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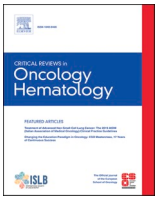

Prevalence, patterns, and determinants of multimorbidity among childhood and adult cancer survivors: A systematic review.

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ABSTRACT

Development of multimorbidity is common among cancer survivors due to their previous cancer, treatments, or changes in lifestyle. We summarized evidence on the prevalence, patterns, and determinants of multimorbidity among childhood and adult cancer survivors. We searched PubMed and EMBASE databases for articles reporting prevalence, patterns, and determinants of multimorbidity in cancer survivors. Finally, 23/500 articles were included. There was a large variation in the prevalence of multimorbidity (13–89%) among cancer survivors. Bone marrow transplantation, radiation, female sex, lower level of physical activity, increasing age, minority ethnicity, low-income, and low-education were associated with a higher prevalence of multimorbidity. Patterns of multimorbidity were both concordant and discordant. In conclusion, multimorbidity is highly prevalent and a major concern among cancer survivors. A personalized care plan that takes into account the identified risk may be beneficial to reduce the burden of multimorbidity and improve the quality of life among cancer survivors.

1. Introduction

Advances in multimodal and risk-based cancer treatment have contributed to the improved survival of children and adults diagnosed with cancer (Curry et al., 2006). However, increasing cancer survival is associated with morbidity, or the coexistence of more than one disease condition, defined as "multimorbidity." (The Academy of Medical Sciences, 2018) Multimorbidity is a major health concern among cancer survivors, (Armenian et al., 2010; Oeffinger et al., 2006) and studies have shown that it is associated with disability, poor quality of life, (Eton et al., 2019) increased healthcare utilization, (Jansana et al., 2021a; Abdelhadi et al., 2022; Harrington et al., 2019) and mortality (Jansana et al., 2021a) in cancer survivors and noncancer populations (McPhail, 2016; Bähler et al., 2015; Zhang et al., 2020). Demers et al. reported that two-thirds of paediatric central nervous system tumor survivors have an increased risk of developing at least one chronic health condition up to 18 years after treatment, (Demers et al., 2021) and Anna et al. showed that more than 80% of long-term breast cancer survivors developed multimorbidity (Jansana et al., 2021a). Even after adjusting for relevant factors such as age and gender, studies have also shown a higher prevalence of multimorbidity among cancer survivors compared to their siblings (Armenian et al., 2010) or the population control (Jiang et al., 2022).

Multimorbidity may differ between cancer survivors and the general population because of some characteristics, such as previous cancer diagnosis, treatment, and lifestyle. Recent systematic reviews on the general population revealed that the prevalence of multimorbidity ranged from 0.7% to 87.3%, and was associated with older age, female sex, and urban residence (Asogwa et al., 2022; Kaluvu et al., 2022). It is still debatable if this holds true for cancer survivors, given their exposure to cancer therapy. In order to identify cancer survivors with a single disease condition who are at increased risk of developing other chronic conditions, it is crucial to understand the prevalence, determinants, and patterns of multimorbidity among this vulnerable population.

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In recent times, owing to the increasing number of survivors worldwide, the concept of multimorbidity in cancer survivors has gained much attention. However, no study has synthesized evidence on the prevalence, patterns, or determinants of multimorbidity among cancer survivors. Knowledge about the burden, patterns, and determinants of multimorbidity among cancer survivors can be essential to supporting appropriate recommendations in evidence-based guidelines for long-term follow-up of cancer survivors or to developing personalized medical and psychological care for this special and high-risk population. This study therefore summarized evidence from published literature on the prevalence, patterns, and associated factors of multimorbidity among cancer survivors.

2. Methods

2.1. Review framework and team

This systematic review followed the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021). A multidisciplinary team of oncologists, epidemiologists, and systematic review methodologists was established based on their experience, publications, and knowledge in the fields of cancer and multimorbidity. The protocol for the review is published in PROSPERO, and the PROSPERO registration number is CRD42022339610.

2.2. Definition of terms and concepts

Cancer survivors were defined as those who had a previous diagnosis of cancer and completed oncological treatments (e.g., chemotherapy, radiotherapy, surgery, or stem cell transplantation (SCT)) and had been in complete remission (no evidence of active cancer). Cancer survivors were grouped into paediatric and adolescent cancer survivors (i.e., survivors of cancer diagnosed before the age of 15, 18, 19, or 21 years, depending on the study or country), as well as adult cancer survivors (age above 18 at the time of cancer diagnosis).

Chronic diseases (CDs) were defined broadly as conditions that last a year or longer and require continuous medical attention, limit activities of daily living, or both (Anone.). Multimorbidity was defined as the co-occurrence of two or more chronic conditions in the same individual (The Academy of Medical Sciences, 2018). The prevalence of multimorbidity was defined as the proportion of cancer survivors with more than one chronic disease condition. Patterns of clusters of chronic diseases were defined as different combinations of chronic conditions assessed among individuals, age groups, and cancer types.

2.3. Search strategy

A complete search strategy was developed by combining Medical Subject Headings (MeSH) such as “Neoplasms”, “Cancer Survivors”, and “Multiple Chronic Conditions” (Supplementary file). A comprehensive literature search was conducted in the following databases: MEDLINE (through PubMed) and EMBASE for articles published until May 2022, without year and language restriction. To complement the electronic search, we also conducted a backward citation check (manual search by checking the reference list) of the included articles for additional eligible studies. The search strategy was developed under the guidance of a librarian at Utrecht University.

2.4. Inclusion and exclusion criteria

Studies were included if they: 1) were original research and 2) assessed multimorbidity (multiple chronic conditions) in cancer survivors. We excluded studies focusing on cancer patients (a current diagnosis of cancer) and comorbidity studies that assessed the coexistance of other conditions with an index disease or primary disease of interest. In addition, review articles, case reports, and case series were excluded.

2.5. Study selection and data extraction

Two authors (OAA and DYQ) independently screened the titles, abstracts, and full texts. When there was a disagreement in opinion, a third author (DB) was consulted. We extracted author(s) name, year of publication, cohort and database, study design, multimorbidity source (self-report or health records), sampling method, survey period, age at survey, sample size, number of CDs, multimorbidity definition, type of survivor (paediatric, adolescent, or adult cancer survivors), primary cancer type, age at cancer diagnosis, and minimum survival after diagnosis from all included papers. Furthermore, cancer treatment type, time since cancer diagnosis or completion of treatment, overall prevalence of multimorbidity, and prevalence of multimorbidity by cancer types, odds/risk ratios, and clusters of chronic diseases were extracted. OAA performed the data extraction, which was reviewed by DYQ and DB.

2.6. Quality assessment

Three reviewers (OAA, DYQ, and DB) independently assessed the risk of bias using the National Institute of Health Quality Assessment Tool for observational cohort and cross-sectional studies (Services UD of H and H, 2014) and the JBI Critical Appraisal Checklist for studies reporting prevalence data (Munn et al., 2015). These tools were used to grade the overall quality of the included studies, which were classified as either good, fair, or poor quality. For the papers that performed multivariable analysis on multimorbidity outcomes among cancer survivors, classification into “good”, “fair”, or “poor” quality was based on 14 criteria (study population, adequate participation rate, similar subject selection or recruitment, and uniform application of eligibility to all participants, sample size estimation, exposure assessment before outcome, sufficient time frame to detect an association, and examination of different levels of exposure) (Armenian et al., 2010; Bluethmann et al., 2021; Kenzik et al., 2016). For papers that assessed prevalence and patterns of multimorbidity only, nine criteria (appropriate sample frame, sampling of study participants, adequacy of sample size, well-described study subjects and the setting, sufficient coverage, valid identification of conditions, reliable assessment of CDs, appropriate statistical analysis, and an adequate response rate) were used for this classification. When there were discrepancies among the three reviewers, a slightly lengthy discussion was initiated until a consensus was reached.

