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Systematic Review

Outcomes in studies regarding older patients with prostate cancer: A systematic review

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ABSTRACT

Introduction: Older patients are often deemed ineligible for clinical research, and many frequently-used endpoints and outcome measures are not as relevant for older patients for younger ones. This systematic review aimed to present an overview of outcomes used in clinical research regarding patients over the age of 65 years with prostate cancer.

Materials and Methods: PubMed and Embase were systematically searched to identify studies on prostate cancer (treatment) in patients aged ≥65 between 2016 and 2023. Data on title, study design, number of participants and age, stage of disease, treatment, and investigated outcomes were synthesized and descriptively analyzed.

Results: Sixty-eight studies were included. Of these most included patients over 65 years, while others used a higher age. Overall, 39 articles (57.3%) reported on survival-related outcomes, 22 (32.4%) reported on progression of disease and 38 (55.9%) used toxicity or adverse events as an outcome measure. Health-related quality of life and functional outcomes were investigated in 29.4%, and cognition in two studies. The most frequently investigated survival-related outcomes were overall and cancer-specific survival (51.3%); however, 38.5% only studied overall survival.

Discussion: The main focus of studies included in this review remains survival and disease progression. There is limited attention for health-related quality of life and functional status, although older patients often prioritize the latter. Future research should incorporate outcome measures tailored to the aged population to improve care for older patients with prostate cancer.

1. Introduction

Prostate cancer is the most commonly diagnosed malignancy, and one of the leading causes of cancer death in men worldwide [1,2]. In 2020, over 1.4 million new diagnosed cases and 375,000 deaths due to prostate cancer were reported globally [2,3]. The median age at diagnosis is 66 years, and >80% of men will have developed prostate cancer by the age of 80 years [1]. Prostate cancer is a slowly progressing disease, often lacking initial or early symptoms when localised. In more advanced stages, lower urinary tract symptoms (LUTS) can occur as a result of prostatic hypertrophy. In older adults, a variety of voiding difficulties can occur from benign prostatic obstruction and, possibly, prostate cancer. Late symptoms of prostate cancer may also include fatigue, loss of muscle strength, and bone pain due to metastatic disease [1,2,4]. There are many different treatment modalities for prostate cancer, including active surveillance or watchful waiting, surgery, radiotherapy (either external beam or brachytherapy), systemic therapies, and palliative care. However, the treatment of choice depends on several factors, including individual life expectancy, cancer stage, and grade [1,5,6].

Due to an increased life expectancy and the high incidence in older age, the number of prostate cancer diagnoses has steadily increased over the last decades, making it a highly prevalent disease among older men [2,7,8]. Fortunately, due to its often indolent course [1,7], there is a

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relatively low risk of dying from localised and regional prostate cancer. However, for older patients diagnosed with intermediate or high-risk prostate cancer, there is a tight balance between the risk of dying due to the disease aggressivity or competing mortality from other diseases [7,9,10]. Older patients with metastatic disease nevertheless experience a substantially higher prostate cancer-related mortality. As adequate management of disease and cancer-related symptoms is often required, frail patients might have a high burden of toxicity and adverse events attributable to prostate cancer treatment.

Despite prostate cancer being a disease of older adults, there is limited focus on developing optimal treatment strategies for this specific patient group. Older patients are often deemed ineligible for clinical research. As a result, only the European Association of Urology (EAU) and International Society of Geriatric Oncology (SIOG) provide specific treatment recommendations for older adults with prostate cancer, which has probably led to suboptimal treatment receipt [7,11]. Furthermore, endpoints and outcome measures frequently used in studies are often not as relevant for older patients as they would be for a younger population [12]. One of the few focus-group studies among older persons have shown that patient-related endpoints, such as functional status and health-related quality of life [13], may be more valuable to assess than overall survival (OS) in older persons. Despite this, OS and tumor-related outcomes remain the primary focus in cancer trials and studies [11,14]. We hypothesize that studies which specifically include older patients will contain patient-related outcomes, whether or not combined with tumor-related outcomes. The objective of this systematic review was to present an overview of outcomes used in published clinical research (both observational data and randomized trials) specifically for older patients with prostate cancer, to assess whether certain outcomes are underrepresented in contemporary research.

