Review

The Pandora's Box of Frailty Assessments: Which Is the Best for Clinical Purposes in TAVI Patients? A Critical Review

Omar Baritello [1,2] , Annett Salzwedel [2] , Simon H. Sündermann [3,4,5], Josef Niebauer [6] and Heinz Völler [2,*]

1   Faculty of Health Sciences Brandenburg, Department of Rehabilitation Medicine, University of Potsdam, 14469 Brandenburg, Germany; omar.baritello@fgw-brandenburg.de
2   Research Group Molecular and Clinical Life Science of Metabolic Diseases, Faculty of Health Sciences Brandenburg, University of Potsdam, 14476 Potsdam, Germany; annett.salzwedel@fgw-brandenburg.de
3   Department of Cardiovascular Surgery, Charité—Universitätsmedizin Berlin, 10117 Berlin, Germany; simon.suendermann@charite.de
4   Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, 13353 Berlin, Germany
5   DZHK (German Center for Cardiovascular Research), Partner Site Berlin, 13353 Berlin, Germany
6   University Institute of Sports Medicine, Prevention and Rehabilitation and Research Institute of Molecular Sports Medicine and Rehabilitation, Paracelsus Medical University, A-5020 Salzburg, Austria; j.niebauer@salk.at
*   Correspondence: heinz.voeller@fgw-brandenburg.de; Tel.: +49-(03)-319774061

Abstract: Frailty assessment is recommended before elective transcatheter aortic valve implantation (TAVI) to determine post-interventional prognosis. Several studies have investigated frailty in TAVI-patients using numerous assessments; however, it remains unclear which is the most appropriate tool for clinical practice. Therefore, we evaluate which frailty assessment is mainly used and meaningful for ≤30-day and ≥1-year prognosis in TAVI patients. Randomized controlled or observational studies (prospective/retrospective) investigating all-cause mortality in older (≥70 years) TAVI patients were identified (PubMed; May 2020). In total, 79 studies investigating frailty with 49 different assessments were included. As single markers of frailty, mostly gait speed (23 studies) and serum albumin (16 studies) were used. Higher risk of 1-year mortality was predicted by slower gait speed (highest Hazard Ratios (HR): 14.71; 95% confidence interval (CI) 6.50–33.30) and lower serum albumin level (highest HR: 3.12; 95% CI 1.80–5.42). Composite indices (five items; seven studies) were associated with 30-day (highest Odds Ratio (OR): 15.30; 95% CI 2.71–86.10) and 1-year mortality (highest OR: 2.75; 95% CI 1.55–4.87). In conclusion, single markers of frailty, in particular gait speed, were widely used to predict 1-year mortality. Composite indices were appropriate, as well as a comprehensive assessment of frailty.

Keywords: frailty tool; TAVI; older patients; elderly; cardiology; mortality

1. Introduction

The proportion of older people (>65 years) is predicted to constantly increase in Europe and reach around 30% of the total population by 2060 [1]. These significant changes to society's structure must be taken into account by the healthcare system. In fact, it is known that aging is associated with several geriatric syndromes, such as cognition impairments, malnutrition, sarcopenia and frailty [2]. The clinical condition of frailty especially has gained international attention in the last decade [3].

Frailty is a complex clinical condition [4], where physiological deteriorations related to the aging process are accentuated and vulnerability to stressors increases [5,6]. According to the definition of physical frailty, malnutrition, unintentional weight loss, decreased strength and endurance as well as impaired physiological functions characterize the frail population [4,7]. Frail patients have a higher risk of death and compromised independence in activities of daily living [8]. Therefore, in older patients with cardiovascular disease

(CVD) undergoing elective transcatheter aortic valve implantation (TAVI), frailty should be evaluated [9].

