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A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer☆

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ABSTRACT

Aim: The aim of this systematic review is to summarise all available data on the use of the G8 screening tool in geriatric oncology, focusing on the diagnostic accuracy of the G8 to predict the presence of impairments on geriatric assessment (GA) and on its association with different clinical outcomes (survival, course of treatment and patient-centred outcomes).
Methods: A systematic search in MEDLINE and EMBASE for studies on the use of the G8 in older patients with cancer.
Results: The literature search identified 8987 reports, of which 54 publications from 46 studies were included (including 18 conference abstracts). 19 studies compared the diagnostic characteristics of the G8 with GA. Median sensitivity and specificity of the G8 for frailty on GA were respectively: 85% and 64%. Out of the 24 studies addressing the association of the G8 with survival, 15 (63%) found the G8 was associated with survival. Six out of fourteen studies (43%) reporting on treatment-related complications found an association between G8 scores and risk of complications. Treatment completion, health care utilisation and patient-centred outcomes were investigated less frequently.
Conclusion: The G8 is a useful diagnostic tool to identify older patients with cancer who require full GA and is associated with survival and treatment-related complications. Future prospective studies should investigate whether the G8 is predictive for other relevant clinical outcomes such as treatment completion and patient-centred outcomes.

Contents

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1. Introduction

Oncologists are confronted with an increasing population of older patients with cancer for whom treatment decisions are needed. Decision-making for these patients is complex and forms a challenge for treating physicians. Because of a scarcity of evidence from large randomized controlled trials, there are limited data on the feasibility and outcomes of different treatment modalities for this population [1–3]. Treatment goals may also be different because older patients with cancer often value maintenance or improvement of quality of life (QOL) over an increase in overall survival [4,5]. In addition, they form a heterogeneous population with major differences for functional and cognitive status as well as for the presence of comorbidities and polypharmacy [6]. As a result, older patients' benefit from treatment can differ and especially those with comorbidity or functional impairments are at risk of adverse health outcomes.

In order to identify fit from unfit patients and to tailor oncologic treatment, some form of geriatric assessment (GA) is increasingly being incorporated in oncologic care, to evaluate the overall health status of an older patient [7]. The majority of older patients with cancer have at least one and often multiple impairments in GA domains, which are frequently undetected with a standard oncologic evaluation. These impairments are associated with increased risk of treatment-related complications, a decline in functioning or QOL and poorer survival [8]. However, not all older patients with cancer require a complete GA and GA is also resource-consuming. Therefore, a two-step approach, starting with a screening tool to identify those older patients with cancer who will benefit from full GA, has been recommended by the International Society of Geriatric Oncology (SIOG) [7].

The G8 was the first such screening tool specifically designed for older patients with cancer [9]. It consists of eight items covering multiple GA domains (Table 1). Seven items are derived from the original 18-item mini nutritional assessment questionnaire (MNA [10]; appetite changes, weight loss, mobility, neuropsychological problems, body mass index, medication and self-reported health) and one item concerns the patient's age. Overall, the G8 score ranges from 0 (heavily impaired) to 17 (not at all impaired), with a cut-off for potential frailty of ≤14. The G8 is easy and quick to administer (median time 5 min) and its diagnostic accuracy has been validated in large independent cohorts [11,12]. Two systematic reviews concluded that the G8 was one of the most robust screening tools currently available [13,14].

Although originally designed to identify those potentially frail older patients who may benefit from GA [9,11], the association of the G8 with clinical outcomes such as treatment complications, physical functioning after treatment and survival has also been studied [12,15]. A review published in 2015 reported on the results of four studies relating the G8 to clinical outcomes [14]. However, the primary aim if this review was not to provide an extensive overview on the association of screening tools with clinical outcomes because it only included studies that reported on the use of screening tools for detection of impairments on GA. Studies reporting on the association with clinical outcomes specifically could thus have been missed. In addition, after the publication of this review, many studies have been published on the association of the G8 and clinical outcomes. Therefore, the aim of the present systematic review is to summarise all currently available data on the use of the G8, focusing on both the comparison of the G8 with GA as well as its association with clinical outcome measures.

2. Materials and Methods

2.1. Search Strategy and Selection Criteria

Our aim was to identify all studies that investigated the G8 screening tool in relation to full GA and clinical outcomes in patients with cancer, independent of age, cancer type or stage of disease.

The following search was performed on July 20th 2018, in both MEDLINE and EMBASE: (((((((neoplasms[MeSH Terms]) OR neoplasm*[tiab]) OR cancer*[tiab]) OR tumor*[tiab]) OR tumor*[tiab]) OR oncolog*[tiab]) OR malignan*[tiab])) AND (((“geriatric 8”[tiab]) OR G8 [tiab]) OR (geriatric assessment[MeSH Terms]) OR (geriatric[tiab] AND assessment*[tiab]) OR ((frailty[MeSH Terms]) OR frail*[tiab])). A date range was applied, because the first publication on the G8 was

Table 1
The original G8 screening tool.

Items	Possible responses (score)
1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
2. Weight loss during the last 3 months?	0 = weight loss >3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
3. Mobility?	0 = bed or chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out
4. Neuropsychological problems?	0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
5. Body mass index (BMI)? (weight in kilograms) / (height in square metres)	0 = BMI <19 1 = BMI 19 to <21 2 = BMI 21 to <23 3 = BMI ≥23
6. Takes more than three prescription drugs per day?	0 = yes 1 = no
7. In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good 0.5 = does not know 1.0 = as good 2.0 = better
8. Age	0 ≥ 85 1 = 80–85 2 ≤ 80
Total score 0–17	Cut-off ≤14: potentially frail

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published in May 2008 as a meeting abstract [16], no limits in age or language were applied.

