articles were published in 14 of the journals (range: 3–19 articles per journal). The investigations focused on twenty-five different cancer types. Four articles reported findings on four or more cancers, and one article did not name the cancer(s) of interest. Approximately 78% of the articles included ten of the twenty-five cancer types (Table 1).

One-hundred and seventeen of the eligible articles (117/159, 74.6%) listed age-specific *medians* compared to mean ages in their respective demographic sections. Of these 117 articles, 1) 63 (53%) reported study populations with median ages ≥60; 2) 29 (24%) reported study populations with median ages ≥65; and 3) 6 (5%) reported study populations withmedian ages ≥70. Information regarding theages of the participants, presented as demographics in the Results sections of the articles, included the following: median and range 61.0%; age categories (e.g., 40 to 64, 65 to 75, ≥ 75) 27.7%; median and interquartile range 12.6%; mean and standard deviation 11.3%; age range 6.3%; and mean and range 5.7% (Table 2). Finally, 75 (47.2%) articles included stratifications of data by age.

Of the articles, 95.6% reported inclusion criteria and of those, 19.1% reported an upper age cut-off. Treatment efficacy was reported in 96.2% of the articles, with 39.9% of these including efficacy stratified by age. The reporting of adverse events or complications among all participants was included in 84.9% of the articles with 8.9% reporting these events stratified by age (Table 2).

In the Discussion sections, treatment efficacy based on age was mentioned in 13.8% of the articles and age stratification of adverse events or complications was only mentioned in 5.7% of the articles. Lastly, 3.8% of the articles reported age-related issues as study limitations (Table 2).

4. Discussion

This systematic review identifies the reporting status of Phase III chemo-therapeutic cancer clinical trials in terms of efficacy and adverse events specific to older adults. In addition, this study investigates the frequency with which these data points were reported in the literature

in order to identify gaps in reporting and opportunities to expand the evidence base for older adults with cancer. Despite ASCO and FDA recommendations [7] pertaining to age distribution and health risk profiles of clinical trial research participants, this systematic review found a dearth in reporting regarding treatment efficacy and adverse events specific to older adults with cancer. When outcomes pertaining to older adults were reported, the results were inconsistent as evidenced by the array of age distributions and varying categorization of “older adults”. Seventy-five percent of the articles in this review reported age-specific medians. Median age is important as it summarizes the age distribution of a study’s population and facilitates the reporting of age stratification. Despite older adults being the majority of patients with cancer [8], reporting of treatment efficacy and adverse events by age was observed in <40% and 9% of the studies, respectively, in this review. This gap in evidence severely limits informed clinical management of older adults with cancer.

Solutions to address this deficiency in reporting include 1) a conscious effort at every level of clinical trial planning to identify and report age-specific issues and 2) the reporting of outcomes stratified by age unless appropriately not relevant. Funding from federal and private entites should not only require the planned and actual recruitment and participation of diverse, older patients, but also the reporting of treatment efficacy, adverse events, and age-related issues pertaining to treatments and outcomes for this population. Protocols for clinical trials should avoid, for example, exclusion criteria related to functional and cognitive status, and also be designed for a priori reporting of subgroup effects by age at study entry [9,10].

We agree that increasing enrollment of older adults in clinical trials is of the utmost importance. Evidence demonstrates that older adults are willing to enroll in trials [11] and have similar treatment-related toxicity profiles compared to that of younger patients [12–14]. Yet, as noted by Levit and colleagues [15],increasing enrollment of older adults in trials alone will not solve the evidence gap. Thus, expanded representation and reporting of older adult-specific research is imperative. One strategy might be the inclusion of broader, more age-specific endpoints, such as the impact of treatment on function and cognition, as well as utilizing innovative trial designs [7,16,17]. Similarly, in addition to the typical outcomes of hospitalization and death, the recognition and reporting of adverse events in a geriatric-specific context is needed. These events include 1) need for skilled nursing facility for rehabilitation; 2) admission to nursing home or need for a higher level of care (e.g., moving to an assisted living facility); 3) caregiver burden; 4) domains of health and functioning (e.g., cognitive, social, and physical); and 5) quality of life. These outcomes are at least equally meaningful to older patients as treatment efficacy and disease survival [18,19]. These outcomes are also provide critical information for the health care team to provide optimal care. The multi-faceted nature of geriatric oncology must be considered. Older adult-specific research efforts need to incorporate biopsychosocial approaches [20] in reporting outcomes.