Older TAVI patients are characterized by decreased physiological functionality (e.g., reduced gait speed), multiple comorbidities and malnutrition, with the prevalence of frailty found to be up to 63% in this population [5,6,10]. Pre-interventional assessment of frailty should be considered alongside common risk scores (e.g., STS score, EuroSCORE) for a better appreciation of the post-interventional prognosis [11]. In the last decade, several investigations have assessed the association of pre-interventional frailty status as an independent predictor of post-interventional mortality. However, due to the lack of consensus on the definition of frailty (e.g., physical frailty, multidimensional) and its measurement (e.g., single markers, composite indices, categorical scales, claims data), the evidence is contradictory [10,12–14] and identification of the most appropriate assessment for clinical practice remains unclear.

Therefore, the aim of our review was to evaluate which frailty assessment is the most commonly used and meaningful for the prediction of short-term, intermediate-term and long-term all-cause mortality in older TAVI patients.

2. Materials and Methods

The electronic database PubMed (May 2020) was systematically searched. Study inclusion criteria were the following: randomized controlled trials (RCTs) or observational studies (prospective and retrospective, respectively) without time restrictions that quantitatively assessed frailty pre-interventionally in older ($\geq$70 years) patients who underwent elective TAVI. The outcome of interest was the association of frailty with all-cause mortality. Identification, screening, eligibility and inclusion processes were performed according to PRISMA guidelines. The included articles were reviewed by two independent researchers. The overall risk of bias in each study was evaluated using the Quality in Prognosis Studies (QUIPS) [15] and the Newcastle-Ottawa Scale (NOS) [16] tools. According to the QUIPS, we classified studies with four or five low-risk domains as having a low risk of bias overall, studies with two or more high-risk domains as having a high risk for bias overall and the remaining studies as showing a moderate risk of bias overall. For the NOS, the sum of positive adjudications was calculated. Studies were then divided into 3 categories: single markers of frailty, multidimensional frailty scales and composite indices. The single markers category comprised studies that assessed only one component of frailty, like physical function, activities of daily living (ADL), blood parameters, body composition, nutritional status and cognition. The multidimensional frailty scales category comprised studies that rated frailty using categorical scales based on clinician judgment. The third category of composite indices encompassed studies that assessed frailty based on an index resulting from the measurement of several frailty components. Furthermore, studies were stratified into short-term ($\leq$30-day), intermediate (>30-day to <1-year) and long-term ($\geq$1-year) mortality.

3. Results

In total, n = 79 studies were included for full-text review (Figure 1) and n = 49 different frailty assessments were identified. All studies were of observational design and most of the findings referred to short- and long-term mortality. The majority of the studies investigated frailty using single markers of frailty, such as physical functionality (e.g., gait speed, handgrip strength), blood parameters (serum albumin), impairments in activities of daily living (ADL), nutritional status/risk (Mini-Nutritional Assessment), cognitive impairments (Mini-Mental State Examination) and body composition (Psoas muscle area index), as shown in Table 1. Several studies used composite indices or multidimensional scales based on clinical judgment (Table 2), and only a few studies defined frailty status based on claimed medical records and comorbidities (Supplementary Material Table S1).
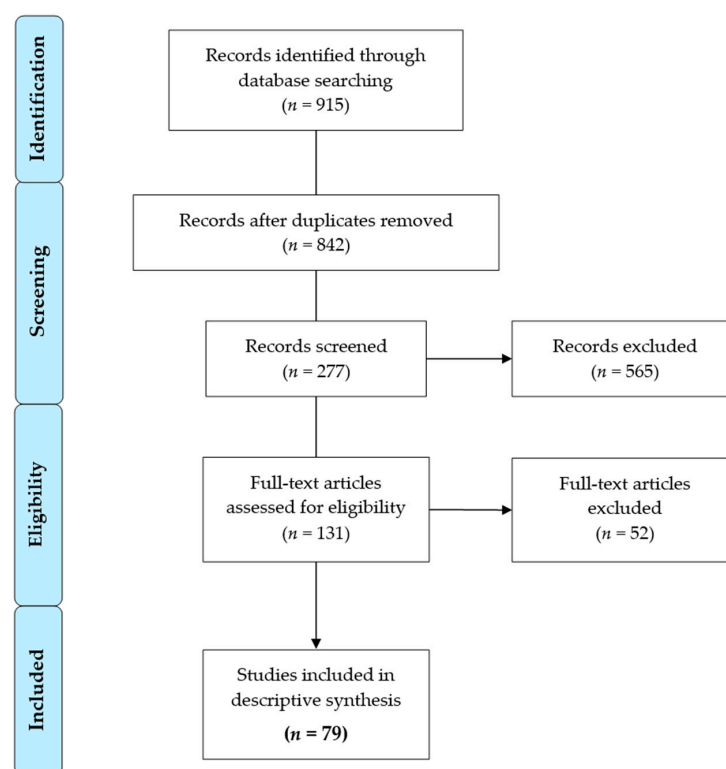
Figure 1. Flow diagram displaying study screening, eligibility and inclusion.