For this systematic review, we included studies evaluating the original eight-item G8 or a modified version derived from the original G8. Studies were considered eligible if they evaluated the performance of the G8 in older patients with cancer, in relation to the two main outcome measures. The first outcome measure was the diagnostic accuracy of the G8 compared with GA. The second outcome measure was the association of the G8 with clinical outcomes, including prognosis (survival), the course of treatment (toxicity or treatment-related complications, serious adverse events, treatment completion and health care utilisation) and patient-centred outcome measures (functioning and quality of life). If outcome data were only available for patients considered frail based on G8, but not for those considered fit (or the reverse), these studies were excluded.

The titles and abstracts of all studies retrieved by the search were assessed by one reviewer (IvW) to determine which warranted further examination. All potentially relevant articles were subsequently screened as full text. If only an abstract was available, an effort was made to find the final report of the study by searching EMBASE and MEDLINE using the names of first, second and/or final authors as well as key words from the title. If multiple publications were available from one study, only the primary study was included (with the largest patient population or with the most relevant results), except when the other manuscripts contained relevant outcomes that were not included in the primary publication.

Finally, references of included studies were cross-referenced to retrieve any additional relevant citations.

2.2. Data Extraction

For each eligible study, data regarding study design and results were independently extracted by two authors (IvW and ES). Items that were extracted were the study population (age, sex, cancer type), method of patient selection, the treatment to be received, the content of the GA, the G8's diagnostic accuracy for frailty compared to GA, and clinical outcomes (survival, course of treatment and patient-centred outcomes).

2.3. Quality Assessment

The methodological quality of each of the studies was assessed independently by two reviewers (IvW and ES), using the Newcastle-Ottowa scale adapted to this subject (Appendix A). Disagreements among the reviewers were discussed during a consensus meeting and in case of persisting disagreement, the assistance of a third reviewer (MH) was sought.

2.4. Data Synthesis and Analysis

We summarised the study results to describe our main outcomes of interest. If necessary, percentages were calculated of patients with an impaired G8 or GA. Moreover, sensitivity, specificity, positive and negative predictive values and relative risks were calculated, based on the results reported in the study. Due to the expected heterogeneity in the study populations, a formal meta-analysis was not considered feasible.

3. Results

3.1. Study Characteristics

The literature search yielded 8987 citations (2968 from MEDLINE and 6019 from EMBASE), of which 2425 were duplicates and 6509 were excluded for other reasons (Fig. 1). Of note, one potentially relevant study was excluded because of quality concerns, including contradictory outcomes and unclear content of the GA [17]. Cross-referencing yielded one additional study [18]. Ultimately, 54 publications from 46 studies were included for this review [9,11,12,18–68], of which 18

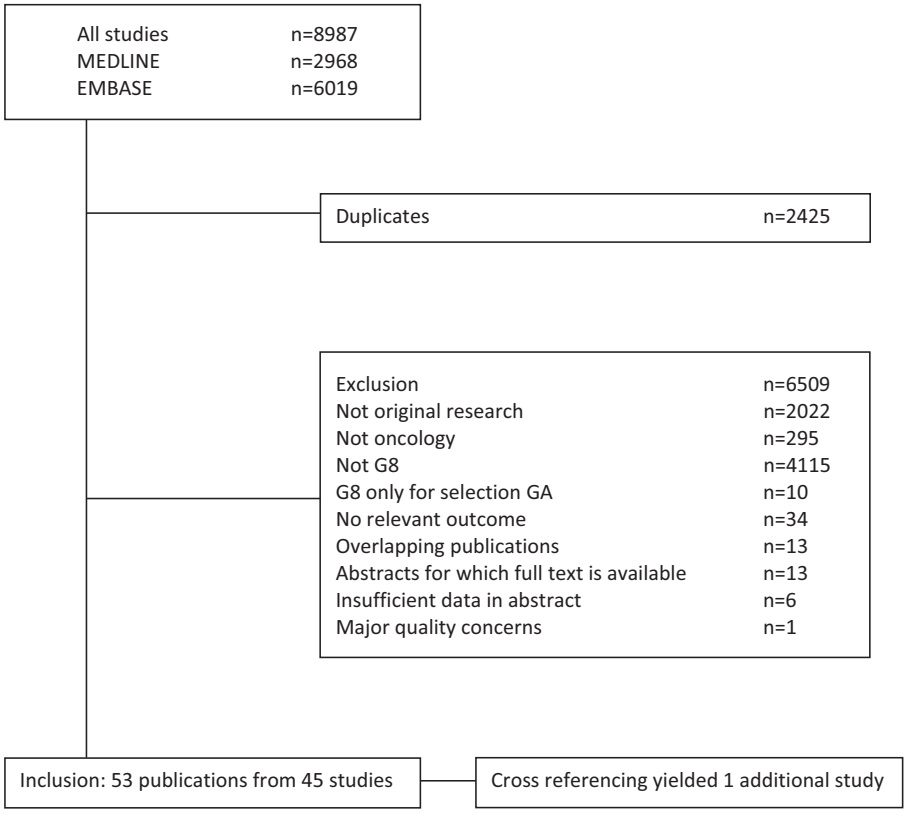

Fig. 1. Search results and study selection.

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Table 2
Included studies.