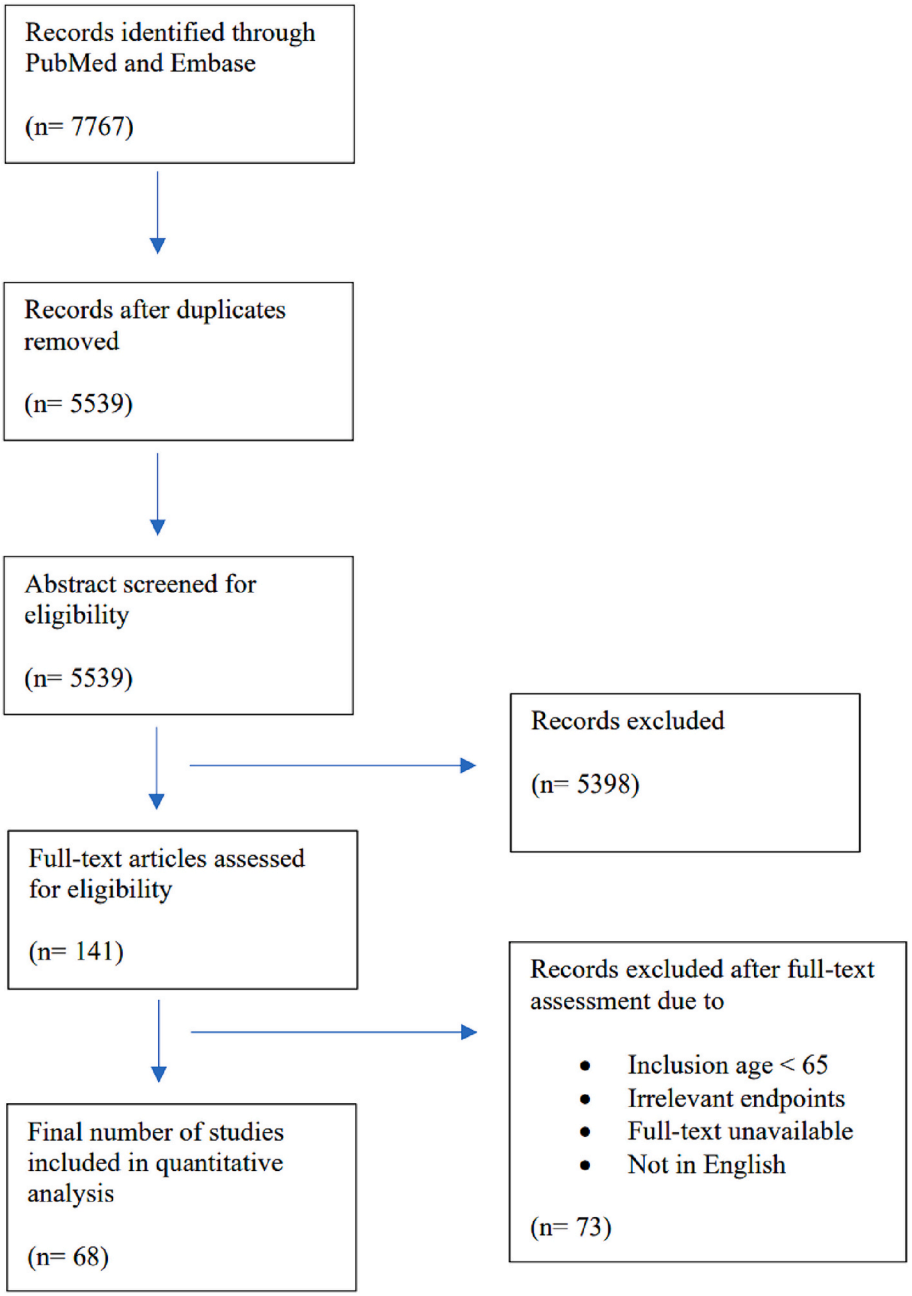

Fig. 1. Flowchart and search details.

2. Methods

2.1. Search Strategy and Article Selection

The search strategy was based on the key words "prostate cancer" and "older patients"; a medical librarian assisted with the search strategy. We searched the available literature in PubMed and Embase from January 2016 up to January 2024. In 2013 the position paper of Wildiers et al. [12] discussing specific clinical end points and their advantages and disadvantages for older individuals was published. The paper stated that patient-related endpoints such as functional status, cognitive function, and quality of life are considered equally or even more important than standard endpoints such as survival and recurrence. We estimated that it would take at least three years for the results to be implemented in clinical studies, and thereby choose the year 2016 as the starting point for our search. Details of the search and a flowchart of the selection of studies are presented in Fig. 1. The protocol for this systematic review was prespecified, but not registered online, and reporting follows the PRISMA guidelines [97]. Two reviewers (KJ, EB) independently selected articles that met the inclusion criteria based on titles and abstracts. Agreement about eligibility was achieved during consensus meetings. Subsequently, the full texts of potentially relevant articles were screened. Articles were selected if they were (1) cohort studies or randomized clinical trials (2) on prostate cancer (3) published between 2016 and January 2024, with (4) a patient population aged exclusively 65 years or older. We had initially planned to include studies on patients over the age of 70 years. However, after the first search only a few such studies were found. A large proportion of the studies defined "older" as higher than 65 years. Therefore, we decided to include studies regarding patients of 65 years and older. Studies that compared younger and older patients or included all age categories were excluded, as were economic and psycho-social studies, case reports, and meta-analyses and systematic reviews.

2.2. Data Extraction & Analysis

The year of publication, study design (prospective/ retrospective cohort, randomized controlled trial [RCT] or phase 1/2 trial), number of patients and age of the study population, stage of disease, treatment, and investigated outcomes were extracted from the selected articles. Studies that reported in more than one paper from the same cohort were all included as they might report different outcome measures; when full-text assessment showed that the same outcomes were reported, we included the paper that was published first. Ambiguities in data extraction and interpretation were resolved in consensus meetings between the two authors.

Disease stage in the included studies was defined as localised disease in case of either stage I or IIa/b. Locally advanced disease was defined as stage IIc and III and stage IV as metastatic prostate cancer [1]. Treatment modalities in the included articles were surgery, cryotherapy, chemotherapy, radiotherapy, targeted therapy (lutetium-177-prostate-specific membrane antigen radionuclide), ablation therapy, hormonal therapy, exercise-intervention programs, and conservative management (active surveillance or watchful waiting, or a combination thereof).

The investigated outcomes were divided into five categories: (1) survival or mortality (as mentioned in the articles), (2) progression of disease, (3) toxicity/adverse events (AE)/hospital admissions, (4) health-related quality of life/functional/geriatric outcomes, and (5) other. Whether the outcome measure was recorded as primary, secondary, or other endpoint was also recorded. If the study only reported on one outcome measure, it was recorded as the primary outcome; if the study did not report or they were all mentioned without separation, then they were all recorded as the primary outcome. An additional analysis was performed for the articles reporting on survival or mortality, further dividing this category into OS versus prostate cancer-specific survival. Lastly, an overview of the health-related quality of life, functional, and geriatric outcome measures, including the measurement tools/instruments, was constructed.

The included articles were stratified according to the age of the study population. For reporting, four subgroups were used based on the inclusion criteria of the different included studies: 65+ or 66+ or 67+ or 68+ (combined in one group), 70+, 75+, and 80 years and over. The investigated outcomes are presented by subgroup, in order to adequately compare usage of outcome measures for the different populations.

3. Results

The literature search in PubMed and Embase yielded a total of 5539 unique records. All titles and abstracts were screened for eligibility, followed by full-text assessment of the 141 remaining titles. After careful consideration, 68 studies [15–82] were included in this review (Fig. 1). Characteristics of the included studies are presented in Table 1.

Most studies were cohort studies. One RCT, one randomized pilot study, and one phase 1/2 trial were included; all study designs were combined in describing the outcome measures used in the included studies. Age range or interquartile range (IQR) are reported in Table 1. Studies often only mentioned a minimum age and no upper age limit. A total of 41 studies (60.3%) included patients aged 65, 66, 67, or 68 years and over. Thirteen studies (19.1%) reported on patients with a minimum age of 70, eight articles (11.8%) specifically included patients aged ≥75, and the remaining six studies (8.8%) restricted their inclusion to age 80 years and older. Overall, 43 studies (63.2%) were on localised or locally advanced (as defined in the articles) prostate cancer, eighteen (26.5%) were on metastatic disease, and seven studies (10.3%) included all stages of prostate cancer.