3. Results

3.1. Results of the literature search

Of 500 articles identified through the electronic databases, 343 articles remained after duplicate removal, and 22 articles were included after full-text review. Through back citation check, we identified an additional article. Finally, 23 articles were eligible and included in this

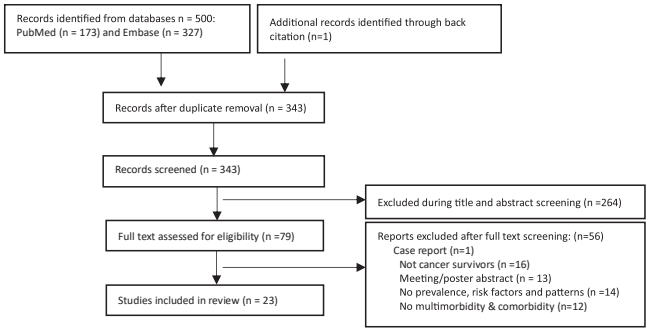

Fig. 1. Flowchart showing the identification and selection of the eligible studies.

review (Fig. 1).

3.2. Study characteristics

The majority (78%) of the included articles were cross-sectional studies (n = 18). Four articles used a retrospective cohort design, (Armenian et al., 2010; Jansana et al., 2021a; Harrington et al., 2019, 2020) while one article employed a case-control design (Keats et al., 2021). The survey period of all the studies ranged between 1970 and 2018. The sample size ranged from 36 (Demers et al., 2021) to 18,133 cancer survivors (Holmes et al., 2014) (Table 1).

Five of the 23 studies assessed only one cancer type (breast cancer (Harrington et al., 2019, 2020; Cohen et al., 2012; Ashing et al., 2014; Foster and Niedzwiedz, 2021) and brain tumors (Demers et al., 2021), whereas 17 investigated multiple cancer types. All articles included adult cancer survivors except for five studies that included childhood and adolescent cancer survivors (Armenian et al., 2010; Harrington et al., 2019; Demers et al., 2021; Harrington et al., 2020; Frederick et al., 2016). The minimum survival time since cancer diagnosis varied between studies. One study included ≥ 17-year cancer survivors, (Cohen et al., 2012) five studies included ≥ 5-year survivors and/or ≥ 2 years from the end of last cancer therapy, (Armenian et al., 2010; Jansana et al., 2021a; Harrington et al., 2019; Demers et al., 2021; Harrington et al., 2020) three studies included at least 2-year survivors after cancer diagnosis (Holmes et al., 2014; Frederick et al., 2016; Warner et al., 2017) and five studies included < 1-year survivors after cancer diagnosis (Abdelhadi et al., 2022; Ashing et al., 2014; Petrova et al., 2021; Foster and Niedzwiedz, 2021; Austin et al., 2019). Nine studies did not provide information on the minimum survival period. The mean follow-up period of cancer survivors (if reported) ranged from 10.1 to 20 years (Demers et al., 2021; Cohen et al., 2012). Due to the heterogeneity of the included studies (e.g., survey period, multimorbidity source, cancer type, years since cancer diagnosis, and age at diagnosis), meta-analysis of the results was not feasible. Table 2 provides an overview of the cancer characteristics of the included studies.

3.3. Risk of bias

The quality of the three papers that assessed the determinants of multimorbidity (Armenian et al., 2010; Bluethmann et al., 2021; Kenzik et al., 2016) was graded as good, even though one paper did not report on the participation rate of the eligible participants (Kenzik et al., 2016). For the other 20 papers, which estimated the proportion of survivors with multimorbidity and the patterns of clustering of chronic conditions, 12 were graded "good," whereas eight were graded "fair." Further information about the grading system can be found in Table S3.

3.4. Prevalence and number of multimorbidities in cancer survivors

The number of CDs used in the definition of multimorbidity ranged from 4 to 24 conditions (Jansana et al., 2021a; Hawkins et al., 2017). Multimorbidity was defined as the coexistence of two or more chronic conditions in the majority of the studies (n = 21/23), except in two studies, in which it was defined as the coexistence of three or more chronic conditions (Jiang et al., 2022; Frederick et al., 2016). Individual disease conditions included in the definition of multimorbidity were self-reported in the majority of the included studies (n = 19/23), except in the four studies that assessed multimorbidity based on data from health records (Jansana et al., 2021a; Harrington et al., 2019; Demers et al., 2021; Harrington et al., 2020). The most frequently reported condition was diabetes mellitus (18 studies, 82%), followed by hypertension (17 studies, 77%), arthritis (17 studies, 77%), pulmonary disease (14 studies, 64%), heart diseases (e.g., heart failure and myocardial infarction; 14 studies, 64%), stroke (14 studies, 64%), and angina/-coronary heart disease (9 studies, 41%). No study reported infectious diseases on the list of chronic conditions among cancer survivors (Tables S1 & S2).

The overall prevalence of multimorbidity varied from 13.4% in a population that survived at least two years since cancer diagnosis to 89% (minimum survival period was not reported) (A.M. et al., 2020; Anone.). The prevalence of multimorbidity ranged from 13.4% to 72.2% in childhood cancer survivors (Demers et al., 2021; Frederick et al., 2016) and from 23.6% to 82.7% in adult cancer survivors (Jansana et al., 2021a; Betts et al., 2022). The prevalence estimate ranged from 13.4% to 82.7% in nine studies that used at least 12 CDs in the assessment of multimorbidity and from 21.1% to 89.0% in 13 studies that used less than 12 CDs in the assessment of multimorbidity (Table 1). Two studies stratified the prevalence of multimorbidity by age and reported a lower prevalence in age 15–39 years (21%) than age 40–64 years (range: 37–57%) and age 65 + years (range: 56–76%) (Cohen et al., 2012; Zakaria, 2021). In one study, recent cancer survivors had a lower prevalence compared to long-term survivors (67% vs. 69%) (Petrova et al., 2021). Studies that assessed the prevalence of multimorbidity by cancer type reported brain and central nervous system (CNS), prostrate, colorectal, and breast cancer as the most common cancer diagnoses in survivors with multimorbidity (Harrington et al., 2020; Keats et al., 2021; Austin et al., 2019) (Table 1). We were not able to stratify multimorbidity by country or continent because almost all the studies were based on the US and Canadian populations, except for two studies that included participants from the UK and Spain (Jansana et al., 2021a; Foster and Niedzwiedz, 2021).