Publication			Study method		Patients					Outcome			
Author	Publication year(s)	Abstract (A) or full text (F)	Study population	Patient selection	Treatment	Number of patients[a]	% male	Age in years (me (di)an, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Agemi [19]	2015	A	Lung cancer	All patients aged ≥70 years candidate for oncological treatment	Various	101	81	79 (70–95)	82		X	X	
Aparicio [20]	2018	F	Metastatic colorectal cancer	Untreated patients aged ≥75 years who completed geriatric questionnaires	CT (± TT)	96	55	80 (75–91)	81		X	X	
Aydin [21]	2016	A	Acute myeloid leukemia	Consecutive, newly diagnosed referrals aged >60 years	CT	69	?	?	?		X		
Baitar [22,23]	2013 2014	F F	Various cancer types	Age ≥ 65 years, newly diagnosed cancer or recurrent disease	Various	170	54	77 (66–97)	76	X		X	
Bellera [9,27]	2012 2015	F A	Various cancer types	Patients aged ≥70 years scheduled to receive first-line chemotherapy	CT	339	59	77 (70–99)	82	X			X
Bonomo [24]	2017	F	Head and neck cancer	Age ≥ 65 years, unsuitable for curatively intended concurrent CTR or high-dose RT by clinical judgement	RT	36	58	78 (65–91)	100		X		
Bononi [25]	2013	A	Various cancer types	Unelected outpatients aged >70 years	Various	530	50	?	69		X		
Boulahssass [26]	2018	F	Various cancer types	Consecutive patients aged >70 years, outpatient or hospitalized	Various	1050	40	82 (70–100)	86		X		
Cvetkovic [28]	2017	A	Indolent B-cel lymphoma	Consecutive patients aged ≥65 years fulfilling criteria for treatment	CT	89	51	75 (65–88)	?		X		
Decoster [29]	2017	F	Colorectal cancer	Age ≥ 70 years, newly diagnosed cancer or cancer progression/relapse	Various	193	62	77 (70–89)	?			X	X
Decoster [30]	2018	F	Metastatic colorectal cancer	Age ≥ 70 years, suitable for first-line chemotherapy	CT	248	62	77 (69–91)	81		X	X	
Denewet [31]	2016	F	Various cancer types	Age ≥ 70 years with new cancer diagnosis or disease progression	Various	205	53	79 (70–93)	86		X		
Dimopoulos [32]	2016	A	Multipel myeloma	Consecutive, unselected patients aged >65 years	TT	144	55	76 (66–92)	?		X		
Dubruille [33,34]	2012 2015	F A	Haematological cancers	Consecutive, inpatients aged ≥65 years, fit enough for chemotherapy	CT	90	57	74 (65–89)	72	X	X	X	
Fagard [35]	2017	F	Colorectal cancer	Patients aged ≥70 years planned for surgery	Surgery	190	55	77 (70–97)	61			X	
Gangopadhyay [36]	2018	F	Various cancer types	Patients aged >65 years who completed CTR	CTR	219	42	78 (65–89)	?			X	
Hamaker [37]	2014	F	Haematological cancers	Consecutive, newly diagnosed patients aged ≥67 years	Various	108	53	78 (67–99)	61	X	X		
Hentschel [38]	2016	F	Various cancer types	Consecutive patients aged ≥63 years referred to a tertiary cancer centre	Various	63	62	73 (63–93)	75	X			
Holmes [39]	2014	F	Haematological cancers	Patients eligible for allo-HCT aged ≥60 years	allo-HCT	50	70	65 (60–73)	56	X			
Kaibori [40]	2016	F	Hepatocellular carcinoma	Consecutive patients scheduled for liver resection aged ≥70 years	Surgery	71	73	77 (70–89)	55		X	X	
Kenig [41]	2015	F	Solid abdominal tumors	Consecutive patients ≥65 years in need of surgery under general anesthesia	Surgery	135	47	75 (65–92)	85	X			
Kenis [12,42]	2014	F A	Various cancer types	Patients aged ≥70 years at diagnosis or at disease progression/relapse	Various	937	37	76 (70–95)	74	X	X		X
Kim [43]	2017	A	Various cancer types	Patients receiving first-line chemotherapy aged ≥70 years	CT	301	?	75 (70–93)	88	X			
Martinez-Tapia [44,45]	2017 2016	F F	Various cancer types	Consecutive newly diagnosed in- and outpatients aged ≥70 years	Various	1333	52	80 (IQR 76–84)	84	X	X		
Matsushita [46]	2018	A	High-risk prostate cancer	Patients aged ≥75 years	Surgery	41	100	77 (IQR 76–79)	39			X	
Middelburg [47]	2017	F	Various cancer types	Patients irradiated with curative intent aged ≥65 years	RT or CRT	380	52	72 (65–96)	44			X	
Molina-Garrido [48]	2013	A	Various cancer types	Patients aged ≥70 years	Various	202	62	80	?		X		

Neve [49]	2016	F	Head and neck cancer	Aged ≥65 years with a primary malignancy	Various	35	63	74 (65–93)	49			X		
Ogawa [50]	2015	A	Lung cancer	Patients with various stages of lung cancer prior to treatment	Various	154	69	> 70 years	60	X				
Osborne [51]	2017	F	Localised prostate cancer	Patients aged ≥70 years planned to receive RT with radical intent	RT	156	100	74 (70–84)	23	X				
Osorio [52]	2016	A	Breast cancer	Consecutive patients aged ≥70 years	Various	92	1	78 (70–94)	?			X		
Pamoukdjian [53]	2017	F	Various cancer types	Consecutive outpatients aged ≥65 years	Various	252	45	81 (SD 6)	88	X				
Pottel [54,55]	2015 2012	F F	Head and neck cancer	Consecutive patients aged ≥65 years eligible for curative therapy	RT or CRT	100	86	72 (65–86)	69	X	X		X	
Runzer-Colmenares [56]	2017	F	Various cancer types	Older patients receiving RT with curative treatment intent	RT	181	100	78 (SD 5)	20			X		
Schulkes [57]	2017	F	Lung cancer	All patients aged ≥70 years	Various	142	62	77 (73–82)	70		X			
Silvestri [58,59]	2018	A	Kidney cancer	Patients aged ≥70 years prior to surgery	Surgery	162	46	77 (SD 6)	60		X	X		
Smets [60]	2014	F	Various cancer types	Patients aged ≥70 years, recently diagnosed with a solid tumor	?	108	35	76 (70–88)	60	X				
Soubeyran [11,68]	2014 2016	F F	Various cancer types	Age ≥ 70 years, before first-line treatment or between two steps of a first-line treatment sequence	Various	1435	30	78 (70–98)	68	X	X			
Souwer [61]	2018	F	Colorectal cancer	Patients aged >70 years receiving non-elective surgery for stage I-III CRC	Surgery	137	55	78 (IQR 75–83)	50		X	X		
Stauder [62]	2015	A	Haematological cancers	At initial diagnosis, age cut-off unclear	?	64	56	79	?		X			
Stokoe [18]	2012	A	Various cancer types	Patients aged ≥65 years	CT	165	?	71 (65–84)	?			X		
Takahashi [63]	2017	F	Various cancer types	Patients aged ≥70 years	?	264	66	75 (70–91)	83		X			
Velghe [64]	2014	F	Haematological cancers	Newly diagnosed patients aged ≥70 years referred to a tertiary hospital	?	50	50	76 (70–87)	76	X				
Von Saint-George [65]	2016	A	Various cancer types	All patients aged ≥70 years	?	50	?	?	41	X				
Wildiers [66]	2018	F	Metastatic breast cancer	Patients aged ≥70 years, or frail patients aged ≥60 years, with life expectancy >12 weeks and performance status according to WHO-scale of 0–3	CT (± HT)	79	0	77	70		X			
Yokom [67]	2018	F	Various cancer types	Patients starting systemic therapy aged ≥70 years	CT	27	71	74 (70–92)	64	X				