Table 1. Summary of the most-used single markers of frailty found to be predictive or not predictive (number of studies and (total patients)) of mortality risk over the short term (≤30 days), intermediate term (>30 days to <1 year) and long term (≥1 year).

Number of Studies and Assessment Type (Frailty Cut-Off)		Time Frame of Mortality Assesment	Predictive of Mortality Risk	
			Predictive	Not Predictive
Single Markers of Frailty				
23	Gait Speed (5-mWT; ≥6 s/6 MWT; unable/slow walker)	Short-term	4 (44,773) [17–20]	6 (27,581) [21,31–35]
		Intermediate	-	1 (232) [36]
		Long-term	11 (41,376) [19,21–30]	5 (5206) [18,34,37–39]
16	Serum albumin (≤3.5 g/dL)	Short-term	5 (42,330) [18,19,21,34,40]	1 (431) [35]
		Long-term	13 (48,844) [19,21–23,34,35,39–46]	2 (605) [18,38]
15	ADL (Katz-index; ≥1 impaired activity)	Short-term	4 (9624) [18,47–49]	3 (1023) [21,51,52]
		Intermediate	2 (2740) [48,50]	-
		Long-term	6 (1405) [18,23–26,47]	8 (5195) [21,38,39,48,50–53]
11	Handgrip strength (BMI normalized/sex stratified)	Short-term	-	5 (5974) [18,21,32,34,51]
		Long-term	5 (1105) [18,23–26]	4 (4588) [21,34,38,39]
9	IADL (Lawton-index; ≥1 impaired activity)	Short-term	-	3 (402) [9,33,51]
		Intermediate	1 (116) [50]	2 (269) [14,54]
		Long-term	2 (329) [50,51]	4 (1285) [9,12,22,55]
9	MMSE (score ≥ 27/30)	Short-term	1 (100) [9]	2 (302) [33,51]
		Intermediate	1 (119) [14]	1 (150) [54]
		Long-term	2 (430) [9,55]	4 (2610) [12,22,40,51]
9	PMAi (CT-scan; tertile BSA normalized/sex stratified)	Short-term	1 (1076) [56]	1 (583) [57]
		Intermediate	1 (232) [36]	-
		Long-term	6 (2804) [25,45,56–59]	2 (1883) [44,60]
7	TUG (≥20 s)	Short-term	1 (100) [9]	2 (302) [33,51]
		Intermediate	1 (119) [14]	1 (150) [54]
		Long-term	3 (774) [9,12,55]	1 (213) [51]

5-mWT: 5-m Walk Test; 6MWT: 6-m Walk Test; ADL: Activities of Daily Living; IADL: Instrumental-ADL; MMSE: Mini-Mental State Examination; PMAi: Psoas Muscle Area index; BSA: Body Surface Area; TUG: Timed Up-and-Go test.