3.5. Determinants of multimorbidity in cancer survivors

Three studies assessed the determinants of multimorbidity (Armenian et al., 2010; Bluethmann et al., 2021; Kenzik et al., 2016) (Table 3). Age at the post-cancer survey, sex, ethnicity, education, cancer stage, poverty, bone marrow transplant (BMT), radiotherapy, total body irritation (TBI), surgery, and physical activity were analysed as determinants of multimorbidity in cancer survivors. One study found that autologous (relative risk [RR] = 1.8; 95% confidence interval [CI] = 1.1–2.8), allogeneic related (RR = 2.8; 95% CI = 2.1–3.7) and allogeneic unrelated (RR = 3.4; 95% CI=2.1–5.6), conditioning with TBI (RR = 2.4; 95% CI = 1.2–4.8), active chronic graft versus host disease (GVHD) (RR = 3.5; 95% CI=2.4–5.1) and resolved chronic GVHD (RR=3.5; 95% CI=2.5–5.0) were associated with a higher risk of multimorbidity in BMT survivors compared to conventionally treated childhood cancer survivors (Armenian et al., 2010). However, when BMT survivors were compared with siblings, BMT survivors were at a higher risk of multimorbidity – (autologous (RR=4.7; 95%CI=3.2–6.8), allogeneic related (RR=5.7; 95%CI=4.8–8.9), allogeneic unrelated (RR=8.9; 95% CI=5.9–13.4).

Another study found that survivors who engaged in more physical activity had lower odds of multimorbidity (Bluethmann et al., 2021). Survivors who reported higher behavioural scores (odds ratio [OR]= 0.79, 95%CI=0.68–0.91), higher physical activity index scores (OR=0.8; 95%CI not reported), higher performance scores including grip strength and fitness (OR= 0.76; 95% CI not reported), and those who reported less than 2 h of television per day versus 5 h (OR=0.17; 95%CI=0.06–0.45) were less likely to report multimorbidity (Bluethmann et al., 2021). However, no significant association was found between the metabolic equivalent of task (MET) hours per week of activity and multimorbidity (Bluethmann et al., 2021).

In terms of multimorbidity cluster, increasing age at post-cancer survey (RR range: 1.02–1.07) and high school versus college education (RR range: 1.31–1.50) (Kenzik et al., 2016) were significantly associated with metabolic multimorbidity cluster, CVD multimorbidity cluster, and major depressive disorder risk (MDDr) + gastrointestinal (GI) + pulmonary multimorbidity cluster. Minority ethnic populations (RR = 1.61; 95% CI = 1.28–2.02) and radiated survivors (RR = 1.29; 95% CI = 1.01–1.64) were more likely to have metabolic multimorbidity cluster. Female sex and poverty (>5% below poverty versus being 0–5%

Table 1
Characteristics of the included studies.

Author and year	Cohort and Database	Inclusion Criteria	Study Design	MM Source	Sampling Characteristics ♯	Survey Period	Sample Size	Age at Survey	Number of CDs	MM Definition	Prevalence (%)
(Harrington et al., 2019)	THM CCAE, USA	Prevalence	Retrospective cohort	ICD-9-CM diagnosis codes	NR	2009–2014	CS (n = 3687)	Mean age: 11.4 years	15	≥ 2	36.3
(Demers et al., 2021)	LTFUC SJUHC	Prevalence	Cross-sectional	ICD-9, ICD-10, and ICPC-2 diagnosis codes	Non-Probability	NR	CS (n = 36)	Mean ± SD (Range): 21 ± 3.3(16–29) years	4 +	≥ 2	72.2
(Cohen et al., 2012)	RCT CALGB 7581	Prevalence	Cross-sectional	Self-reported	Probability	1975–1980	CS (n = 153)	Mean (Range): 64.5 (40–86) years	22	≥ 2	Age 40–64 years (57.0) and age 65–86 years (75.7)
(Harrington et al., 2020)	THM CCAE, USA	Prevalence and patterns	Retrospective cohort	ICD-9-CM diagnosis codes	NR	2009–2014	CS (n = 3687)	Mean age ± SD: 11.4 ± 4.1 years	NR	≥ 2	36.3
(Betts et al., 2022)	MEPS	Prevalence	Cross-sectional	Self-reported validated by pharmacies & a subset of HCP	Probability	2008–2017	CS (n = 601) and NCS (n = 2404)	Range: 18–39 years	8	≥ 2	23.6
(Abdelhadi et al., 2022)	MEPS	Prevalence	Cross-sectional	Self-reported	Probability	2011–2016	CS (n = 2326)	Range: 18–65 + years	12	≥ 2	51.1
Armenian et al. 2010	CCSS and BMTSS	Prevalence and risk factors	Retrospective cohort	Self-reported	Probability	1970–1986	BMTSS CS (N = 145), CCSS CS (n = 7207), and NCS (n = 4020)	Mean ± SD (Range) years: BMTSS 24.0 ± 8.4 (5.37–44.96), CCSS 25.1 ± 7.9 (8.8–49.1), Siblings 26.6 ± 9.2 (1.8–56.2)	6	≥ 2	BMTSS: 59.3
(Jiang et al., 2022)	NHIS	Prevalence	Cross-sectional	Self-reported	Probability	2002–2018	CS (n = 30,728) and NCS (n = 454,505)	Range: 18–75 + years	10	≥ 3	2002 − 2003: 43.7 and 2016 − 2018: 46.6
(Kenzik et al., 2016)	SEER cancer registries linked with the MHOS	Prevalence, patterns and risk factors	Cross-sectional	Self-reported	Probability	1998–2013	CS (n = 5991)	Mean ± SD (Range): 77.7 ± 6.0 (65–104) years	12	≥ 2	70.0
(Ashing et al., 2014)	California Cancer Registry, hospital registries, and support groups.	Prevalence	Cross-sectional	Self-reported	Mixed methodology sample	NR	CS (n = 320)	Mean ± SD (Range): 54.2 ± 11.4 (50–64) years	8	≥ 2	52.0
(Bluethmann et al., 2021)	NHANES	Prevalence and risk factors	Cross-sectional	Self-reported	Probability	2011–2014	Overall (n = 9620), NCS (n = 8754), CS (n = 866)	Mean± SD: 62 ± 0.62 years	10	≥ 2	89.0
(Petrova et al., 2021)	NHANES	Prevalence	Cross-sectional	Self-reported	Probability	2007–2018	Overall (n = 2073): recent CS (n = 853, and long-term CS (n = 1220)	Recent survivors: Mean ± SD (Range) 58.6 ± 13.1 (18–79) years and Long-term survivors: Mean ± SD (Range): 61.2 ± 11.9 (18–79) years	16	≥ 2	Recent CS: total 66.6, pre dx 65.4, post dx 9.9 and Long-term survivors: total 67.1, pre dx 31.5, post dx 52.1
(Ekenga et al., 2022)	HRS	Prevalence and patterns	Cross-sectional	Self-reported	Probability	2014–2016	CS (n = 633)	Mean ± SD (Range): 58.9 ± 3.4 (51 +) years	6	≥ 2	64.0
(Frederick et al., 2016)	REACH	Prevalence	Cross-sectional	Self-reported	Probability	NR	CS (n = 268)	Range: 12–49 years.	12	≥ 3	13.4
(Foster and Niedzwiedz, 2021)	UK Biobank	Prevalence	Cross-sectional	Self-reported	Non-Probability	2006–2010	CS (n = 8438)	Range: 40–70 years	10	≥ 2	30.1

(*continued on next page*)

Table 1 (*continued*)