Levit and colleagues [15] concluded that academic journals should incentivize researchers to report more detailed age distributions and health risk profiles of research participants. We, as members of the Advocacy Committee of the Cancer and Aging Research Group, believe that this reporting should be standard practice and a customary component of the reviewing rubric adhered to by journal review boards and editors. We challenge Geriatric, Geriatric

Oncology, and Oncology-focused journals to be the first to implement these criteria. In addition, as Witham and colleagues [9] have encouraged, the outcomes of older adult study participants should be reported and discussed within the main paper and not solely as supplementary data.

In summary, the enrollment of older patients with cancer in clinical trials and the reporting of results are in need of change through conscious efforts that can ultimately improve the treatment decisions and clinical outcomes for this burgeoning yet underserved population.

Based on our findings, we propose the following recommendations:

1. Conduct clinical trials targeting all patients, regardless of age, if they meet other eligibility criteria.
2. Report the median age of study participants.
3. Utilize age stratification reporting methods automatically when ≥25% of the study cohort is ≥65 years of age.
4. Utilize age stratification reporting methods automatically when the median age of the study participants is ≥60 years of age.
5. Stratify the following by age: 1) demographic profile; 2) intervention results; 3) existence of adverse events; and 4) any other relevant results
6. Report results by age stratification preferably in the main section of manuscripts, if not possible due to word count and page limits as supplementary data.
7. Discuss the implications of the findings (e.g., treatment efficacy, adverse events or complications) specific to older adults.
8. Describe age-related issues as study limitations when applicable.

These recommendations extend those put forth in the 2013 IOM [3], 2015 ACSO [2], and 2017 ASCO, the US Food and Drug Administration [7] reports, the CONSORT statement 2010 [21],and and the European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology 2013 position article [22]. We provide specific recommendations to facilitate funders, journal editors, and cancer researchers in identifying important factors required in translating evidence into clinical practice.

Many of the articles included in this review presented data demographics and adverse events in tables. Few presented data segregated by age group (younger adults, older adults) in these tables. In an attempt to assist in implementing the recommendations pertaining to the stratification of data by age group, two templates are offered (See Tables 3 and 4).

4.1. Limitations

There are limitations to our analysis. The reviewed articles included articles published online or only in print between July 1, 2016 to June 30, 2017, which limits the application of findings published before or after this time frame. The review focused on Phase III pharmaceutical trials and excluded Phase I, Phase II, and Phase II/III (aggregated data) studies, treatments that included radiation and/or surgery, case studies, cross-sectional studies, and qualitative studies. If all studies were included our results might be more generalizable, but they would be limited in their scientific rigor and/or accuracy in comparing different study designs.

5. Conclusion

This systematic review identifies the reporting of Phase III chemo-therapeutic cancer clinical trial results of efficacy and adverse events in older patients. This review also investigates the frequency with which these data points were reported in the literature as a means to identify gaps in reporting and opportunities to expand the knowledge base related to geriatric oncology. Results of our systematic review suggest that there is inadequate reporting of treatment efficacy and adverse events as well as discrepancies as to how older age is defined, considered, and reported. This sparse and varied reporting critically limits the evidence base for treating older patients with cancer. There is a significant and timely need to design all clinical trials to include older adults and utilize a broad array of geriatric-specific outcomes. Incorporating these geriatric-specific outcomes as well as reporting the age-stratified data in a standardized and comprehensive manner can lead to better-informed treatment strategies for older adults with cancer.