3.1. Outcome Measures

The investigated outcome measures reported per study can be found in Table 2. Most studies used multiple outcome measures. Overall, 39 articles (57.3%) reported on survival-related outcomes, 22 (32.4%) reported on progression of disease (as defined in the articles), and 38 studies (55.9%) used toxicity and/or adverse events as an outcome measure. Health-related quality of life and functional outcomes were investigated in 20 studies (29.4%); the tools that were used are mentioned in Table 3. Ten articles (14.7%) reported on other outcome measures that did not fit into the previous categories. These included adherence, costs, pharmacokinetic evaluation, implementation of treatment, and a diagnosis of high-risk prostate cancer.

The investigated outcomes were stratified according to age group (Fig. 2). Of the 41 articles on patients aged ≥65, 22 (53.7%) reported on survival, eight studies (19.5%) used progression of disease, and 26 articles (63.4%) used toxicity and/or adverse events as an outcome. Eleven studies (26.8%) incorporated quality of life or functional outcomes. Five studies (12.2%) also used other outcome measures: costs, implementation of treatment, and pharmacokinetic evaluation. Of the thirteen studies on patients aged ≥70, seven (53.8%) used a survival outcome, six studies (46.2%) monitored progression of disease, six (46.2%) investigated toxicity and/or adverse events, and four (30.8%) reported on quality of life and/or functional outcomes. Four articles (30.8%) included other outcome measures: adherence and implementation of treatment. Eight studies included patients aged ≥75. Four of these (50%) used survival outcomes, four (50%) investigated progression of disease, four (50%) looked into toxicity and/or adverse events, and four (50%) used health-related quality of and/or functional outcomes. One article (12.5%) used another outcome measure, namely diagnosis of high-risk prostate cancer. Lastly, there were six articles on patients aged ≥80. All six of them (100%) used survival-related outcomes, four (66.7%) reported on progression of disease, two (33.3%) investigated toxicity and/or adverse events, and one (16.7%) used a functional outcome (pain control). No 'other' outcome measures were investigated in this age category.

Table 1
Characteristics of the included studies.

Publication			Study setting and population				
Author	Year	Country	Setting	N	Age	Stage	Treatment
Alibhai [15]	2021	Canada	Prospective cohort, multicenter	155	≥ 65 (65–90)	Metastatic	Chemotherapy, radiotherapy, hormonal therapy
Alibhai [16]	2021	Canada	Prospective cohort, multicenter	71	≥ 65 (65–90)	Metastatic	Chemotherapy, hormonal therapy
Baik [17]	2017	United States	Retrospective cohort, registry	1,238,879	≥ 67	All stages	Hormonal therapy
Capogrosso [18]	2018	Italy	Prospective cohort, single-centre	252	≥ 70 (IQR: 72–76)	Localised	Surgery, whole-gland ablation therapy
Couderc [19]	2020	France	Prospective cohort, single-center	31	≥ 70 (70–88)	Localised or locally advanced	Hormonal therapy, radiotherapy
Couderc [20]	2021	France	Retrospective cohort, single-center	101	≥ 80 (IQR: 80–94)	Localised, locally advanced	Hormonal therapy, radiotherapy
Cuccia [21]	2020	Italy	Retrospective cohort, single-center	95	≥ 75 (75–88)	Localised, locally advanced	Radiotherapy
Cuccia [22]	2020	Italy	Retrospective cohort, single-center	24	65–89	Localised, locally advanced	Radiotherapy
Cui [23]	2022	China	Phase I/II trial, single-center	33	≥ 65	Localised, locally advanced	Radiotherapy
Daskivich [24]	2016	United States	Retrospective cohort, registry	44,521	≥ 66	Localised	All treatments
Dell'Oglio [25]	2016	United States	Retrospective cohort, registry	23,790	≥ 80 (IQR: 81–86)	Localised	Radiotherapy, hormonal therapy, conservative management
Della Pepa [26]	2017	Italy	Prospective cohort, multicenter	24	≥ 70 (70–87)	Metastatic	Chemotherapy
Droz [27]	2016	Multiple	Prospective cohort, registry	333	68–93	Locally advanced, metastatic	Chemotherapy, hormonal therapy
Fisher-Valuck [28]	2022	United States	Retrospective cohort, registry	19,920	≥ 80	Localised, locally advanced	All treatments
Gild [29]	2018	United States	Retrospective cohort, registry	82,938	≥ 66 (IQR: 68.8–70.0)	Localised	Hormonal therapy
Goineau [30]	2020	France	Prospective cohort, multicenter	208	≥ 75 (75–89)	Localised	Radiotherapy
Honecker [31]	2018	Germany	Prospective cohort, multicenter	98	≥ 70	All stages	Chemotherapy, hormonal therapy, radiotherapy
Hu [32]	2017	United States	Retrospective cohort, registry	15,591	≥ 66	Localised, locally advanced	Surgery
Jacobs [33]	2017	United States	Retrospective cohort, registry	49,810	≥ 66	Localised, locally advanced	Radiotherapy
Jang [34]	2018	United States	Retrospective cohort, registry	13,856	≥ 65	Locally advanced	Surgery, radiotherapy, hormonal therapy
Jayadevappa [35]	2019	United States	Retrospective cohort, registry	6296	≥ 66	Localised, locally advanced	All treatments
Ko [36]	2021	Republic of Korea	Retrospective cohort, registry	13,952	≥ 70	Localised	Surgery, radiotherapy
Ko [37]	2021	Republic of Korea	Retrospective cohort, multicenter	1110	≥ 75	Localised	Surgery, radiotherapy
Kwon [38]	2021	United States	Retrospective cohort, registry	7557	≥ 65	Localised	Surgery, radiotherapy, conservative management
Leibowitz [39]	2020	Israel	Retrospective cohort, single-center	24	≥ 75 (75.1–91.9)	Metastatic	Targeted therapy
Liu [40]	2016	China	Prospective cohort, single-center	67	≥ 65 (68–87)	Localised, locally advanced	Radiotherapy
Lu-Yao [41]	2020	United States	Retrospective cohort, registry	3876	≥ 65 (IQR: 70–82)	All stages	Hormonal therapy
Manokumar [42]	2016	Canada	Prospective cohort, single-center	47	≥ 65	Metastatic	Chemotherapy, hormonal therapy
Mareschal [43]	2017	Switzerland	Prospective cohort, single-center	35	68–76	Localised, locally advanced	Hormonal therapy, radiotherapy
Mazzola [44]	2020	Italy	Prospective cohort, single-center	40	≥ 65 (65–85)	All stages	Radiotherapy
Momota [45]	2020	Japan	Prospective cohort, multicenter	540	65–82	All stages	Surgery, radiotherapy, hormonal therapy
Moschini [46]	2019	United States	Retrospective cohort, registry	84,397	≥ 66 (67–77)	Localised, locally advanced	Radiotherapy, surgery
Narita [47]	2020	Japan	Retrospective cohort, multicenter	605	66–78	Metastatic	Hormonal therapy
Nguyen [48]	2021	Luxembourg	Prospective cohort, single-center	150	≥ 70 (69–86)	Localised, locally advanced	Radiotherapy
Onishi [49]	2016	Japan	Retrospective cohort, single-center	20	68–85	Metastatic	Hormonal therapy
Osborne [50]	2017	United Kingdom	Prospective cohort, multicenter	178	≥ 70	Localised, locally advanced	Radiotherapy