Author and year	Cohort and Database	Inclusion Criteria	Study Design	MM Source	Sampling Characteristics ♯	Survey Period	Sample Size	Age at Survey	Number of CDs	MM Definition	Prevalence (%)
(Guy et al., 2017)	MEPS	Prevalence	Cross-sectional	Self-reported	Probability	2008–2013	CS (n = 10,293), NCS (n = 135,151)	Range: 18–80 + years	8	≥ 2	67.2
(Hawkins et al., 2017)	NHIS	Prevalence and patterns	Cross-sectional	Self-reported	Probability	2010–2013	Overall: n = 48,181, CS (n = 3184) and NCS (44,997)	Range: < 39–65 + years	6	≥ 2	38.7
(Austin et al., 2019)	HINTS	Prevalence	Cross-sectional	Self-reported	Probability	2014–2017	NR	Range: 18–75 + years	5	≥ 2	51.0
(Jansana et al., 2021b)	SURBCAN	Prevalence and patterns	Retrospective cohort	ICPC-2 and (ICD-9) and (ICD-10)	Non-Probability	2012–2016	CS (n = 6512)	Mean (10th, 90th): 66.0 (50.3, 83.1) years	24	≥ 2	82.7
(Keats et al., 2021)	PATH	Prevalence	Retrospective, nested case–control	Self-reported	Non-Probability	NR	6832 (CS = 1708) and Matched NCS 6832)	Range: 35–69	20	≥ 2	52.6
(Warner et al., 2017)	HRS	Prevalence	Cross-sectional	Self-reported	Probability	2010 – 2012	Overall: n = 15,808 (CS (n = 2025) and NCS (n = 13,783)).	Range: 50 +	13	≥ 2	68.9
(Zakaria, 2021)	CCHS	Prevalence	Cross-sectional	Self-reported	Probability	2015–2018	overall: n = 64593 (CS (n = 708) and current cancer (n = 113), NCS (n = 63772)	Range: 15 +	9	≥ 2	Age 15–39 years (21.1), age 40–64 years (37.4 |), and age 65 + years (55.7)
(Holmes et al., 2014)	BRFSS	Prevalence	Cross-sectional	Self-reported	Probability	2009	CS (n = 18,133) and NCS (n = 94,407)	Range: 65 +	5	≥ 2	67.5

*ABBREVIATIONS: *post–end of treatment, physical activity index (PAI), National Health and Nutrition Examination Survey (NHANES), Health Related Quality of Life (HRQOL) , Not Reported (NR), Truven Health MarketScan (r) Commercial Claims and Encounters (THM CCAE) database United States, Long-term follow-up clinic at the Sainte Justine University Hospital Centre (LTFUC SJUHC), Medical Expenditure Panel Survey (MEPS), National Health Interview Survey (NHIS), Healthcare Providers HCP, The Surveillance, Epidemiology and End Results (SEER), Medicare Health Outcomes Survey (MHOS), Behavioral Risk Factor Surveillance System (BRFSS), National Health and Nutrition Examination Survey (NHANES), Canadian Community Health Survey (CCHS), Health and Retirement Study (HRS), Atlantic Partnership for Tomorrow's Health (PATH) cohort, The Survival Breast Cancer (SURBCAN) cohort study, REACH (Research Evaluating After-Cancer Health), Health Information National Trends Survey (HINTS), International Classification of Primary Care, version 2 (ICPC-2) and International Classification of Diseases, version 9 (ICD-9) and 10 (ICD-10), Electronic Healthcare Record (EHR) Cancer survivors (CS), Non-Cancer survivors (NCS), Multimorbidity (MM), Randomized control trial (RCT), Diagnosis (dx), Bone Marrow Transplant Survivor Study (BMTSS).*

♯ Probability sampling is referred to as random sampling, including four-stage stratified cluster; complex, multistage; and two-stage stratified sampling. Non-probability sampling included convenience sampling.

Table 2
Overview of included studies according to cancer characteristics.

	Author, and year	Cancer Type	Age at Cancer Diagnosis	Minimum Survival after Diagnosis	Treatment	Time since Cancer Diagnosis or Completion of Treatment	Multimorbidity Prevalence by Cancer Type
CHILDHOOD AND ADOLESENCT CANCER SURVIVORS	Harrington et al. (2019)	Different cancer types	Mean (range): 11.4 (2–18) years	2 years *	NR	2 + Years	NR
	Demers et al. (2021)	Brain tumors	Mean ± sd (range): 8.9 ± 5.1 (0–19) years	5 years or 3 *	Cranial and spinal radiation therapy= 24 (66.6), Cranial radiation therapy= 11 (30.1), No radiation therapy= 1(2.8)	Mean (SD) range: 10.1 (3.8) 4.0 – 18 years since completion of treatment	NR
	Harrington et al. (2020)	Different cancer types	Mean (range): 11.4 (2–18) years	2 years *	NR	2 + Years	Brain/CNS cancer 47.2%
	Frederick et al. (2016)	Different cancer types	Range: 0–15 + years	2 years and ≥ 1 *	Chemo, Radiation, Bone Marrow Transplant	Mean (Range): 13.1 (range 2–46 years).	NR
	Armenian et al. (2010)	AML, ALL, HL, and NHL	Range: ≤ 21 year	5 years	HSCT, Chemotherapy, Radiation	Median time: 11.0 years (range, 2.3–25.9)	NR
AYA	Abdelhadi et al. (2022)	Different cancer types	Range: 15–39 years of age	< 1 year	NR	Range: 0–20 +	NR
ADULT CANCER SURVIVORS	Cohen et al. (2012)	Breast cancer	NR	17 years	NR	Mean (range): 20 (17–25) years	NR
	Betts et al. (2022)	Different cancer types	Range: ≥ 18 years	NR	NR	NR	NR
	Jiang et al. (2022)	Different cancer types	Range: ≥ 18 years	NR	NR	NR	NR
	Kenzik et al. (2016)	Different cancer types	Mean (range): 75 months (65–103)	NR	Radiation: 2096 (35.0), surgery: 3896 (65.0)	Mean (SD) range: 16.1 (16.2) 0–145 months	NR
	Ashing et al. (2014)	Breast cancer	Range: ≥ 18 years	1 years	Chemotherapy: 213 (67), Radiation: 222 (69), Hormone therapy: 207 (65), Lumpectomy:188 (59), and Mastectomy: 124 (39)	NR	NR
	Bluethmann et al. (2020)	NR	NR	NR	NR	Mean (SE) 95%CI: 10.4, 0.52, (9.37, 11.44)	NR
	Petrova et al. (2021)	Different cancer types	Range: ≥ 18 years	Recent survivors: 1 year and long-term survivors: 6 years	NR	Recent survivors: Range: 1–5 years and Long-term survivors: Range: 6–20 +	NR
	Ekenga et al. (2022)	Different cancer types	NR	NR	NR	> 60% of the participants were 5 + years	NR
	Foster et al. (2021)	Breast cancer	NR	< 1 year	NR	Range < 1–5 + years	NR
	Guy et al. (2017)	Different cancer types	NR	NR	NR	Mean (range): years 10.80 (0–20 +)	NR
	Hawkins et al. (2017)	Different cancer types	NR	NR	NR	Range: < 2–11 +	NR
	Austin et al. (2019)	Different cancer types	NR	< 1 year	NR	Range: < 1–10	Colorectal cancer 60.8%, prostate cancer 49.8%, and breast cancer 46.3%
	Jansana et al. (2021)	Breast cancer	Range: ≥ 18 years	5 years	Surgery: 96.9%	Range: 5–10 +	
	Keats et al. (2021)	Different cancer types	NR	NR	NR	NR	Breast cancer: 48.4%, Colorectal cancer: 44.7%, Prostate cancer 50.9%, other cancers (bronchus and lung, liver, ovary, pancreas, stomach, esophagus, larynx, trachea, rectum, cervix, uterus, kidney, bladder, brain, thyroid, non-Hodgkin's-