Appendix A. Data Entry of Phase III Cancer Treatment Trial Literature

A.1. Reviewer and Article Information

doi only	
Reviewer name	
Article title	
Date of publication	
Journal	British Journal of Cancer
	Cancer
	European Journal of Cancer
	Lancet
	Lancet Oncology
	Annals of Oncology
	NEJM
	Journal of Clinical Oncology
	CA: A Cancer Journal for Clinicians
	Journal of the NCI
	Cancer Research
	International Journal of Cancer
	Neuro-Oncology
	Cancer Treatment Reviews
	Journal of the National Comprehensive Cancer Network
	Advances in Cancer Research
	Other
Other journal title	

Cancer site (select all that apply)	Breast
	Prostate
	Lung
	Colorectal
	Gynecologic
	Bladder
	Kidney
	Leukemia
	Lymphoma
	Melanoma
	Pancreas
	Thyroid
	Head & Neck
	Brain
	Four or more
	Other GI
	Other
Please specify the other type of GI cancer	
Please specify other type of cancer	
Methods Section (Full Text)	
Are any “inclusion/exclusion criteria” included in the methods section?	Yes
	No
Do the inclusion/exclusion criteria include an “upper age cut-off point”?	Yes
	No
Results Section (Full Text)	
How is “age” presented in the demographics	Age categories
	Age range
	Mean/Standard Deviation
	Median/Standard Deviation
	Mean/Range
	Median/Range
	Other
Please specify	
Is there a component of the Results Section that “stratified by age”? (presents data for different age groups such as 45 to 64 and 65 and older)	Yes
	No
What are the “age stratification categories”?	Yes
	No
Is effectiveness of “cancer treatment” presented in the Results Section?	Yes
	No
Is there an age stratification subset analysis of the effectiveness of the cancer treatment?	Yes
	No
Are “adverse events/complications” presented in the Results Section?	Yes
	No

Is there an age stratification analysis for adverse events/complications?	Yes
	No
Discussion (Full Text)	
Is the effective of cancer treatment based on age discussed?	Yes
	No
Is the lack of effectiveness of cancer treatment results based on age listed as a study limitation?	Yes
	No
Are age stratification “adverse events/complications” discussed”?	Yes
	No
Is the lack of data on adverse events/complications based on age listed as a study limitation?	Yes
Is there lack of other age-related issues/items mentioned as a study limitation?	Yes
	No

Appendix B. List of Articles in Systematic Review

References

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Box 1

Key Word Search for PubMed and Embase.

PubMed

(((“Clinical Trial, Phase III”[Publication Type] OR “Clinical Trials, Phase III as Topic” [Mesh] OR “phase 3 trial”[All Fields] OR “phase III trial”[All Fields]) AND (“Neoplasms”[Mesh] OR “cancer”[All Fields] OR “cancers”[All Fields] OR “cancerous” [All Fields] OR “tumor”[All Fields] OR “tumors”[All Fields] OR “tumour”[All Fields] OR “tumours”[All Fields] OR “neoplasm”[All Fields] OR “neoplasms”[All Fields] OR “neoplastic”[All Fields] OR “malignant”[All Fields] OR “malignancy”[All Fields] OR “malignancies”[All Fields] OR “metastatic”[All Fields] OR “metastasis”[All Fields] OR “metastases”[All Fields])) NOT (“case reports”[Publication Type] OR “guideline” [Publication Type] OR “practice guideline”[Publication Type] OR “review”[Publication Type] OR “meta analysis”[Publication Type] OR systematic[sb])) Filters: Publication date from 2016/07/01 to 2017/06/30; English; Adult: 19+ years

Embase

(‘phase 3 clinical trial’/de OR ‘phase 3 clinical trial’:it OR ‘phase 3 clinical trial (topic)’/de OR ‘phase 3 trial’ OR ‘phase iii trial’) AND (‘neoplasm’/exp. OR ‘cancer’ OR ‘cancers’ OR ‘cancerous’ OR ‘tumor’ OR ‘tumors’ OR ‘tumour’ OR ‘tumours’ OR ‘neoplasm’ OR ‘neoplasms’ OR ‘neoplastic’ OR ‘malignant’ OR ‘malignancy’ OR ‘malignancies’ OR ‘metastatic’ OR ‘metastasis’ OR ‘metastases’) NOT (‘case reports’:it OR ‘guideline’:it OR ‘practice guideline’:it OR ‘review’:it OR ‘meta analysis’:it OR ‘systematic’:it OR ‘conference abstract’:it OR ‘conference paper’:it OR ‘letter’:it OR ‘note’:it OR ‘editorial’:it OR ‘surgery’:ab,ti OR ‘surgeries’:ab,ti OR ‘surgical’:ab,ti) AND [embase]/lim NOT ([embase]/lim AND [medline]/ lim) AND ([adult]/lim OR [young adult]/lim) AND [english]/lim AND [2016–2017]:py