(*continued on next page*)

Table 1 (*continued*)

Publication			Study setting and population				
Author	Year	Country	Setting	N	Age	Stage	Treatment
Parikh [51]	2021	United States	Clinical trial, single-center	9	66–88	Metastatic	Niclosamide, hormonal therapy
Paterson [52]	2016	United Kingdom	Prospective cohort, registry	335	≥ 70	Localised, locally advanced	Radiotherapy, hormonal therapy, surgery
Rescigno [53]	2022	Italy	Prospective cohort, multicenter	234	≥ 70 (73–82)	Metastatic	Hormonal therapy
Ryu [54]	2018	Republic of Korea	Retrospective cohort, multicenter	191	≥ 75 (75–82)	Localised	Surgery, hormonal therapy
Ryu [55]	2016	Republic of Korea	Retrospective cohort, multicenter	270	≥ 65 (65–77)	Localised, locally advanced	Surgery
Sajid [56]	2016	United States	Randomized pilot study	19	≥ 65 (67–93)	Localised, locally advanced	Hormonal therapy, exercise-intervention
Schmid [57]	2016	United States	Retrospective cohort, registry	26,482	≥ 65 (IQR: 67.7–72.8)	Localised, locally advanced	Surgery
Serrano [58]	2021	France	Prospective cohort, multicenter	402	≥ 70 (IQR: 77–85)	All stages	All treatments
Shah[59]	2018	United States	Retrospective cohort, registry	11,049	≥ 66	Localised	Conservative management, cryotherapy
Shayegan [60]	2022	Canada	Retrospective cohort, registry	602	≥ 66 (IQR: 68–76)	Metastatic	Chemotherapy
Shayegan [61]	2022	Canada	Retrospective cohort, registry	944	≥ 66 (IQR: 70–80)	Metastatic	Chemotherapy, hormonal therapy, radiotherapy
Silecchia [62]	2018	Italy	Prospective cohort, single-center	45	≥ 75 (IQR: 77–79)	Localised, locally advanced	Cryotherapy
Sivaraman [63]	2016	France, United States	Retrospective cohort, multicenter	1008	≥ 70	Localised, locally advanced	Surgery
Soleimani [64]	2021	Canada	Retrospective cohort, registry	278	≥ 80	Metastatic	Hormonal therapy
Suarez-Almazor [65]	2022	United States	Retrospective cohort, registry	54,953	≥ 66 (66–99)	Localised, locally advanced	Hormonal therapy
Sun [66]	2016	United States	Retrospective cohort, registry	3295	≥ 66 (IQR: 72–83)	Metastatic	Surgery, hormonal therapy
Tosoian [67]	2017	United States	Retrospective cohort, single-center	274	≥ 75 (75.3–80.2)	Localised, locally advanced	Radiotherapy
Traboulsi [68]	2020	Canada	Retrospective cohort, multicenter	302	≥ 65 (66–75)	Localised, locally advanced	Surgery
Tsai [69]	2017	United States	Retrospective cohort, registry	9772	≥ 66	All stages	Hormonal therapy
Tsuchiya [70]	2019	Japan	Prospective cohort, multicenter	6	70–85	Metastatic	Hormonal therapy
Tward [71]	2016	United States	Retrospective cohort, registry	2392	≥ 65	Localised, locally advanced	Radiotherapy
Ueno [72]	2018	Japan	Prospective cohort, multicenter	1220	67–76	Localised	Surgery, hormonal therapy
Vatandoust [73]	2018	Australia	Retrospective cohort, registry	1888	≥ 70 (70–89)	Localised	All treatments
Villumsen [74]	2019	Denmark	Randomized control trial	46	≥ 65	Locally advanced,	Exercise-intervention
Vinh-Hung [75]	2020	United States	Retrospective cohort, single-centre	59	≥ 75 (74.9–93.8)	Metastatic	Hormonal therapy
Wallis [76]	2016	United States	Retrospective cohort, registry	60,476	≥ 65 (65–79)	Localised	Surgery, radiotherapy
Wallis [77]	2021	Canada	Retrospective cohort, registry	3556	≥ 66	Metastatic	Hormonal therapy
Wallis [78]	2018	Canada	Retrospective cohort, registry	2439	≥ 65	Metastatic	Chemotherapy, hormonal therapy
Wang [79]	2021	China	Retrospective cohort, single-center	16	≥ 80 (80–87)	Metastatic	Chemotherapy, hormonal therapy
Williams [80]	2017	United States	Retrospective cohort, registry	29,571	≥ 65 (66–75)	Localised	Surgery, radiotherapy
Wu [81]	2022	Taiwan	Retrospective cohort, registry	659	≥ 80	Localised, locally advanced	Surgery, radiotherapy, hormonal therapy
Zhang [82]	2019	China	Retrospective cohort, single-center	104	65–85	Locally advanced, metastatic	Radiotherapy, hormonal therapy

Comparing outcomes measures by age group, we observed that survival or mortality was an outcome measure for the first age group (aged 65+, 66+, 67+, or 68+) in 54% of the studies, for the second group aged 70+ in 54% of the studies, for the third group aged 75+ in 50% of the studies, and for the fourth group aged 80+ in 100% of the studies. Progression of disease was more often an outcome measure as the age cutoff increased: 19% in studies in the youngest group, 46% for ages 70+, 50% for ages 75+ and 67% of the studies with 80+ as age cutoff. Toxicity, adverse events, or hospital admissions were studied less often as age increased: 63% in the youngest group, 46% for ages 70+, 50% for ages 75+, and only 33% for ages 80+. Finally, quality of life or functional or geriatric outcomes were studied in 27% of the youngest group, 31% for ages 70+, 50% for ages 75+, and 17% for the 80+ group.