(*continued on next page*)

Table 2 (*continued*)

Author, and year	Cancer Type	Age at Cancer Diagnosis	Minimum Survival after Diagnosis	Treatment	Time since Cancer Diagnosis or Completion of Treatment	Multimorbidity Prevalence by Cancer Type
						lymphoma, leukemia, and others) 56.4%
Warner et al. (2017)	Different cancer types	NR	2 years	NR	Mean: 12 + years	NR
Zakaria et al. (2021)	Different cancer types	NR	NR	NR	NR	NR
Holmes et al. (2013)	Different cancer types	Range: ≥ 18 years	2 years	NR	Range 2 + year	NR

ABBREVIATIONS: *post–end of treatment, physical activity index (PAI), Adolescent and young adult (AYA), National Health and Nutrition Examination Survey (NHANES), Health Related Quality of Life (HRQOL) Not Reported (NR), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and acute lymphoblastic leukaemia (ALL), Hematopoietic stem cell transplantation (HSCT) and acute myeloid leukaemia (AML).

below poverty) were associated with CVD and MMDr+GI+Pulmonary multimorbidity cluster. However, neither sex nor poverty level were associated with metabolic multimorbidity cluster (Kenzik et al., 2016). In addition, neither cancer stage nor surgery was associated with any of the three clusters (metabolic multimorbidity, CVD multimorbidity, and MMDr+GI+Pulmonary multimorbidity clusters) (Kenzik et al., 2016).

3.6. Patterns of clusters of chronic diseases

Five studies assessed patterns of multimorbidity in cancer survivors using latent class analysis (Harrington et al., 2020; Ekenga et al., 2022) exploratory factor analysis, (Kenzik et al., 2016) hierarchical cluster analysis (Jansana et al., 2021a) and descriptive methods (Hawkins et al., 2017) (Table 4). The CNS, metabolic, mental, CVD, endocrine, musculoskeletal (MSK), thyroid, cardiometabolic, and respiratory clusters were the reported patterns of clusters of CDs present in survivors of cancer. Mental disorder was also reported to cluster with other CDs, such as MSK, (Jansana et al., 2021a) pulmonary, (Kenzik et al., 2016; Harrington et al., 2020) cardiometabolic, (Ekenga et al., 2022) endocrine and CNS (Harrington et al., 2020). In addition, MSK clustered with CVD, (Jansana et al., 2021a) whereas CNS clustered with the endocrine group (Harrington et al., 2020). Two studies reported other miscellaneous CDs (consisting of diverse types of conditions) patterns (Jansana et al., 2021a; Ekenga et al., 2022).

4. Discussion

Cancer survivors are at increased risk of developing multimorbidity even after years of their primary cancer diagnosis. We summarized, for the first time, the prevalence, determinants, and patterns of multimorbidity in cancer survivors. Our review, which included 23 studies, showed that overall, the prevalence of multimorbidity varied from 13.4% to 89%. Prevalence varied by age at cancer diagnosis, with childhood cancer survivors having lower prevalence (range: 13.4–72.2%) compared to adult cancer survivors (range: 23.6–82.7%). Brain/CNS, lung, prostrate, colorectal, and breast cancer were among the most common cancer diagnoses in survivors with multimorbidity. While diabetes mellitus, hypertension, arthritis, pulmonary disease, and heart disease were the most frequently reported conditions. BMT, radiation therapy, TBI, female sex, less physical activity, increasing age at post-cancer survey, minority ethnicity, low income, and low education level were associated with increased risk of developing different clusters of multimorbidity in cancer survivors. CNS, metabolic, mental, cardiovascular, endocrine, musculoskeletal, thyroid, cardiometabolic, and respiratory clusters were the most commonly reported concordant patterns of clustering of multimorbidity in cancer survivors.

We found a large variation and a higher prevalence of multimorbidity among the population of cancer survivors. Other reviews have reported similar variation in the prevalence of multimorbidity but only focused on the general population in low- and middle-income countries (Asogwa et al., 2022; Kaluvu et al., 2022; Abebe et al., 2020) and high-income countries (Violan et al., 2014; Marengoni et al., 2011). These variations could be explained by the heterogeneity in sample size, study setting, time since cancer diagnosis, age at cancer diagnosis, type and number of chronic diseases reported as well as the sources of information on CDs (self-reports). For example, in some studies, participants reported only four chronic diseases, (Hawkins et al., 2017) whereas in others, participants reported up to 24 chronic diseases (Jansana et al., 2021a). The number and type of CDs included in the definition of multimorbidity are extremely important in estimating the prevalence of multimorbidity prevalence (Fortin et al., 2012).

Although many cancer survivors bear a huge burden of physical and mental CDs, studies on the determinants of multimorbidity in this population are limited. In this review, only three studies assessed the determinants of multimorbidity, with each risk factor being assessed only once in all three studies. For instance, the study by Armenian et al. was the only study that assessed multimorbidity after BMT (Armenian et al., 2010). Both autologous and allogeneic BMT survivors were at increased risk of multimorbidity, highlighting the need for regular monitoring of BMT survivors as well as a comprehensive improvement in the prophylaxis and management of GVHD in the risk population.

One study conducted among individuals 65 years old or older in the United States showed that female cancer survivors have a lower risk of CVD multimorbidity clusters as well as MDDr+GI+ pulmonary multimorbidity clusters (Kenzik et al., 2016). Gender disparity attributed to genetic, molecular, and sex hormones may explain the gender difference in the prevalence of multimorbidity. For example, sex has been linked to a wide range of health outcomes, including the efficacy and toxicity of cancer therapies (Kim et al., 2018). It has been reported that women undergo less aggressive medical therapy for advanced diseases than men, and men have higher overall cancer incidence rates compared to women (Siegel et al., 2022; Harichand-Herdt et al., 2009).

Consistent with previous research conducted in the general population, older age and lower socioeconomic status were associated with an increased prevalence of multimorbidity. Older age is an established risk factor for many chronic diseases, as it is associated with a variety of cellular and molecular malfunctions (World Health Organization, 2015). The association between age and multimorbidity is well established in studies conducted in the general population. Importantly, this review supports the previous finding that one additional year constitutes an additional risk of developing one or more chronic conditions (Asogwa et al., 2022; Kaluvu et al., 2022; Abebe et al., 2020; Violan et al., 2014; Fortin et al., 2012).

One study investigated the association between physical activity and

Table 3
Risk Factors for Multimorbidity.