Table 2. Summary of the most-used multidimensional frailty scales and composite indices found to be predictive or not predictive (number of studies and (total patients)) of mortality risk over the short term (≤30 days), intermediate term (>30 days to <1 year) and long term (≥1 year).

Number of Studies and Assessment Type (Frailty Cut-Off)		Time Frame of Mortality Assessment	Predictive of Mortality Risk	
			Predictive	Not Predictive
Multidimensional Frailty Scales				
9	CFS (score ≥ 5/9)	Short-term	2 (2757) [32,40]	1 (1020) [13]
		Long-term	4 (3557) [13,40,61,62]	4 (2099) [37,63–65]
6	CSHA (score ≥ 5/7)	Short-term	1 (6339) [49]	2 (2936) [48,52]
		Intermediate	-	1 (2624) [48]
		Long-term	4 (3026) [24–26,48]	1 (312) [52]
Composite indices				
7	4 items (score ≥ 3/4; gait speed, serum albumin, handgrip strength, ADL)	Short-term	3 (1254) [13,39,66]	2 (533) [23,68]
		Long-term	6 (1957) [13,23,38,39,66,67]	-
6	5 items (score ≥ 3/5; gait speed, handgrip strength, exhaustion, low physical activity, unintentional weight loss)	Short-term	3 (2062) [13,21,69]	-
		Intermediate	1 (137) [70]	-
		Long-term	5 (3014) [13,21,69,71,72]	-
5	EFT (score ≥ 3/5; chair rise test, MMSE, serum albumin, hemoglobin)	Short-term	3 (2502) [13,73,74]	-
		Long-term	4 (3257) [13,37,73,74]	1 (142) [75]
5	Bern scale (score ≥ 3/7; MMSE, MNA, TUG, BADL, IADL, pre-clinical mobility disability)	Short-term	2 (1120) [9,13]	-
		Intermediate	1 (119) [14]	-
		Long-term	3 (1450) [9,13,55]	1 (344) [12]

CFS: Clinical Frailty Scale; CSHA: Canadian Study of Health Aging; ADL: Activities of Daily Living; IADL: Instrumental-ADL; MMSE: Mini-Mental State Examination; BADL: Basic-ADL; TUG: Timed Up-and-Go test; MNA: Mini-Nutritional Assessment; EFT: Elderly Frailty Toolset.

In Supplementary Material Table S1 displays the characteristics of all included studies and the assessment of bias. This is followed by a summary of the results of the most commonly used assessments (Table 3).

Table 3. Summary of the outcomes (multivariate analysis) of the most-used assessments for all-cause mortality.

Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	Intermediate	Long-Term
Gait speed: 5-mWT or 6MWT				
appwnd [17]	≥6 s	OR 3.17 (95% CI 1.17–8.59)		
Chauhan et al., 2016 [23]				HR 2.62 (95% CI 1.25–5.52)
Dziewierz et al., 2017 [26]		HR 14.71 (95% CI 6.50–33.30)		
Forcillo et al., 2017 [18]		predictive		OR 0.45; *p* = 0.06
Hermiller et al., 2016 [34]		not predictive		HR 1.42 (95% CI 1.06–1.91)
Kiani et al., 2020 [19]		dichotomous ≤ 0.83: HR 1.21 (95% CI 1.00–1.47)		dichotomous ≤ 0.83; HR 1.36 (95% CI 1.23–1.50)
Kleczynski et al., 2017 [24]				linear: HR 2.83 (95% CI 2.01–3.98) dichotomous: HR 124.12 (95% CI 21.92–702.72)