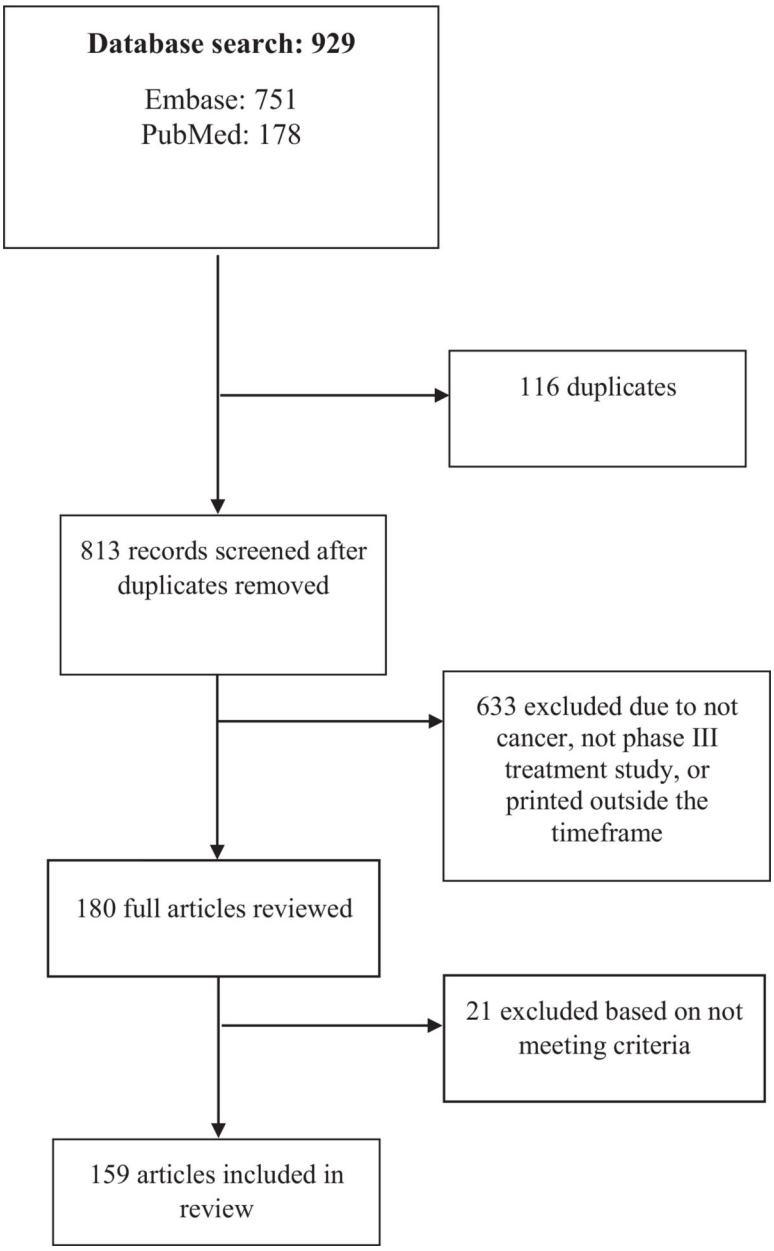

Fig. 1.

Flow Chart according to PRISMA Framework". Footnote: Modified From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6 (7): e1000097. doi:https://doi.org/10.1371/journal.pmed100009

Table 1

Journals and cancer sites included in the systematic review (n = 159 articles).