Author & year	Outcome	Exposure factor (Normative category vs. Reference Category)	OR/RR
Armenian et al. (2010)	Multimorbidity (≥ 2 conditions)	BMTSS vs. Sibling	RR: 5.7 (4.9,6.7)
	Multimorbidity (≥ 2 conditions)	Autologous BMTSS vs. Sibling	RR: 4.7 (3.2,6.8)
	Multimorbidity (≥ 2 conditions)	Allogeneic related BMTSS vs. Sibling	RR: 5.7 (4.8,8.9)
	Multimorbidity (≥ 2 conditions)	Allogeneic unrelated BMTSS vs. Sibling	RR: 8.9 (5.9,13.4)
	Multimorbidity (≥ 2 conditions)	BMTS vs. CT_CCS	RR: 2.6 (1.7,3.8)
	Multimorbidity (≥ 2 conditions)	Autologous BMTS vs. CT_CCS	RR: 1.8 (1.1,2.8)
	Multimorbidity (≥ 2 conditions)	Allogeneic related BMTS vs. CT_CCS	RR: 2.8 (2.1,3.7)
	Multimorbidity (≥ 2 conditions)	Allogeneic unrelated BMTS vs. CT_CCS	RR: 3.4 (2.1,5.6)
	Multimorbidity (≥ 2 conditions)	Conditioning with TBI BMTS vs. CT_CCS	RR: 2.4 (1.2,4.8)
	Multimorbidity (≥ 2 conditions)	Active chronic GVHD BMTS vs. CT_CCS	RR: 3.5 (2.4,5.1)
	Multimorbidity (≥ 2 conditions)	Resolved chronic GVHD BMTS vs. CT_CCS	RR: 3.5 (2.5,5.0)
Kenzik et al. (2016)	Metabolic multimorbidity cluster	Age at post-cancer survey	RR: 1.03 (1.02,1.05)
	CVD multimorbidity cluster	Age at post-cancer survey	RR: 1.07 (1.05,1.09)
	MDDr+GI+ Pulmonary multimorbidity cluster	Age at post-cancer survey	RR: 1.02 (1.01,1.04)
	Metabolic multimorbidity cluster	Sex (Female vs. male)	RR: 0.92 (0.73,1.18)
	CVD multimorbidity cluster	Sex (Female vs. male)	RR: 0.63 (0.47,0.85)
	MDDr+GI+ Pulmonary multimorbidity cluster	Sex (Female vs. male)	RR: 0.48 (0.39,0.59)
	Metabolic multimorbidity cluster	Race/ethnicity minority vs. White	RR: 1.61 (1.28,2.02)
	CVD multimorbidity cluster	Race/ethnicity minority vs. White	RR: 0.78 (0.57,1.07)
	MDDr+GI+ Pulmonary multimorbidity cluster	Race/ethnicity minority vs. White	RR: 0.57 (0.45,0.71)
	Metabolic multimorbidity cluster	Education high school vs. Collage	RR: 1.31 (1.03,1.66)
	CVD multimorbidity cluster	Education high school vs. Collage	RR: 1.37 (1.04,1.81)
	MDDr+GI+ Pulmonary multimorbidity cluster	Education high school vs. Collage	RR: 1.50 (1.24,1.81)
	Metabolic multimorbidity cluster	Poverty level: > 5% below poverty vs. 0% - < 5%below poverty	RR: 1.12 (0.87,1.44)
	CVD multimorbidity cluster	Poverty level: > 5% below poverty vs. 0% - < 5%below poverty	RR: 1.45 (1.05,1.99)
	MDDr+GI+ Pulmonary multimorbidity cluster	Poverty level: > 5% below poverty vs. 0% - < 5%below poverty	RR: 1.27 (1.03,1.57)
	Metabolic multimorbidity cluster	Stage: Localized vs. In situ	RR: 0.88 (0.60,1.27)
	CVD multimorbidity cluster	Stage: Localized vs. In situ	RR: 0.86 (0.55, 1.34)
	MDDr+GI+ Pulmonary multimorbidity cluster	Stage: Localized vs. In situ	RR: 0.99 (0.72,1.36)
	Metabolic multimorbidity cluster	Stage: Regional vs. In situ	RR: 1.05 (0.70,1.57)
	CVD multimorbidity cluster	Stage: Regional vs. In situ	RR: 0.94 (0.58,1.52)
	MDDr+GI+ Pulmonary multimorbidity cluster	Stage: Regional vs. In situ	RR: 0.99 (0.70,1.39)
	Metabolic multimorbidity cluster	Stage: Distant vs. In situ	RR: 1.12 (0.68,1.85)
	CVD multimorbidity cluster	Stage: Distant vs. In situ	RR: 1.04 (0.57,1.89)
	MDDr+GI+ Pulmonary multimorbidity cluster	Stage: Distant vs. In situ	RR: 0.89 (0.57,1.39)
	Metabolic multimorbidity cluster	Unknown vs. In situ	RR: 1.02 (0.49,2.12)
	CVD multimorbidity cluster	Unknown vs. In situ	RR: 0.82 (0.35,1.95)
	MDDr+GI+ Pulmonary multimorbidity cluster	Unknown vs. In situ	RR: 0.82 (0.44,1.53)
	Metabolic multimorbidity cluster	Radiation yes vs. No	RR: 1.29 (1.01,1.64)
	CVD multimorbidity cluster	Radiation yes vs. No	RR: 1.03 (0.75,1.42)
	MDDr+GI+ Pulmonary multimorbidity cluster	Radiation yes vs. No	RR: 0.77 (0.62,0.96)
	Metabolic multimorbidity cluster	Unknown vs. No radiation	RR: 1.51 (0.78, 2.93)
	CVD multimorbidity cluster	Unknown vs. No radiation	RR: 1.08 (0.45,2.61)
	MDDr+GI+ Pulmonary multimorbidity cluster	Unknown vs. No radiation	RR: 0.66 (0.34,1.28)
	Metabolic multimorbidity cluster	Surgery yes vs. No	RR: 1.34 (0.99,1.81)
	CVD multimorbidity cluster	Surgery yes vs. No	RR: 1.26 (0.88,1.82)
	MDDr+GI+ Pulmonary multimorbidity cluster	Surgery yes vs. No	RR: 1.09 (0.86,1.40)
	Metabolic multimorbidity cluster	Unknown vs. No surgery	RR: 1.12 (0.69,1.82)
	CVD multimorbidity cluster	Unknown vs. No surgery	RR: 1.23 (0.72,2.10)
	MDDr+GI+ Pulmonary multimorbidity cluster	Unknown vs. No surgery	RR: 1.00 (0.70,1.43)
Bluethmann et al. (2020)	Multimorbidity (≥ 2 conditions yes vs no)	MVPA (MET-hours/week) 0.7–7.49 vs. 0	OR: 2.31 (0.78,6.82)
		MVPA (MET-hours/week): 7.5–14.9 vs. 0	OR: 0.64 (0.27,1.51)
		MVPA (MET-hours/week): 15.22.49 vs. 0	OR: 0.57 (0.18,1.86)
		MVPA (MET-hours/week): 22.5 + vs. 0	OR: 0.62 (0.28,1.38)
		TV (hours/day) 0 vs + 5	OR: 0.22 (0.07,0.65)
		TV (hours/day) 1–2 vs+ 5	OR: 0.17 (0.06,0.45)
		TV (hours/day) 2–3 vs + 5	OR: 0.37 (0.14,1.02)
		TV (hours/day) 3–4 vs + 5	OR: 0.55 (0.21,1.45)
		Estimated Fitness Q2 vs. Q1	OR: 0.4 (0.10,1.56)
		Estimated Fitness Q3 vs. Q1	OR: 0.18 (0.06,0.56)
		Estimated Fitness Q4 vs. Q1	OR: 0.09 (0.03,0.29)