Table 3. *Cont.*

Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	Intermediate	Long-Term
Patel et al., 2019 [35]		OR 2.21 (95% CI 0.63–7.74)		
Sathananthan et al., 2019 [37]				OR 0.78 (95% CI 0.35–1.72)
A.J. Altisent et al., 2017 [28]	unable/slow/fast			slow walker: HR 2.30 (95% CI 1.35–3.93)
Green et al., 2013 [27]				unable: HR 1.85 (95% CI 1.26–2.72)
Alfredsson et al., 2016 [20]		per 0.2 m/s decrease: OR 1.16 (95% CI 1.06–1.28)		
Steinvil et al., 2018 [21]		dichotomous: OR 1.74 (95% CI 0.36–8.50)		dichotomous: OR 2.34 (95% CI 1.03–5.32)
Kano et al., 2017 [30]				dichotomous: OR 2.01 (95% CI 1.20–3.38)
van der Wulp et al., 2020 [22]	≤0.8 m/s			HR 2.5 (95% CI 1.4–4.5)
Green et al., 2015 [38]				per unit decrease: HR 1.37 (95% CI 0.53–3.45)
Green et al., 2012 [39]				each quartile: HR 1.19 (95% CI 0.82–1.66)
Assmann et al., 2016 [33]	0.75 m/s	HR 0.11 (95% CI 0.10–1.43)		
Saji et al., 2016 [36]	0.5 m/s		dichotomous: not predictive; $p = 0.174$	
Dvir et al., 2013 [29]	<50 m			<50m: HR 1.69 (95% CI 1.28–2.47)
Arnold te al. 2018 [31]	unable/quartile	linear: OR 0.95 (95% CI 0.89–1.02); dichotomous: OR 1.27 (95% CI 1.02–1.58)		
Shimura et al., 2017 [32]	n.s.	not predictive		
Serum albumin				
Bogdan et al., 2016 [42]	≤3.5 g/dL			baseline low level: HR 2.02 (95% CI 1.04–3.91)
Berkovitch et al., 2020 [43]				low level: HR 1.92 (95% CI 1.09–3.38)
Chauhan et al., 2016 [23]				HR 3.12 (95% CI 1.80–5.42)
Green et al., 2015 [38]				per unit decrease: HR 1.25 (95% CI 0.88–1.79)
Green et al., 2012 [39]				HR 1.51 (95% CI 1.03–2.21)
Kiani et al., 2020 [19]		dichotomous: HR 1.29 (95% CI 1.12–1.48)		dichotomous: HR 1.50 (95% CI 1.40–1.60)
Michel et al., 2019 [44]				dicohtomous: HR 2.10 (95% CI 1.53–2.87)
Patel et al., 2019 [35]		not predictive		
Shimura et al., 2018 [40]		HR 2.36 (95% CI 1.64–3.40)		not predictive
Steinvil et al., 2018 [21]		dichotomous: OR 8.21 (95% CI 1.04–64.70)		dichotomous: OR 2.21 (95% CI 1.12–4.37)
van der Wulp et al., 2020 [22]				HR 2.30 (95% CI 1.30–4.00)
Hermiller et al., 2016 [34]	≤3.3 g/dL	dichotomous: HR 1.60 (95% CI 1.04–2.47)		dichotomous: HR 1.40 (95% CI 1.04–1.91)
Forcillo et al., 2017 [18]	≤3.4 g/dL	per 1g/dL decrease: OR 0.26; $p = 0.02$		not predictive; OR 0.53; $p = 0.07$
Grossman et al., 2017 [41]	≤4.0 g/dL			per 0.5 g/dL decrease: HR 3.03 (95% CI 1.66–5.26)