? not reported.

Allo-HCT = allogeneic stem cell transplantation; CT = chemotherapy; CRT = chemo(radio)therapy; HT = hormonal therapy; IQR = interquartile range; RT = radiotherapy; SD = standard deviation; TT = targeted therapy; WHO = World Health Organisation.

Note: If details regarding the G8 cut-off used in the study were lacking ($n = 6$; all but one conference abstracts), we presumed that the validated cut-off of ≤14 was used.

[a] Shown patient number is the number for which analysis with the G8 were possible.

were conference abstracts [18,19,21,22,26,27,36,37,40,42,44,46,49,53,54,56,59,63].

The characteristics of these 46 studies are summarised in Table 2. The first publications were from 2012 [9,18,33,55] and the majority of studies (74%) were published in the past four years. Median sample size was 143 patients (range 27–1435) and me(di)an age of the included patients ranged from 65 to 82 years. Study populations were heterogeneous, with 43% focusing on patients with various cancer types [9,11,12,18–21,25,30,32,36–39,41,42,47,51,55,57,59,62,64,65]. Two studies specifically mentioned they also included hospitalized patients [26,44,45], while one study included hospitalized patients only [33,34]. Seventeen studies evaluated patients receiving various treatment regimens [11,12,19,22,23,25,26,29,31,37,38,42,44,45,48–50,52,53,57], eleven focused on patients receiving chemotherapy [9,18,20,21,27,28,30,33,34,36,43,66,67], five on radio(chemo)therapy [24,47,51,54–56], six on surgery [35,40,41,46,58,59,61], one on targeted therapy [32] and one on allogeneic stem-cell transplantation [39]. For five studies, the treatment was unknown [60,62–65].

For outcomes, 19 studies addressed the comparison of the diagnostic accuracy of the G8 compared to GA [9,11,12,22,34,37–39,41,43,44,50,51,53,55,60,64,65,67]. 24 studies described the association of the G8 with survival [11,12,20,22,24–26,28,31,34,39,42,48,49,52,54,56,57,60,19,61, 63,66, 67], 17 studies reported on the association of the G8 with course of treatment [18–20,23,29,30,33,35,36,40,46,47,49,52,56,58,59,61], and four studies addressed the association between the G8 and patient-centred outcomes [12,27,29,42,54]. According to the G8, the median prevalence of frailty was 70% (range 20–100%).

In addition, three studies assessed the diagnostic performance of two modified versions of the G8 compared to GA [44,53,68] and one publication addressed the prognostic value of one of the modified G8 versions [45].

3.2. Quality Assessment

The results of the quality assessment can be found in Fig. 2. Detailed results per publication are listed in Appendix B. The overall quality of the studies was good. In two studies there was a high risk of bias because there was >10% missing data for the G8 [18,38]. In another study the description of the method of geriatric evaluation was insufficient with a high risk of bias as a consequence [50]. Duration of follow-up was not mentioned in fifteen publications [18,19,21,25,28,30,32,36,47,49,52,58,59,62,63]. Five publications had loss to follow-up rates over 10% [12,27,29,42,54], while another 22 publications did not provide sufficient information to assess adequacy of follow-up [18,19,21,24,25,28,30–33,36,37,46,48,49,52,56–60,62].

Of the 24 studies reporting on the association of the G8 with survival, fourteen studies specifically mentioned the sociodemographic and/or clinical characteristics survival analyses were adjusted for [16,20,26,30,32,34,37,40,45,48,54,57,63,66] and seven performed multivariate analysis but did not report for which covariates they adjusted [12,19,21,24,25,28,31]. For another two studies it was unclear whether they performed univariate or multivariate analysis [59,62] and one study only did an univariate analysis [61].

3.3. Diagnostic Accuracy of the Original G8 Versus GA

For the 19 studies assessing the G8 in relation to GA [9,11,12,22,34,37–39,41,43,44,50,51,53,55,60,64,65,67], Table 3 shows the content of this assessment and Fig. 3 demonstrates the relationship between sensitivity and false-positives for the different studies. GA varied from five to nine geriatric domains with a median of seven. Eighteen out of 19 studies (95%) assessed functional status (ADL and/or iADL) [9,11,12,28,31–33,35,37,38,45,47,50,55,58,59,62,64], and seventeen out of 19 studies (89%) assessed mood [9,11,12,28,31–33,35,37,38,47,50,55,58,59,62,64] and nutrition [9,11,12,28,31–33,35,37,38,47,50,55,58,59,62,64]. Cognition (n = 16, 84%) [9,11,12,28,31–33,35,37,38,47,50,55,58,62,64], mobility and/or falls (n = 15, 79%) [9,11,28,31–33,35,37,38,45,47,50,58,59,62,64] and comorbidity (n = 14, 74%) [9,11,12,28,33,35,38,47,50,55,58,59,62,64] were also commonly included while polypharmacy (n = 6, 32%) [9,11,12,28,33,35,38,47,50,55,58,59,62,64], social support (n = 6, 32%) [12,22,37,39,51,67] and fatigue (n = 1, 5%) [34] were less frequently included.