(continued on next page)

Table 3 (*continued*)

Author & year	Outcome	Exposure factor (Normative category vs. Reference Category)	OR/RR
		Estimated Fitness Q5 vs. Q1	OR: 0.09 (0.03,0.34)
		Grip Strength Q2 vs. Q1	OR: 0.60 (0.16,2.22)
		Grip Strength Q3 vs. Q1	OR: 0.27 (0.07,1.02)
		Grip Strength Q4 vs. Q1	OR: 0.19 (0.07,0.54)
		Grip Strength Q5 vs. Q1	OR: 0.11 (0.03,0.34)
		Higher vs. lower behavior scores	OR: 0.79 (0.68,0.91)
		Higher vs. lower performance scores (grip strength and fitness)	OR: 0.76 (95% CI not reported)
		Higher vs. lower physical activity index scores	OR: 0.8 (95% CI not reported)

Abbreviation: RR (Relative risk), OR (Odd ratio), Moderate-to-vigorous intensity physical activity (MVPA), Metabolic equivalent task (MET), Television (TV), Quintiles (Q1 to Q5), cardiovascular disease (CVD), Major Depressive Disorder risk (MDDr), Gastrointestinal (GI), Bone Marrow Transplant Survivor (BMTS), Conventionally treated Childhood Cancer Survivor (CT_CCS), Confidence interval (CI).

multimorbidity among the noninstitutionalized civilian US population (Bluethmann et al., 2021). Higher physical activity and less screen time were inversely associated with multimorbidity. Physical activity after cancer treatment has been shown to be beneficial during cancer survivorship care. The American College of Sports Medicine's guidelines suggest that exercise is crucial for survivors and can be a therapeutic intervention for some morbidities (Anone.). However, 75% of survivors found it challenging to adhere to the key components of the physical activity recommendation, largely due to barriers such as low motivation, fatigue, pain, difficulty remaining disciplined, and financial ability (Prasad et al., 2014; Romero SAD et al., 2019; Blanco et al., 2012). To optimize physical activity uptake in order to reduce multimorbidity, guidelines that take into account the interests and preferences of survivors should be developed.

This review found different patterns of clustering among chronic conditions. Patterns of clustering were both concordant and discordant. This included within disease clusters (clustering within respiratory, CNS, endocrine, mental, CVD, musculoskeletal, metabolic, and thyroid diseases) and between disease clusters (different combinations of chronic diseases, including clustering of mental disorders with either MSK, endocrine, CNS, GI, pulmonary, respiratory, or cardiometabolic conditions; clustering of MSK disorders with cardiovascular diseases; and clustering of CNS disorders with endocrine disorders). Cardiometabolic clustering is a long-reported pattern in the general population, and it can be interpreted as a concordant pattern of clustering due to shared risk factors and pathophysiological pathways (Asogwa et al., 2022; Abebe et al., 2020; Violan et al., 2014). Also, in agreement with studies conducted in the general population, mental disorders were reported to cluster with conditions such as cardiometabolic, respiratory, and MSK conditions (Asogwa et al., 2022). To our knowledge, clustering of mental disorders with endocrine, CNS, GI and pulmonary disorders is a pattern that is not commonly reported in the general population (Asogwa et al., 2022; Violan et al., 2014). Concordant and discordant clustering of diseases underscores the need for preventive strategies and a multidisciplinary approach in the management of multimorbidity, especially in this high-risk population.

4.1. Implication and recommendations

This review identified vulnerable groups of cancer survivors for surveillance and management of multimorbidity. Findings from this study can inform recommendations in survivorship care guidelines and support the development of high-quality follow-up care that addresses multiple chronic conditions in cancer survivors. Evidence-based Guidelines for Follow-Up of Survivors of Childhood Cancer 5 years after diagnosis, recommended risk-based, systematic, and consistent long-term follow-up but did not consider multimorbidity (Children's Oncology Group, 2018; Late Effects of Childhood Cancer task force of Dutch Childhood Oncology group, 2010). Our review indicated a high prevalence of multimorbidity among early survivors that transitioned from active cancer care into survivorship care clinics (Abdelhadi et al., 2022; Ashing et al., 2014; Petrova et al., 2021; Foster and Niedzwiedz, 2021; Austin et al., 2019) and long-term childhood and adult cancer survivors (Jansana et al., 2021a; Harrington et al., 2019; Demers et al., 2021; Harrington et al., 2020; Cohen et al., 2012; Petrova et al., 2021). This indicated a need for multimorbidity-based complex care for this population.

Survivors had both concordant and discordant clusters of multimorbidity, based on five papers included in this study. Thus, understanding disease clustering could be crucial in identifying those survivors with a single condition at increased risk of developing other CDs. Disease clustering supports multidisciplinary collaboration, which is incorporated into the survivorship guidelines to manage the care needs of the survivors (Late Effects of Childhood Cancer task force of Dutch Childhood Oncology group, 2010). In addition, our findings support current survivorship guidelines and highlight the importance of educating survivors on the long-term risk of CDs and the need to participate in a survivorship care program for long-term health monitoring (Late Effects of Childhood Cancer task force of Dutch Childhood Oncology group, 2010).

The association of BMT with multimorbidity seen in one study underscores the need for BMT survivors to receive long-term follow-up care that includes frequent screening, monitoring, and surveillance. Furthermore, considering the fact that lower physical activity is associated with multimorbidity, it may be necessary to deploy lifestyle-changing interventions to improve survivors' lives.

Finally, most of the included studies were cross-sectional surveys, and only a few of the studies assessed determinants and patterns of clusters of multimorbidity among cancer survivors, with each risk factor being assessed only once in the studies. The paucity of research focusing on multimorbidity in cancer survivors may have an effect on the design of interventions for survivors with multimorbidity. It might create a barrier to achieving comprehensive and coordinated risk-based health care for the management of multimorbidity in early- and long-term cancer survivors. Above all, the validation of determinants and patterns of clusters of multimorbidity in many cancer survivors is required. This should incorporate the use of longitudinal and interventional study designs in the evaluation of determinants of multimorbidity, putative causal pathways, and patterns of clustering of diseases over time.

4.2. Strengths and limitations of this review

To our knowledge, this is the first systematic review evaluating the prevalence, patterns, and determinants of multimorbidity in childhood and adult cancer survivors. This review employed a comprehensive search strategy to identify all the eligible studies, minimizing the risk of missing potentially relevant studies. Moreover, by not imposing restrictions on language or a year of publication, it is unlikely that selection bias would be an issue. Limitations to this review include the following: Firstly, the included articles employed a cross-sectional design, and hence it is not possible to infer any causal relationship for the identified associated factors of multimorbidity. Secondly, in all the included studies, there was no uniform identification and assessment of

Table 4
Patterns of multimorbidity.