Table 3. *Cont.*

Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	**Intermediate**	**Long-Term**
Krishnan et al., 2019 [45]	n.s.			higher level: HR 0.30 (95% CI 0.20–0.50)
ADL—Katz-index				
Cockburn et al., 2015 [52]	score < 6/6	OR 1.07 (95% CI 0.64–1.77)		HR 0.86 (95% CI 0.71–1.05)
Dziewierz et al., 2017 [26]				dichotomous; HR 13.92 (95% CI 6.29–30.79)
Green et al., 2015 [38]				HR 1.59 (95% CI 0.93–2.70)
Green et al., 2012 [39]				HR: 2.13 (95% CI 0.97–4.71)
Kleczynski et al., 2017 [24]				per point decrease: HR 6.06 (95% CI 3.15–11.64) dichotomous: HR 20.06 (95% CI 6.93–58.02)
Kleczynski et al., 2018 [25]				predictive
Martin et al., 2017 [49]		per point drop: OR 1.27 (95% CI 1.11–1.44)		
Martin et al., 2018 [48]		OR 2.10 (95% CI 1.39–3.15)	HR 1.74 (95% CI 1.19–2.55)	HR 1.23 (95% CI 0.86–1.75)
Puls et al., 2014 [47]		HR 3.05 (95% CI 1.40–5.70)		higher score: HR 2.50 (95% CI 1.60–3.90)
Forcillo et al., 2017 [18]	score ≤ 4/6	not predictive		OR 0.80; *p* = 0.04
Steinvil et al., 2018 [21]		OR 2.43 (95% CI 0.58–10.20)		OR 1.43 (95% CI 0.59–3.45)
Goudzwaard et al., 2018 [51]		not predictive		linear: HR 1.50 (95% CI 1.21–1.90) dichotomous: HR 1.80 (95% CI 0.85–3.70)
Bureau et al., 2017 [50]	score < 5/6		predictive	not predictive
Chauhan et al., 2016 [23]				HR 2.45 (95% CI 1.42–4.22)
Szekely et al., 2019 [53]	n.s.			not predictive
Handgrip strength				
Chauhan et al., 2016 [23]	BMI/sex			HR 3.31 (95% CI 1.01–10.85)
Forcillo et al., 2017 [18]		not predictive		predictive
Green et al., 2015 [38]				HR 1.02 (95% CI 0.99–1.05)
Green et al., 2012 [39]				HR 1.18 (95% CI 0.84–1.66)
Goudzwaard et al., 2018 [51]		not predictive		
Hermiller et al., 2016 [34]		not predictive		not predictive
Steinvil et al., 2018 [21]		dichotomous: OR 2.24 (95% CI 0.28–17.80)		dichotomous: OR 1.63 (95% CI 0.66–4.06)
Dziewierz et al., 2017 [26]	weak/mild/strong			HR 28.84 (95% CI 10.54–78.87)
Kleczynski et al., 2017 [24]				HR 37.93 (95% CI 10.63–135.35)
Kleczynski et al., 2018 [25]				predictive
Shimura et al., 2017 [32]	n.s.	not predictive		