Frailty based on GA was defined as the presence of one or more geriatric conditions in six studies [9,11,44,51,53,64] and two or more in twelve studies [12,22,34,37–39,41,43,50,55,60,67]. For one study [65], the cut-off used to define frailty was not mentioned. Study populations showed a wide variation in the prevalence of frailty as diagnosed by GA; a median of 73% patients was considered frail (range 31–94%, Table 3). In studies using the cut-off of ≥1, the prevalence of frailty ranged from 31% to 94%, and in studies using a cut-off of ≥2, the range was 32% to 80%.

The sensitivity of the G8 to detect potential frailty ranged from 38% to 97% with a median of 85% (Table 3). The specificity was lower, with a median of 64% (range 28%–100%). Thus, the G8 yielded 15% false-negative results, meaning potentially frail patients were incorrectly identified as fit and 36% false-positive, i.e. fit patients identified as potentially frail. Positive and negative predictive value ranged from 37% to 100% and from 19% to 86% respectively (with medians of 86% and 56% respectively). There did not seem to be a difference in performance of the G8 comparing the cut-off of 1 or more impaired domains versus 2 or more impaired domains; for studies using a cut-off of ≥1 to define frailty on GA, median sensitivity and specificity were 85% and 65% respectively (range 45%–90% and 35%–100%), while for studies using a cut-off of ≥2, median sensitivity and specificity were 84% and 61% respectively (range 38%–97% and 28%–80%).

3.4. Association Between the Original G8 and Clinical Outcomes

Fifteen out of 24 studies addressing survival found that frailty based on the G8 was associated with a higher risk of mortality (63%, Table 4) [11,12,19–21,24–26,28,30–32,34,37,40,45,48,54,57,59,61–63,66]. An association between the G8 and survival was found in four out of

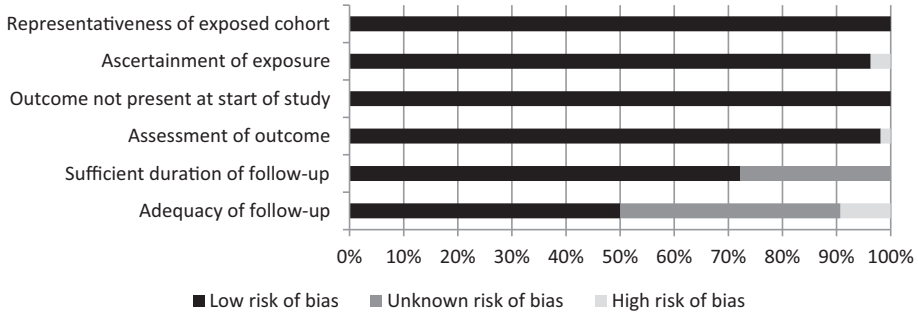

Fig. 2. Outcome of the quality assessment. Details are reported in Appendix 1a (quality assessment questionnaire) and 1b (assessment per study).

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Table 3
Diagnostic performance of the original G8 compared to a geriatric assessment.

Study	Number of domains in GA	Domains in GA	*n*=	cut-off GA impaired	% frail on G8	% frail on GA	SE (%)	SP (%)	PPV (%)	NPV (%)
Von Saint-George [65]	6	mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	?	41	31	74	74	86	56
Bellera [9]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	339	1+	82	94	85	65	97	21
Martinez-Tapia [44]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	729	1+	81	87	87	58	93	41
Osborne [51]	5	ADL, iADL, mobility/falls, social support, polypharmacy	156	1+	23	31	45	84	55	78
Pamoukdjian [53]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	252	1+	88	94	90	35	95	19
Soubeyran [11]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	1435	1+	68	80	77	64	90	40
Velghe [64]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	1+	76	88	89	100	100	55
Baitar [22]	8	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, comorbidity	170	2+	76	64	92	52	78	78
Dubruille [34]	9	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity, polypharmacy, fatigue	90	2+	72	80	79	56	88	40
Hamaker [37]	8	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, polypharmacy	108	2+	61	70	69	79	89	50
Hentschel [38]	6	cognition, mood, iADL, nutrition, mobility/falls, polypharmacy	63	2+	75	36	38	63	37	64
Holmes [39]	9	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, comorbidity, polypharmacy	50	2+	56	66	70	71	83	55
Kenig [41]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	135	2+	85	73	97	44	83	84
Kenis [12]	7	cognition, mood, ADL, iADL, nutrition, social support, comorbidity	937	2+	74	74	87	59	86	61
Kim [43]	6	cognition, mood, ADL, iADL, nutrition, mobility/falls	301	2+	88	73	94	28	79	60
Ogawa [50]	?	Unclear	154	2+	60	32	82	51	44	86
Pottel [55]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	2+	67	69	86	75	88	71
Smets [60]	6	cognition, mood, ADL, iADL, nutrition, comorbidity	108	2+	60	48	87	64	69	84
Yokom [67]	8	cognition, mood, iADL, nutrition, mobility/falls, social support, comorbidity, polypharmacy	27	2+	64	79	73	80	94	40

? = not reported.
ADL = activities of daily living; iADL = instrumental activities of daily living; GA = geriatric assessment; NPV = negative predictive value; PPV = positive predictive value; SE = sensitivity; SP = specificity.

eight studies addressing patients receiving chemotherapy and/or radiotherapy (50%) [20,21,24,28,30,34,54,66] and none of the three studies on surgery [40,58,61]. Eleven out of thirteen studies in patients receiving varying treatments found an association between frailty on the G8 and survival (85%) [11,12,19,25,26,31,32,37,45,48,57,62,63]. Details of differences between patients considered frail versus fit according to the G8 with regards to overall survival and progression-free survival are listed in Table 4.