Most of the studies in the youngest group reported survival as primary outcome, while for the group aged 70+ survival was more often mentioned as secondary outcome; for the groups aged 75+ and 80+ it

Table 2
Outcome measures used in the included studies, stratified by age group.

Age Group	Author	Outcome measures				
		Survival/ Mortality	Progression of Disease	Toxicity/ Adverse Events/ Hospital Admissions	Quality of life/ Functional/ Geriatric	Other
65+, 66+, 67+ or 68+[a]	Alibhai (JAMA) [15]				X (Prim)	
	Alibhai (Cancer) [16]			X (Prim)		
	Cuccia (Strahlentherapie und Onkologie) [22]	X (Sec)	X (Sec)	X (Prim)		
	Cui [23]	X (Prim)	X (Prim)	X (Additional Prim)		
	Jang [34]	X (Prim)		X (Sec)		
	Kwon [38]	X (Prim)		X (Prim)		
	Liu [40]			X (Prim)		
	Lu-Yao [41]	X (Prim)		X (Sec)		
	Manokumar [42]				X (Prim)	
	Mazzola [44]			X (Sec)	X (Prim)	
	Momota [45]	X (Sec)			X (Prim)	
	Ryu (2016) [55]	X (Prim)		X (Prim)		
	Sajid [56]				X (Prim)	
	Schmid [57]	X (Prim)		X (Prim)		X (Prim)
	Traboulsi [68]			X (Prim)	X (Prim)	
	Tward [71]			X (Prim)		
	Villumsen [74]				X (Prim & Sec)	
	Wallis (2016) [76]			X (Prim)		
	Wallis (2018) [78]			X (Prim)		
	Williams [80]			X (Prim)		
	Zhang [82]	X (Prim)	X (Prim)	X (Prim)		
	Daskivich [24]	X (Prim)				
	Gild [29]			X (Prim)		
	Hu [32]	X (Prim)	X (Prim)			
	Jacobs [33]					X (Prim)
	Jayadevappa [35]	X (Prim)		X (Prim)		X (Prim)
	Moschini [46]			X (Prim)		
	Narita [47]	X (Prim)	X (Prim)			
	Parikh [51]			X (Prim)		X (Sec)
	Shah[59]	X (Prim)		X (Prim)		
	Shayegan (Prostate Cancer and Prostatic Diseases) [60]	X (Prim)		X (Prim)		
	Shayegan (Urologic Oncology) [61]	X (Prim)				
	Suarez-Almazor [65]	X (Prim)			X (Prim)	
	Sun [66]			X (Prim)		X (Sec)
	Tsai [69]			X (Prim)		
	Wallis (2021) [77]	X (Prim)				
	Baik [17]	X (Sec)			X (Prim)	
	Ueno [72]	X (Prim)	X (Sec)		X (Sec)	
	Droz [27]	X (Prim)	X (Prim)	X (Prim)		
	Mareschal [43]				X (Prim)	
	Onishi [49]	X (Prim)	X (Prim)	X (Prim)		
70+	Capogrosso [18]	X (Sec)	X (Prim)	X (Sec)	X (Sec)	
	Couderc (2020) [19]				X (Prim)	
	Della Pepa [26]			X (Prim)		
	Honecker [31]					X (Prim)
	Ko (Journal of Robotic Surgery) [36]	X (Prim)	X (Sec)			
	Nguyen [48]	X (Sec)	X (Sec)	X (Prim)	X (Sec)	
	Osborne [50]			X (Prim)		
	Paterson [52]		X (Prim)	X (Sec)	X (Sec)	
	Rescigno [53]	X (Prim)	X (Prim)			X (Prim)
	Serrano [58]	X (Sec)				X (Prim)
	Sivaraman [63]	X (Prim)				
	Tsuchiya [70]		X (Prim)	X (Prim)		
	Vatandoust [73]	X (Prim)				X (Prim)
75+	Cuccia (Aging Clinical and Experimental Research) [21]	X (Prim)	X (Prim)	X (Prim)	X (Prim)	
	Goineau [30]				X (Prim)	

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Table 2 (*continued*)

Age Group	Author	Outcome measures				
		Survival/ Mortality	Progression of Disease	Toxicity/ Adverse Events/ Hospital Admissions	Quality of life/ Functional/ Geriatric	Other
	Ko (ICUrology) [37]	X (Prim)				
	Leibowitz [39]		X (Prim)	X (Prim)		
	Ryu (2018) [54]	X (Prim)		X (Prim)		
	Silecchia [62]		X (Prim)	X (Prim)	X (Prim)	
	Tosoian [67]					X (Prim)
	Vinh-Hung [75]	X (Prim)	X (Prim)		X (Prim)	
80+	Couderc (2021) [20]	X (Prim)	X (Prim)	X (Prim)		
	Dell'Oglio [25]	X (Prim)				
	Fisher-Valuck [28]	X (Prim)				
	Soleimani [64]	X (Prim)	X (Prim)			
	Wang [79]	X (Prim)	X (Prim)	X (Prim)	X (Prim)	
	Wu [81]	X (Prim)	X (Sec)			

[a] Studies using an age cut-off of 65, 66, 67 or 68 were combined and sorted by age cut-off and author name, Prim = Primary outcome measure, Sec = Secondary outcome measure.

was, however, recorded mainly as a primary outcome or not separated from other outcome measures. Progression was mostly mentioned as a primary outcome for all ages and adverse events were more often reported as a secondary outcome. Patient-related outcomes were mostly recorded as primary outcomes in the youngest group, the 75+ group, and the 80+ group, but more often as secondary outcomes for the 70+ group, although authors often did not separate the outcome measures.