Variables	N	%
Journal titles		
Lancet Oncology	19	11.9
New England Journal of Medicine	19	11.9
Journal of Clinical Oncology	18	11.3
Annals of Oncology	7	4.4
European Journal of Cancer	6	3.8
Lancet Hematology	5	3.1
Lancet	5	3.1
British Journal of Cancer	5	3.1
Lung Cancer	3	1.9
British Journal of Hematology	3	1.9
BMC Cancer	3	1.9
Haematologica	3	1.9
Other[a]	63	39.6
Cancer site		
Breast	25	15.7
Lung	17	10.7
Colorectal	16	10.1
Multiple Myeloma	14	8.8
Leukemia	12	7.5
Prostate	9	5.7
Lymphoma	9	5.7
Melanoma	8	5.0
Gynecologic	7	4.4
Pancreas	6	3.8
Other	36	22.6

[a]Other joumals include: Cancer, The Oncologist, Tumori Joumal, The Prostate, The Journal of Community and Supportive Oncology, Targeted Oncology, Surgery Today, Supportive Care in Cancer, Sarcoma, Research and Reports in Urology, Quality of Life research, Pancreatology, Oncortargets and Therapy, Neoplasia, medicine, Leukemia and Lymphoma, Leukemia, Lancet Gastroenterology and Hepatology, Journal of Translational Medicine, Journal of Thoracic Oncology, JAMA, Journal of Hematology and Oncology, Journal of Geriatric Oncology, Journal of Gastroenterology, Journal of Clinical Endocrine Metabolism, Journal of Cancer Research and Therapeutics, Journal of Cancer Research and Clinical Oncology, JAMA Oncology, International Journal of Hematology, Gynecological Oncology, European Urology, Clinics, Clinical Translational Oncology, Clinical Pharmacology and Therapeutics, Clinical Colorectal Cancer, Clinical Breast Cancer, Chinese Clinical Oncology, Cancer Research and Treatment, British Journal of Clinical Pharmacology, Breast Cancer Research and Treatment, Blood Cancer, Biomedicine and Pharmacotherapy, Asian Journal of Urology, Anticancer Drugs, Annals of Hematology, American Journal of Hematology, Acta Oncologica, American Journal of Clinical Oncology: Cancer Clinical Trials.

Table 2

Results on extracted data (n = 159 articles).

Variables	N	%
Methods section		
Inclusion Criteria Included	152	95.6
Upper Age Cut-off in Inclusion/Exclusion Criteria	29	19.1
Results section		
Age presentation in demographics		
Age categories	44	27.7
Age Range	10	6.3
Mean/Standard Deviation	18	11.3
Mean/Range	9	5.7
Median/Range	97	61.0
Median/Interquartile Range	20	12.6
Other	14	8.8
Stratified by age in any section of Results	75	47.2
Effectiveness of Cancer Treatment	153	96.2
Effectiveness of Cancer Treatment Stratified by Age	61	39.9
Adverse Events/Complications	135	84.9
Adverse Events/Complications Stratified by Age	12	8.9
Discussion section		
Effectiveness of Treatment Based on Age	22	13.8
Adverse Events/Complications Based on Age	9	5.7
Limitations		
Effectiveness of Treatment Based on Age	1	0.7
Adverse Events/Complications Based on Age	1	0.7
Lack of Other Age-Related Issues	6	3.8

Table 3

Template 1: Demographic data comparing two treatment modalities.

Characteristics	Treatment 1 (N = xxx)		Treatment 2 (N = xxx)	
	Younger[a]	Older	Younger	Older
Gender				
Female	n (%)	n (%)	n (%)	n (%)
Male	n (%)	n (%)	n (%)	n (%)
Age (years)				
Median (IQR)	n (%)	n (%)	n (%)	n (%)
Disease				
Type of cancer	n (%)	n (%)	n (%)	n (%)
Type of cancer	n (%)	n (%)	n (%)	n (%)
ECOG				
0	n (%)	n (%)	n (%)	n (%)
1	n (%)	n (%)	n (%)	n (%)
2	n (%)	n (%)	n (%)	n (%)

[a]Replace with age range of group.

Table 4

Template 2: Adverse events by grade.

Adverse Event	Grade							
	1		2		3		≥ 4	
	Younger[a]	Older	Younger	Older	Younger	Older	Younger	Older
Anemia	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anorexia	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Diarrhea	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fatigue	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Increased creatinine	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutropenia	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Thrombocytopenia	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Note: Include adverse events stratified by age and treatment arm.

[a]Replace with age range of group.