Fourteen studies addressed chemotherapy toxicity or treatment-related complications [18,19,23,29,30,33,35,36,40,46,47,56,58,61] and six of these found that a low G8 score was associated with the occurrence of toxicity or treatment-related complications (43%) [18,36,40,46,56,58]. One additional study addressed a composite endpoint including safety and efficacy, and found a positive association in the univariate analysis, which was no longer significant after correcting for potential confounders [20]. All three studies separately reporting toxicity rates for fit and frail patients based on the G8 found significantly higher rates of chemotherapy- and/or radiotherapy-related toxicity in the latter, with relative risks varying from 1.4 to 11.3 [18,47,56]. In four studies on the incidence of post-operative complications, relative risks for complications for potentially frail patients compared to fit patients ranged from 1.1 to 14.7; differences were significant in three out of four studies [35,40,58,61]. Four studies reported on treatment completion [19,30,47,52] and none found an association between low G8 scores and non-completion. Of the four studies evaluating the association between the G8 and health care utilisation [40,49,59,61], only one study [40] (25%) found that a G8 score < 14 was associated with a longer median postoperative hospital stay.

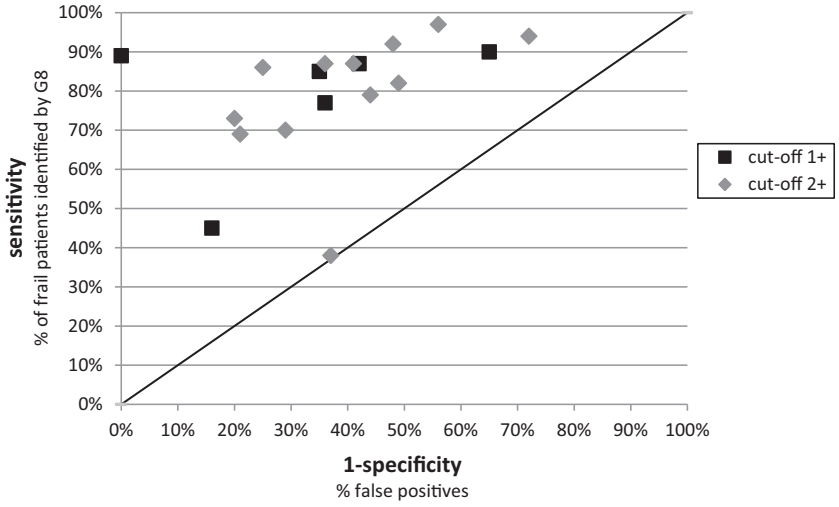

Fig. 3. Sensitivity and 1-specificity of the original G8 for frailty on geriatric assessment (GA) based on the presence of one or more (cut-off 1+) or two or more (cut-off 2+) geriatric conditions on GA for the different studies.

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Table 4
Associations between the original G8 and treatment-related toxicity or complications and between the original G8 and survival.

Publication	Study design				Outcome		
Author	Study population	Type of cancer treatment	*n*=	Me(di)an Follow-up	Toxicity or complications	Survival	Comparison of survival frail vs fit[a]
Aydin [21]	Acute myeloid leukemia	CT	85	?		+/++	
Cvetkovic [28]	Indolent B-cel lymphoma	CT	89	?		+/++	
Decoster [30]	Metastatic colorectal cancer	CT	252	2–3 months	+/−−	+/−−	PFS 8.7 vs 11.4 months
Dubruille [34]	Haematological cancers	CT	90	?	−	−	
Stokoe [18]	Various cancer types	CT	165	?	+		
Aparicio [20]	Metastatic colorectal cancer	CT (± TT)	102	20.4 months		−	
Wildiers [66]	Metastatic breast cancer	CT (± HT)	80	20.7 months		+/++	6-month OS 88% vs 100% 12-month OS 67% vs 100%
Baitar [23]	Various cancer types	CT or CRT	85	1 month	−/−−		
Gangopadhyay [36]	Various cancer types	CRT	219	?	+/++		
Bonomo [24]	Head and neck cancer	RT	37	13 months		+/−−	
Runzer-Colmenares [56]	Various cancer types	RT	181	10.2 months	+/++		
Middelburg [47]	Various cancer types	RT or CRT	409	?	+/−−		
Pottel [54]	Head and neck cancer	RT or CRT	100	?		+/++	36-month OS 36% vs 70%
Fagard [35]	Colorectal cancer	Surgery	190	?	+/−−		
Kaibori [40]	Hepatocellular carcinoma	Surgery	71	> 6 months after hepatectomy	+/++	−	
Matsushita [46]	High-risk prostate cancer	Surgery	41	?	+/++		
Silvestri [58,59]	Kidney cancer	Surgery	162	40.6 months	+	−	
Souwer [61]	Colorectal cancer	Surgery	139	At least 6 months	−	−	1-month OS 96% vs 96% 6-month OS 94% vs 96%
Dimopoulos [32]	Multipel myeloma	TT	144	?		+/++	
Stauder [62]	Haematological cancers	?	64	?		+	
Takahashi [63]	Various cancer types	?	264	?		+/++	Median OS 10.7 vs 25.6 months
Agemi [19]	Lung cancer	Various	101	?	−	+/++	
Bononi [25]	Various cancer types	Various	530	?		+/++	
Boulahssass [26]	Various cancer types	Various	1050	3.3 months		+/−−	
Decoster [29]	Colorectal cancer	Various	193	2–3 months	−/−−		
Denewet [31]	Various cancer types	Various	205	?		+/++	
Hamaker [37]	Haematological cancers	Various	108	33.6 months		+/++	12-month OS 36% vs 88%[b]
Kenis [12]	Various cancer types	Various	937	19 months		+/++	OS at 20 months ≈ 60% vs 90%[c]
Martinez-Tapia [45]	Various cancer types	Various	1333	26.5 months		+/++	Median OS 13.1 vs 76 months
Molina-Garrido [48]	Various cancer types	Various	202	7.2 months		?/−−	
Schulkes [57]	Lung cancer	Various	142	16.1 months		+/++	12-month OS 46% vs 79%
Soubeyran [11]	Various cancer types	Various	1167	12.4 months		+/++	