Table 3. *Cont.*

Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	**Intermediate**	**Long-Term**
IADL—Lawton index				
Assmann et al., 2016 [33]	score < 8/8	HR 0.92 (95% CI 0.71–1.20)		
Boureau et al., 2017 [54]			not predictive	
Bureau et al., 2017 [50]			predictive (*p* = 0.065)	predictive (*p* = 0.0061)
Eichler et al., 2017 [12]				not predictive
Goudzwaard et al., 2018 [51]		not predictive		linear: HR 1.20 (95% CI 1.07–1.33) dichotomous: HR 2.30 (95% CI 1.06–4.90)
Schoenenberger et al., 2018 [55]				HR 1.23 (95% CI 0.67–2.28)
Schoenenberger et al., 2012 [14]			linear: OR 1.46 (95% CI 1.13–1.89) dichotom: OR 2.19 (95% CI 0.91–5.27)	
Stortecky et al., 2012 [9]		linear: OR 1.39 (95% CI 0.91–2.11) dichotom: OR 1.19 (95% CI 0.27–5.31)		linear: OR 1.25 (95% CI 0.92–1.70) dichotomous: OR 1.52 (95% CI 0.92–9.83)
van der Wulp et al., 2020 [22]				HR 1.50 (95% CI 0.90–2.30)
Mini-Mental State Examination (MMSE)				
Assmann et al., 2016 [33]	score < 27/30	HR 0.98 (95% CI 0.77–1.25)		
Boureau et al., 2017 [54]			HR 1.02 (95% CI 0.82–1.26)	
Eichler et al., 2017 [12] Goudzwaard et al., 2018 [51] Schoenenberger et al., 2018 [55]		not predictive		not predictive dichotomous: HR 1.60 (95% CI 0.76–3.22) dichotomous: HR 2.35 (95% CI 1.33–4.14)
Schoenenberger et al., 2012 [14]			linear: OR 2.64 (95% CI 1.55–4.50) dichotomous: OR 3.18 (95% CI 1.38–7.29)	
Shimura et al., 2018 [40]				not predictive
Stortecky et al., 2012 [9]		linear: OR 2.85 (95% CI 1.35–6.17) dichotomous: OR 7.62 (95% CI 1.44–40.19)		linear: OR 2.72 (95% CI 1.40–5.31) dichotomous: OR 2.98 (95% CI 1.07–8.31)
van der Wulp et al., 2020 [22]				not predictive
Psoas muscle area index (PMAi)				
Mamane et al., 2015 [58]	tertile/sex			female: HR 0.88 (95% CI 0.78–0.99)
Kleczynski et al., 2018 [25]				predictive
Kofler et al., 2018 [56]		L3: OR 0.082 (95% CI 0.011–0.589) L4: OR 0.049 (95% CI 0.005–0.536)		L3: OR 0.200 (95% CI 0.083–0.482) L4: OR 0.083 (95% CI 0.029–0.235)
Saji et al., 2016 [36]			HR 1.53 (95% CI 1.06–2.21)	

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Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	Intermediate	Long-Term
van Mourik et al., 2018 [57]		HR 0.32 (95% CI 0.05–1.91)		female mid-PMA: HR 0.14 (95% CI 0.05–0.45) female high PMA: HR 0.38 (95% CI 0.16–0.99)
Garg et al., 2016 [60]	2 groups (cut-off/sex)			not predictive
Krishnan et al., 2019 [45]				HR 2.50 (95% CI 1.10–4.60)
Foldyna et al., 2018 [59]	quartile/sex			HR 1.90 (95% CI 1.35–2.68)
Michel et al., 2019 [44]				not predictive
Timed Up-and-Go test (TUG)				
Boureau et al., 2017 [54]	≥20 sec		dichotomous: OR 0.39 (95%CI 0.11–1.41)	
Eichler et al., 2017 [12]				dichotomous: OR 5.12 (95% CI 1.64–16.01)
Goudzwaard et al., 2018 [51]		not predictive		linear: HR 1.10 (95% CI 1.02–1.09) dichotomous: HR 1.80 (95% CI 0.77–4.18)
Schoenenberger et al., 2018 [55]				dichotomous: HR 3.41 (95% CI 1.95–5.97)
Schoenenberger et al., 2012 [14]			linear: OR 1.64 (95% CI 1.26–2.12) dichotom: OR 4.23 (95% CI 1.83–9.77)	
Stortecky et al., 2012 [9]		linear: OR 1.83 (95% CI 1.10–3.05) dichotomous: OR 13.77 (95% CI 1.62–111.01)		linear: OR 1.74 (95% CI 1.24–2.45) dichotomous: OR 6.65 (95% CI 2.15–20.52)
Assmann et al., 2016 [33]	≤12.5 sec	HR 1.04 (95% CI 0.94-1.16)		
Clinical Frailty Scale (CFS)				
Miura et al., 2017 [63]	score ≥ 4/9			HR 1.84 (95% CI 0.45–7.55)
Yokoyama et al., 2019 [64]				HR 1.03 (95% CI 0.60–1.86)
Afilalo et al., 2017 [13]	score ≥ 5/9	dichotomous: OR 1.87 (95% CI 0.99–3.53)		dichotomous: OR 2.40 (95% CI 1.63–3.52)
Sathananthan et al., 2019 [37]				not predictive
Seiffert et al., 2014 [62]	score ≥ 6/9			per SD increase: HR 1.31 (95% CI 1.13–1.52)
Shimura et al., 2017 [32]	5 classes			per class increment: HR 1.28 (95% CI 1.10–1.49)
Honda et al., 2019 [61]	n.s.	HR 1.42 (95% CI 1.04–1.95)		HR 1.44 (95% CI 1.04–1.99)
Shimura et al., 2018 [40]				per point increase: HR 1.17 (95% CI 1.01–1.35)