3.2. Survival and Functional Measures

Among the 39 articles using a survival-related outcome measure, 15 studies (38.5%) used OS, four (10.3%) used disease-specific survival, and the remaining 20 articles (51.3%) investigated both (Supplemental Table 1). In the ≥65 group, four studies used only disease-specific survival. In higher age groups, overall survival was always included, often (but not exclusively) in combination with disease-specific survival.

An overview of the functional measures used is presented in Table 3. Twenty articles (29.4%) used health-related quality of life and/or other functional outcome measures. Seven studies used quality of life-scales to determine functional outcomes. Other frequently used measures were physical function (including body composition and muscle strength), lower urinary tract symptoms, incontinence, and potency. Two studies looked at fall risk and two other studies investigated pain control. Three studies examined primarily geriatric outcomes (i.e., cognitive function, risk of Alzheimer's disease and dementia, and frailty); although preservation of cognitive function is an important goal among older adults, only two studies reported on this outcome measure. There was variability in the assessment tools or instruments that were used to assess the outcome measures, however the International Index of Erectile Function (IIEF-5) and the International Prostate Symptoms Score (IPSS) were used more often, as well as the European Organization for Research and Treatment of Cancer (EORTC) quality of life (QLQC 30).

4. Discussion

In this systematic review, we found that survival outcomes were most frequently used in cohort studies and clinical trials in patients over the age of 65 years with prostate cancer, closely followed by toxicity or adverse events. Functional outcome measures are underreported; a mere 29.4% assessed quality of life or functional status.

Prostate cancer is a disease primarily of older adults. Therefore, evaluation of life expectancy and health status prior to clinical decision-making is important [83]. The SIOG Prostate Cancer Working Group has established a guideline for the treatment of older adults with prostate cancer. Based on a systematic evaluation of health status using the G8 [84] and the Mini-Cog [85] screening tools, the older population is divided into three groups: fit, vulnerable, and frail. Treatment should be decided on accordingly, following discussion in a multidisciplinary team and consultation with the patient [83]. Our results imply that, unfortunately, there is only moderate guidance from the studies that were included in this review. Everyday clinical practice would benefit from more and larger studies including the outcome measures deemed important by older patients with prostate cancer, preferably assessed in focus group studies. The majority of the studies still used the standard outcomes, despite the SIOG paper of 2013 stating that although these endpoints are important to assess the efficacy of treatment, patient-related endpoints are crucial to weigh risks and benefits of treatment [12]. These endpoints would also benefit everyday clinical treatment decisions and patient information, as, for example, quality of life and functional capacity are essential to determine if patients can tolerate a certain treatment and to have a informed shared decision-making process. Furthermore, potential loss of functional capacity might make the difference between independent living and institutionalization of older patients [91]. Last, it has been suggested that older patients, in order to receive adjuvant therapy, are less willing to trade absolute survival gain for negative impact on quality of life, functional dependence, and cognitive function [91]. Consequently, including these endpoint and outcomes in future studies might benefit and inform everyday clinical practice and treatment shared decision-making.

Treatment can have a negative impact on quality of life and functional status, which makes it crucial to incorporate patient-related outcomes in prostate cancer research. While this holds true for patients of all ages, it is especially important among patients with a high level of competing morbidity from other diseases, such as older adults. Patients should always be informed on the potential negative impacts and side effects that may accompany a treatment modality, and measures should be taken to maximize post-treatment quality of life [86,87].

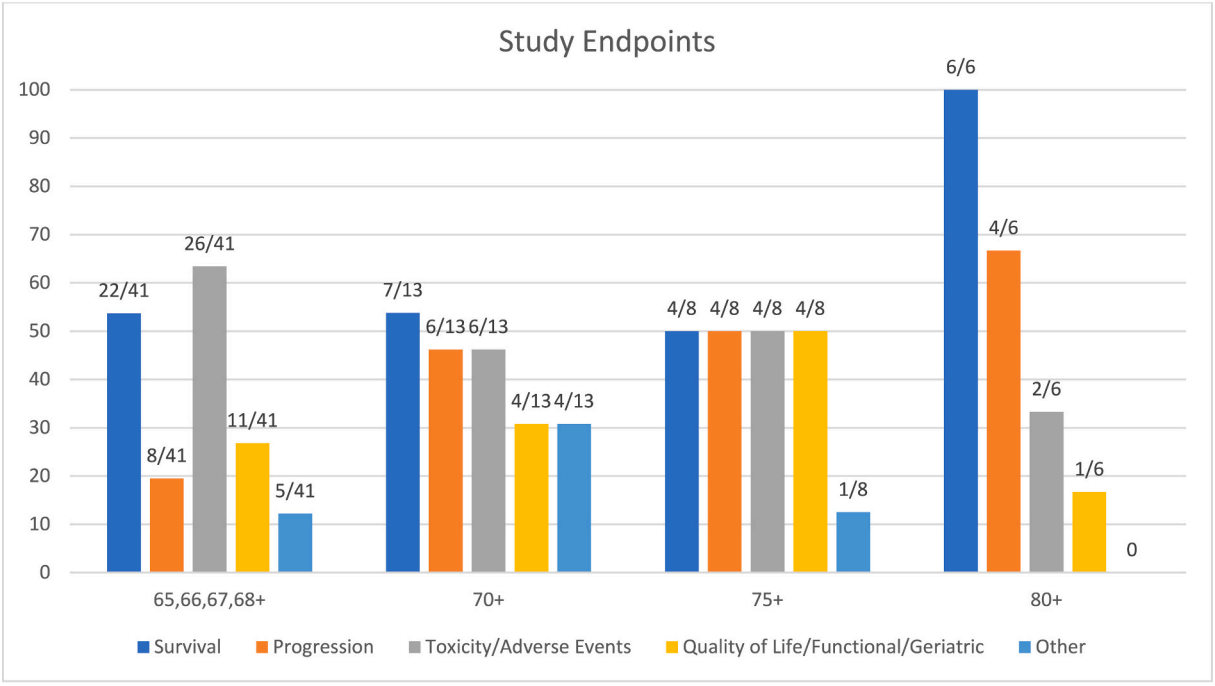
This review demonstrates that the emphasis in prostate cancer research lies primarily on tumor-related factors, such as survival and disease progression. However, qualitative research and focus group studies have shown that older or frail patients prioritize other outcome measures [12,88,89]. Preserving autonomy, functionality, and quality of life are often deemed more important than extending life per se [88]. Akpan et al. [13] developed a standard set of health outcome measures to improve the quality of provided care which are specific to the older persons in general. The recommended outcomes are a combination of survival, functional, cognitive, and quality of life measures. Regardless of this development, extensive qualitative research and preference elicitation studies specifically on older patients with prostate cancer is currently still lacking. The first step, identifying the status quo, has been set by this review; next steps would involve focus groups and one-to-one interviews with patients and (informal) caregivers and physicians, and

Table 3
Functional outcome measures, as mentioned in the included studies, by age category.