? = not reported; − = no association on univariate analysis, multivariate analysis including G8 in model not performed or unclear whether not finding an association was the result of univariate or multivariate analysis; + = association on univariate analysis, multivariate analysis including G8 in model not performed or unclear whether finding an association was the result of univariate or multivariate analysis; −/−− = no association on univariate or multivariate analysis; +/−− = association on univariate analysis, no association on multivariate analysis; +/++ = association on multivariate analysis.
CT = chemotherapy; CRT = chemo(radio)therapy; HT = hormonal therapy; OS = overal survival; PFS = progression-free survival; RT = radiotherapy; TT = targeted therapy.
[a] Bold value indicates *P*-value ≤ .05.
[b] In patients receiving standard treatment.
[c] Percentages estimated from figure.

Four studies addressed patient-centred outcomes, including functional decline ($n = 3$) [12,27,29,42] and quality of life ($n = 1$) [54]. Three studies found that a G8 score ≤ 14 was independently associated with either functional decline [12,27,42] or lower QoL (75%) [48] while the fourth study did not find an association [29].

3.5. Performance of Modified G8 Versions

Two modified G8 versions were evaluated in three studies to assess its diagnostic performance compared to GA [44,53,68]. One of these studies investigated a modified G8 containing six items that independently predicted impaired GA: weight loss, neuropsychological problems, polypharmacy, self-rated health, performance status and a history of heart failure or coronary artery disease [44]. This modified G8, with a cut-off of ≥6 of 35 points for potential frailty, outperformed the original G8 with sensitivity of 89.2% vs 87.2%, specificity of 79.0% vs 57.7%, positive predictive value of 96.5% vs 93.1% and negative predictive value of 52.8% vs 40.9% for the modified G8 and original G8 respectively. In a first external validation of this modified G8 sensitivity and specificity were 89.3% and 64.7% respectively [53]. In addition, an impaired score on this modified G8 was independently associated with poorer 1- and 3-years survival [45].

The second modified G8 replaced the item on neuropsychological problems in the original G8 by a 4-item iADL score [68]. This modified G8 used the same cut-off value for potential frailty as the original G8 (≤14). Sensitivity of the iADL-modified G8 was not different from that of the original G8 (77% vs 77%) but its specificity was significantly higher (67% vs 64% for the original G8, $p < .05$).

4. Discussion

This systematic review of 46 studies on the performance of the G8 shows that, although the G8 was originally developed as a screening tool to detect vulnerable older patients with cancer who may benefit from more elaborate GA, many studies also evaluated its association with survival and treatment-related complications. We found a good sensitivity for the G8 compared to GA to detect potentially frail patients. In addition, almost two-thirds of the studies that assessed the association of the G8 with survival and 43% of the studies on treatment-related complications found that low G8 scores were associated with poorer outcomes. Evidence on treatment completion, health care utilisation and patient-centred outcomes was limited, but a trend towards more functional decline and poorer QoL in patients with low G8 scores was observed while an association between frailty based on G8 and treatment completion or health care utilisation was not found.

This systematic review has some limitations. First, some of the included studies have not been published in full text reports (yet), which limited the amount of available data on the execution and results

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of the study. Furthermore, study populations were heterogeneous, investigating different levels in frailty status, a wide range of cancer types, stages and treatment modalities, thus hampering extrapolation of these results to individual oncology practice. In addition, the content of the GA differed considerably between studies, as did the cut-off value that was used to define frailty. This is likely the consequence of the current lack of consensus on the definition of frailty [69]. The definition that is used will influence the prevalence of frailty in a study population and similarly the diagnostic performance of the G8 in predicting potential frailty. Moreover, the scales and instruments used to assess the different domains differed as well. This also means that a formal meta-analysis could not be performed. Importantly, not all studies evaluating the association of the G8 with clinical outcome measures reported the direction or size of the effect nor was it always clear how outcome measures were defined. Furthermore, many studies only showed data for included patients receiving the treatment in question but did not report specifically on the preceding patient selection. Thus, it was not possible to assess generalizability of study results. Despite these limitations, this systematic review provides a valuable overview of all currently available evidence on the use of the G8 and shows that it may be used to aid physicians' treatment decision making in older patients with cancer by identifying potentially frail patients and those who are at increased risk for adverse clinical outcomes.

The high sensitivity of the G8 compared to a more elaborate GA is in line with results from two earlier systematic reviews that compared the diagnostic performance of the various available screening tools in older patients with cancer [13,14]. Both concluded that, compared to other frailty screening tools, the G8 was among the most sensitive and most frequently studied. Our review included fifteen studies that were published after these prior reviews, but median sensitivity and specificity of the G8 were not very different to what those reviewers found: sensitivity of 87% [13] and 86% [14], and specificity of 61% [13] and 60% [14] respectively.

It can be argued that the performance of the G8 compared to GA is not perfect; specificity and negative predictive value of the G8 were moderate to poor, presumably because of the high prevalence of frailty in older patients with cancer (on average 73% of the patients were frail on GA). To improve the diagnostic performance of the G8 and to rationalise the use of medical resources, several studies evaluated a modified version of the G8 [44,53,68]. These modified versions had higher specificity than the original G8 without compromising on sensitivity. However, only one study evaluated the prognostic value of the modified G8 for survival and studies on other important outcome measures are currently lacking [45].