Author and year	Analysis #	Patterns of Clustering	Definition of Each Cluster: Individual Chronic Diseases	Type of Clustering	Prevalence (%)
Harrington et al. (2020)	Latent class analysis	Respiratory	Allergic rhinitis and asthma	Concordant	35.4%
Harrington et al. (2020)	Latent class analysis	CNS	Brain and neuropathies, hereditary CNS conditions (including hydrocephalus), paralysis and epilepsy	Concordant	22.4%
Harrington et al. (2020)	Latent class analysis	Mental health	Mood disorders, attention deficit hyperactivity disorder, anxiety disorders, and adjustment disorders	Concordant	22.2%
Harrington et al. (2020)	Latent class analysis	Endocrine	Non-thyroid endocrine disorders and thyroid disorders	Concordant	16.2%
Harrington et al. (2020)	Latent class analysis	CNS with endocrine group	Brain conditions, neuropathies, hydrocephalus, other hereditary CNS conditions, vision loss, non-thyroid endocrine disorders, other eye disorders and mood disorders	Concordant /Discordant*	3.8%.
Harrington et al. (2020)	Latent class analysis	CNS with mental	CNS with mental	Concordant /Discordant*	34.7%
Harrington et al. (2020)	Latent class analysis	Mental with endocrine	Mental with endocrine	Concordant /Discordant*	19.8%
Harrington et al. (2020)	Latent class analysis	CNS with endocrine group and mental	CNS with endocrine group and mental	Concordant /Discordant*	80.4%
Harrington et al. (2020)	Latent class analysis	Mental with Respiratory	Mental with General Pediatric Morbidity	Concordant /Discordant*	20.7%
Kenzik et al. (2016)	Exploratory factor analysis	CVD	MI, angina, CHF, other heart conditions, and stroke	Concordant	7.7%
Kenzik et al. (2016)	Exploratory factor analysis	Musculoskeletal	Hip/knee, arthritis of hand/wrist, and sciatica	Concordant	29
Kenzik et al. (2016)	Exploratory factor analysis	Metabolic	Diabetes and HBP	Concordant	17.6%
Kenzik et al. (2016)	Exploratory factor analysis	Mental pulmonary with GI	MDDr, pulmonary, and GI conditions	Concordant /Discordant*	8.7%
Ekenga C et al. (2022)	Latent class analysis	Mental pulmonary with cardiometabolic	High blood pressure, diabetes, lung disease, cardiovascular disease (heart disease or stroke), psychiatric disorders, and arthritis.	Concordant /Discordant*	21%
Ekenga C et al. (2022)	Latent class analysis	Cardiometabolic with mental	High blood pressure, diabetes, cardiovascular disease (heart disease or stroke), psychiatric disorders, and arthritis.	Concordant /Discordant*	68%
Ekenga C et al. (2022)	Latent class analysis	Cardiometabolic	High blood pressure, diabetes, cardiovascular disease (heart disease or stroke), and arthritis.	Concordant	11%
Hawkins et al. (2017)	Descriptive method	Mental health condition	Depression and anxiety	Concordant	59%
Jansana et al. (2021)	Hierarchical cluster analysis	Miscellaneous	Observed prevalence of the CCS-CD within each cluster: Mood disorders, Asthma, Blindness and vision defects, Miscellaneous	Concordant /Discordant*	29.9%
Jansana et al. (2021)	Hierarchical cluster analysis	Miscellaneous	Hypertension, diabetes mellitus without complication, cataracts, overweight and other types of overfeeding, cardiac dysrhythmias, glaucoma, other ear and sense organ disorders, dementia and other neurodegenerative conditions	Concordant /Discordant*	28.3%
Jansana et al. (2021)	Hierarchical cluster analysis	Mentalmusculoskeletal	Anxiety disorders and pathological fracture	Concordant	9.7%
Jansana et al. (2021)	Hierarchical cluster analysis	Musculoskeletal (MSK) and cardiovascular	Disorders of lipid metabolism, cataract, spondylosis, intervertebral disc disorders, other back problems, osteoarthritis, mood disorders, cardiac dysrhythmias, osteoporosis, other inflammatory condition of skin	Concordant /Discordant*	9.6%
Jansana et al. (2021)	Hierarchical cluster analysis	Thyroid disorders	Thyroid disorders	Concordant	5.3%

Abbreviations: Central nervous system (CNS), cardiovascular diseases (CVD), clinical classification software-chronic diseases (CCS-CD), congestive heart failure (CHF), major depressive disorder risk (MDDr), gastrointestinal (GI), myocardial infarction (MI), high blood pressure (HBP).
* Late effect conditions that are concordant in their aetiology and risk factor, may be discordant in their pathophysiological pathway and management.
 # cluster analyses: Hierarchical cluster analysis is a statistical method aimed at classifying heterogeneous populations into homogeneous groups based on available features, reducing the number of observations or cases by consolidating them into a smaller set of clusters. The descriptive method describes and group individuals with the same type and number of chronic conditions. Latent class analysis is a model-based clustering method that can identify underlying subgroups within a population by examining a set of observed indicator variables in the data. The individuals within a group were similar to one another and different from individuals in other groups. Exploratory factor analysis is a technique within factor analysis whose overarching goal is to identify the underlying relationships between measured variables.

chronic health conditions. Most of the included studies used self-reported outcomes, while a few used ICD-9, ICD-10, and ICPC-2 diagnosis codes. Self-reported outcomes may be subject to recall bias, leading to under- or overreporting of disease conditions, although some evidence suggests a high level of agreement between information from self-reports and that of health records (Louie et al., 2000). In addition, the number of chronic health conditions varied from four to 24. The number and type of CDs included in the definition of multimorbidity are relevant in estimating its prevalence. The lack of consensus on the identification and assessment of chronic health conditions and the definition and classification of multimorbidity have given rise to huge variations in prevalence estimates. As suggested by the Academy of Medical Science (AMS), a uniform definition, identification, assessment, and reporting system for multimorbidity is needed for improved understanding of its burden and epidemiology in cancer survivors (The Academy of Medical Sciences, 2018). Thirdly, due to the few studies included and the heterogeneity of the included studies (e.g., survey period, multimorbidity source, cancer type, years since cancer diagnosis, and age at diagnosis), meta-analysis of the results was not feasible. Only a few studies examined the determinants of multimorbidity in cancer survivors; hence, we could not address this in sufficient depth, and caution should be employed in interpreting the results.

5. Conclusion

This review demonstrated that multimorbidity is highly prevalent among cancer survivors, has different patterns, and is associated with several patient, lifestyle, and treatment-related factors. Only a few of the studies assessed the determinants and patterns of clusters of multimorbidity among cancer survivors, with each risk factor being assessed only once in the studies. Hence, large, rigorous cohort studies are required to comprehensively examine the risk factors of multimorbidity for improved risk stratification of cancer survivors. However, a more personalized care plan that takes into account the identified risk may be beneficial to reduce the burden of multimorbidity and improve quality of life among this special population with complex needs.

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CRediT authorship contribution statement

Ogechukwu A. Asogwa, Daniel Boateng: Study concepts and design. **Ogechukwu A. Asogwa, Dan Yedu Quansah**: Literature research, Data extraction. **Ogechukwu A. Asogwa, Daniel Boateng, Dan Yedu Quansah**: Review of data extraction, Risk of bias assessment. **Ogechukwu A. Asogwa, Daniel Boateng, Dan Yedu Quansah, Daniel Boakye, Obiageli Ntukogu Ezewuiro**: Methodology, Interpretation of result, Critically review of the manuscript. **Ogechukwu A. Asogwa**: Narrative synthesis and draft of the manuscript, Overall content as guarantor. **Daniel Boateng**: Supervision.

Declaration of Competing Interest

The authors declare no competing interests with respect to this research. However, Daniel Boakye is an employee of Philip Morris Global Studio Limited, UK.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.104147.

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