Age Group	Author	Specified QoL, Functional, Geriatric Outcomes	Measurement tools
65+, 66+, 67+ or 68+	Alibhai [15]	• Cognitive function	Trail Making Test part A, Trail Making Test part B, and Montreal Cognitive Assessment (MoCA)
	Manokumar [42]	• Daily function	• Older Adults Resource Study Instrumental Activities of Daily Living
		• Physical function	• Grip strength, the Timed Up and Go test, and Timed Chair Stands
		• QoL	• Functional Assessment of Cancer Therapy (FACT)-Prostate (P) and -General (G) questionnaires
		• Vulnerability • Levels of social support (SS) and social activities limitation (SAL)	• VES-13 questionnaire • Medical Outcomes Study questionnaires
		• Falls	• Self-reported
	Mazzola [44]	• Quality of life	EORTC QLQ-C30
	Momota [45]	• Frailty	Geriatric 8 screening tool
	Sajid [56]	• Physical performance	• Short Physical Performance Battery
		• Functional abilities	• Handgrip dynamometer
		• Muscle mass/ strength	• Chest press repetition maximum test:
		• Muscular mass	• DEXA Scan
		• Aerobic capacity	• 6-min walk test
	Traboulsi [68]	• Continence • Potency	• International Prostate Symptoms Score (IPSS) questionnaire • Sexual Health Inventory for Men (SHIM) questionnaire
	Villumsen [74]	• Physical function	• 6-min walking test
		• Body composition	• Bodystat Quadscan 4000 bioelectrical impedance analyzer
		• Quality of life • Fatigue	• EORTC QLQ-C30, FACT-P • FACT-Fatigue
	Suarez-Almazor [65]	• Any fracture • Major osteoporotic fracture	Dual-energy x-ray absorptiometry (DXA) screening
	Baik [17]	• Risk of Alzheimer's disease • Risk of dementia	As recorded in the Medicare Master Beneficiary Summary File
	Ueno [72]	• Health-related quality of life	Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8) and the Expanded Prostate Cancer Index Composite
	Mareschal [43]	• Prostate cancer related quality of life • Body composition • Physical function	• Questionnaire Clark et al.
		• Psychological status	• Body mass index), fat-free mass index, and fat mass index • Six-Minute Walk Test, Timed Up & Go, handgrip strength • Mini Mental State Examination and Hospital Anxiety and Depression scale
70+	Capogrosso [18]	• Urinary function	Short form International Continence Society (ICS) and IPSS
	Couderc [19]	• Sarcopenia • Muscle strength	• Gait speed and Timed up and go test
		• Fall risk • Muscle mass • Geriatric frailty	• Hand grip strength test • One Leg Balance test and history of falls • Appendicular Skeletal Muscle Mass measured with DXA
		• Nutritional status	• G8 screening tool, vulnerability score with ECOG-PS, ADL and IADL
		• Cognitive disorders	• Body Mass Index, Albumin level, Mini Nutritional Assessment scale and protein intake • Mini Mental State Examination and Clock Drawing test
	Nguyen [48]	• Quality of life	IPSS, patient-reported Urinary Incontinence QOL and the International Index of Erectile Function (IIEF-5) Scale Urinary Incontinence QOL
	Paterson [52]	• Proctitis	• European Organization for Research and Treatment of Cancer and the Radiation Therapy Oncology Group grading system of radiation proctitis
		• Incontinence	• Self-administered International Consultation on Incontinence Questionnaire-Urinary Incontinence
75+	Cuccia [21]	• Post-treatment health-related quality of life	Expanded Prostate Cancer Index Composite
	Goineau [30]	• Early patient-reported quality of life after treatment	IPSS, IIEF-5, EORTC QLQC 30
	Silecchia [62]	• Lower urinary tract symptoms	• IPSS
		• Erectile function • Urinary incontinence	• IIEF-5 • Assessment of pad usage
	Vinh-Hung [75]	• Pain score • Performance status	• Analog scale of 0 to 10 • Eastern Cooperative Oncology Group
80+	Wang [79]	• Pain control	Amount of analgesic consumed and symptom descriptions

based on the results, preference elicitation studies can be performed. Next, trial and cohort studies should be designed with a quantitative assessment of the balance between benefits and harms, especially in this area where treatment decisions are generally preference sensitive.

Previous similar reviews on breast cancer in the older population also concluded that there is little regard for functional and other patient-related outcomes in contemporary research, and for the older population in general [90,91]. Studying functional status or quality of life in patients requires additional questionnaires and tests that need to be appropriately adapted for the study population. This is a time-consuming procedure that needs to be accounted for in trial planning [90,92]. Additionally, there are multiple tools, instruments, and questionnaires in use and some standardization would benefit the field. The International Index of Erectile Function and the International Prostate Symptoms Score were used in four (of the 20) studies, and the EORTC QLQC 30 was also used in several studies, but some more consistency and standardization across the research is recommended to compare and