To our knowledge, we are the first to provide a comprehensive systematic review on the association of the G8 with different clinical outcomes. It is remarkable that, even in a wide variety of tumor types, treatments and settings, a screening tool as short and easy to administer as the G8 is associated with several of these outcomes. This is a major strength of this screening tool, and our review confirms this association. While three out of four studies on patient-centred outcomes found an independent association between functional decline or QoL and the G8, more studies are needed to strengthen this finding. Furthermore, the association of the G8 with health care utilisation and treatment completion should also be more thoroughly investigated. However, given its shortness, it seems a lot to expect the G8 to refine prognosis, goal of care discussions, tailored treatment and advanced care planning. Therefore, the G8 cannot replace full GA or clinical judgement but is useful in a two-step approach followed by GA for potentially frail patients.

In conclusion, this systematic review shows that the G8 screening tool has been widely studied in older patients with cancer. The G8 may help physicians make informed treatment decisions by identifying patients who require full GA and because a low G8 score is associated with survival and treatment-related complications. Future prospective studies should evaluate whether the G8 predicts course of treatment and patient-centred outcomes.

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Conflicts of Interest

P. Soubeyran received speaker honoraria for conferences from Celgene and Teva Pharmaceuticals, he is an advisory board member of BMS, Teva, Sandoz and Pfizer Pharmaceuticals and he received invitations to meetings from Celgene, Teva and Astra-Zeneca.
All remaining authors have declared no conflicts of interest.

Contribution

IvW: literature search, study design, data collection, data analysis, writing, figures.
ES: literature search, study design, data collection, data analysis, writing, approval of final document.
MH: study design, writing, approval of final document.
LvH: writing, approval of final document.
ME: writing, approval of final document.
PS: writing, approval of final document.
CB: writing, approval of final document.

Appendix A. Quality Assessment, Based on the Newcastle-Ottowa Scale

Selection	1. Representativeness of the exposed cohort	+ truly representative of the average older cancer patient + somewhat representative of the average older cancer patient − selected group of users ? no description of the derivation of the cohort
	2. Ascertainment of exposure	+ G8 taken in all patients − G8 not taken in all patients (> 10% missings)
	3. Demonstration that outcomes of interest (comparison G8 with GA and/or clinical outcomes) were not present at start of study	+ yes − no
Outcome	1. Assessment of outcome (comparison G8 with GA and/or clinical outcomes)	+ clear description of method of assessment[a] − unclear description of method of assessment ? no description
	2. Was follow-up long enough for outcome to occur? Comparison G8 with GA: always Chemotherapy toxicity: end of treatment Postoperative morbidity: 30 days	+ yes − no ? not mentioned

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Treatment completion: end of treatment
Survival: 6 months[a]
Health care utilisation: 30 days
Physical functioning/quality of life: 3 months
3. Adequacy of follow-up of cohorts[b]

+ complete follow-up: all subjects accounted for
+ subjects lost to follow-up unlikely to introduce bias: loss to follow-up <10%
− follow-up rate <90%
? no statement

GA = geriatric assessment.
[a] It was judged that survival data with a follow-up time shorter than 6 months, excluding treatment-related mortality, were not relevant to clinical practice.
[b] Comparison G8 with GA as outcome of interest: clearly defined which domains of GA were evaluated and/or which questionnaire were used.

Appendix B. Quality Assessment of Included Studies

Publication	Selection		Outcome			
Author	Representativeness of exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Agemi [19]	+	+	+	+	?	?
Aparicio [20]	+	+	+	+	+	+
Aydin [21]	+	+	+	+	?	?
Baitar [22,23]	+	+	+	+	+	+
Bellera [9]	+	+	+	+	+	+
Bellera [27]	+	+	+	+	+	–
Bonomo [24]	+	+	+	+	+	?
Bononi [25]	+	+	+	+	?	?
Boulahssass [26]	+	+	+	+	+	+
Cvetkovic [28]	+	+	+	+	?	?
Decoster [29]	+	+	+	+	+	–
Decoster [30]	+	+	+	+	?	?
Denewet [31]	+	+	+	+	+	?
Dimopoulos [32]	+	+	+	+	?	?
Dubruille [34]	+	+	+	+	+	+
Dubruille [33]	+	+	+	+	+	?
Fagard [35]	+	+	+	+	+	+
Gangopadhyay [36]	+	+	+	+	?	?
Hamaker [37]	+	+	+	+	+	?
Hentschel [38]	+	–	+	+	+	+
Holmes [39]	+	+	+	+	+	+
Kaibori [40]	+	+	+	+	+	+
Kenig [41]	+	+	+	+	+	+
Kenis [12,42]	+	+	+	+	+	–
Kim [43]	+	+	+	+	+	+
Martinez-Tapia [44,45]	+	+	+	+	+	+
Matsushita [46]	+	+	+	+	+	?
Middelburg [47]	+	+	+	+	?	+
Molina-Garrido [48]	+	+	+	+	+	?
Neve [49]	+	+	+	+	?	?
Ogawa [50]	+	+	+	–	+	+
Osborne [51]	+	+	+	+	+	+
Osorio [52]	+	+	+	+	?	?
Pamoukdjian [53]	+	+	+	+	+	+
Pottel [54]	+	+	+	+	+	–
Pottel [55]	+	+	+	+	+	+
Runzer-Colmenares [56]	+	+	+	+	+	?
Schulkes [57]	+	+	+	+	+	?
Silvestri [58,59]	+	+	+	+	?	?
Smets [60]	+	+	+	+	+	?
Soubeyran [11,68]	+	+	+	+	+	+
Souwer [61]	+	+	+	+	+	+
Stauder [62]	+	+	+	+	?	?
Stokoe [18]	+	–	+	+	?	?
Takahashi [63]	+	+	+	+	?	+
Velghe [64]	+	+	+	+	+	+
Von Saint-George [65]	+	+	+	+	+	+
Wildiers [66]	+	+	+	+	+	+

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(*continued*)

Publication	Selection		Outcome			
Author	Representativeness of exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Yokom [67]	+	+	+	+	+	+

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