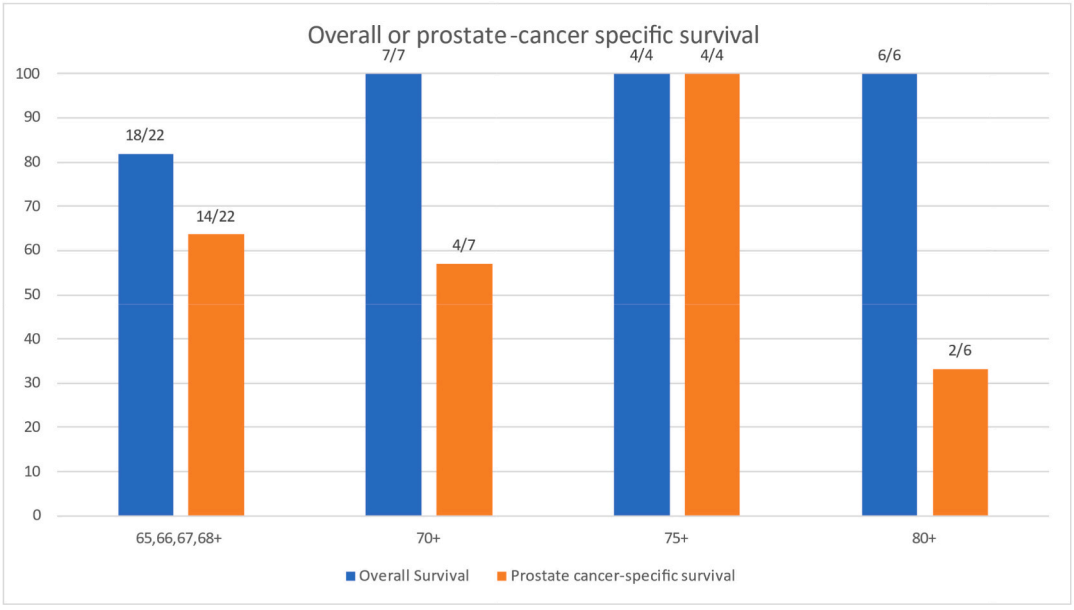


Fig. 2. Distribution of outcome measures according to age group.

synthesize the data more easily. Also, a standard set of tools, instruments, and questionnaires could benefit future clinical trials and observational research. Since older adults with cancer are a very specific subgroup, acquiring funding for studies can be difficult [91]. Generally, the interest for specifically studying the older population may be more limited for the pharmaceutical industry, as increased toxicity in frail persons or unexpected/unrelated events may lower the uptake of novel therapies in clinical practice [93]. In consequence, geriatric endpoints are rarely integrated into industry-instigated studies. All these arguments are presumably reasons for the overall lack of research on older patients.

However, including patient-related endpoints is crucial to weigh risks and benefits of treatment in older patients. The standard endpoints, in addition to overall survival, disease-free survival, or cancer-specific survival remain important to assess treatment efficacy, but other endpoints such as quality of life or preservation of functional status are essential to determine if patients can tolerate certain treatments [91]. For example when deciding on treatment (watchful waiting, active surveillance versus local therapy) for low-risk prostate cancer, quality of life and functional outcomes seem to be more important than survival as endpoint for the older patients. Loss of functional capacity seems to be related with survival for older patients with breast cancer [94]. Moreover, it can make the difference between independence and dependence during daily activities or institutionalization. Besides, older patients have an increased risk of non-cancer related mortality. Therefore, the exclusion of patient-related outcomes leads to less pronounced absolute therapy survival benefits. Careful balancing between treatment benefits and side effects is critical in this patient group [95].

Choosing the most appropriate end points for clinical trials which include older patients necessitates a very careful reflection on the

ultimate therapy goals [95]. While overall survival remains important, disease-specific survival should also be evaluated in trials with older patients. There is discussion that health-related quality of life, preservation of functional capacity and independence are important end points in clinical trials for the older population and should be included more often [95], but composite end points such as the combination of efficacy with health-related quality of life or functional outcomes can also be used to define the treatment benefit. Refining clinical trial design is central to study the effects of new therapies in older patients and to improve care. This review, and particularly the overview of studies that included patient- and older adult- related outcomes, might inform future clinical research, both clinical trials and observational research, and future post-marketing studies evaluating new anticancer agents. Including a geriatric assessment and patient-related outcomes next to survival outcomes should be considered in the planning phase of studies with any design as they specifically focus on older patients. More focus groups should be conducted to assess the preferences in outcome measures of older patients with prostate cancer, and more larger studies should be directed specifically at these older individuals.

4.1. Limitations

To our knowledge, this systematic review is the first to investigate outcomes used in studies among older patients with prostate cancer. Some limitations need to be considered.

First, operationalizing the eligibility assessment and data extraction for the age of patients included in studies was challenging, since they often did not provide a lower or upper limit or range. We had to exclude all studies in which the included age group was unclear. Furthermore, we extended eligibility criteria to patients aged $\geq$65 years instead of the initially planned $\geq$70 years for a more solid assessment, as a significant proportion of the studies defined "older" patients as aged 65 years and above. A few studies made a comparison between younger and older patients. For this systematic review, we chose to exclude these papers as well, as we anticipated that studies including solely older patients would be more likely to report on patient-related outcomes, whether or not combined with tumor-related outcomes, than those including both younger and older patients. Second, it proved difficult to extract the included stages of disease from articles. Studies often used slightly different grading/staging systems and different definitions for locally advanced cancer. We defined locally advanced as stage IIc and III cancer, in line with the majority of the articles. With respect to the limitations of the systematic review, we limited the search to the two most commonly used databases; including more databases or studies in other language might have yielded more results. A further limitation might be that we only included cohort studies or RCTs. Qualitative studies might have provided additional insights, which may be considered in further research.

Last, we made no distinction between the included stages of disease or treatment modalities when comparing the outcome measures used. For a follow-up study this would be valuable, since the course of disease and, therefore, treatment of choice depends on the stage [92,96]. Different outcome measures might be prioritized depending on the course of treatment.

5. Conclusion

In conclusion, there is limited attention on patient-centered outcome measures in prostate cancer research. Even in older patients, the focus remains on survival and disease progression rather than quality of life and functional status, although research has shown that older patients often prioritize the latter.

Overall, it is remarkable how few studies are available on older patients with prostate cancer. More focus group and qualitative research should be conducted for this specific group to identify patients' preferred outcome measures. Emphasis on the evaluation of life expectancy and health status in older patients prior to treatment would lead to optimized medical decision-making. Moreover, a critical assessment and implementation of tailored outcome measures is needed to improve care for older patients with prostate cancer.

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CRediT authorship contribution statement

Kim F.T. Jochems: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Dominik Menges:** Validation, Writing – review & editing. **Dafne Sanchez:** Validation, Writing – review & editing. **Nienke A. de Glas:** Methodology, Validation, Resources, Writing – review & editing. **Hans Wildiers:** Validation, Writing – review & editing. **Daniel Eberli:** Validation, Writing – review & editing. **Milo A. Puhan:** Resources, Validation, Writing – review & editing. **Esther Bastiaannet:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

No conflict of interest for all authors.

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Appendix A. Supplementary data

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