Table 3. *Cont.*

Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	Intermediate	Long-Term
Canadian Study of Health Aging scale (CSHA)				
Martin et al., 2018 [48]	score ≥ 5/7	OR 1.46 (95% CI 0.96–2.23)	HR 1.37 (95% CI 0.94–2.01)	HR 1.61 (95% CI 1.14–2.29)
Dziewierz et al., 2017 [26]				score > 5: HR 39.10 (95% CI 15.85–96.46)
Kleczynski et al., 2018 [25]	4 classes			predictive
Kleczynski et al., 2017 [24]				per point increase: HR 3.82 (95% CI 2.46–5.94) dichotomous: HR 64.65 (95% CI 17.35–240.94)
Cockburn et al., 2015 [52]	n.s.	OR 0.99 (95% CI 0.63–1.57)		not predictive
Martin et al., 2017 [49]		not predictive		
4 items composite index				
Afilalo et al., 2017 [13]	score ≥ 3/4	dichotomous: OR 2.65 (95% CI 1.28–5.49)		dichotomous: OR 3.04 (95% CI 1.98–4.66)
Huded et al., 2016 [68]		not predictive		
Okoh et al., 2017 [66]		higher score: HR 1.65 (95% CI 1.01–2.66)		score 4/4: HR 1.84 (95% CI 1.06–3.17)
Okoh et al., 2019 [67]				HR 1.84 (95% CI 1.23–2.69)
Green et al., 2015 [38]	score ≥ 5–6/12			linear: HR 1.12 (95% CI 1.02–1.22) dichotomous: HR 2.18 (95% CI 1.27–3.75)
Green et al., 2012 [39]		OR 2.20 (95% CI 1.02–4.60)		linear: HR 1.15 (95% CI 1.02–1.30) dichotomous: predictive tertile: HR 1.71 (95% CI 1.01–2.89)
Chauhan et al., 2016 [23]	n.s.	not predictive		score ≤ 2: HR 2.00 (95% CI 0.85–4.71) score 3: HR 3.05 (95% CI 1.24–7.46) score 4: HR 8.56 (95% CI 3.38–21.67)
5 items composite index				
Afilalo et al., 2017 [13]	score ≥ 3/5	dichotomous: OR 1.45 (95% CI 0.77–2.72)		dichotomous: OR 1.63 (95% CI 1.12–2.37)
Ewe et al., 2010 [71]				HR 4.20 (95% CI 2.00–8.84)
Rogers et al., 2018 [69]		dichotomous: OR 5.06 (95% CI 1.36–18.80)		dichotomous: OR 2.75 (95% CI 1.55–4.87)
Shi et al., 2018 [70]			OR 2.20 (95% CI 0.20–8.00)	
Steinvil et al., 2018 [21]		higher score: OR 15.30 (95% CI 2.71–86.10)		score ≥3: OR 2.23 (95% CI 1.14–4.34)
Abramowitz et al., 2016 [72]	n.s.			HR 2.04 (95% CI 1.31–3.20)

Table 3. *Cont.*

Assessment Type and Authors	Frailty Cut-Off (n.s.: Not Specified)	Mortality		
		Short-Term	Intermediate	Long-Term
Elderly Frailty Toolset (EFT)				
Afilalo et al., 2017 [13]	score ≥ 3/5	dichotomous: OR 3.29 (95% CI 1.73–6.26)		dichotomous: OR 3.72 (95% CI 2.54–5.45)
Drudi et al., 2018 [73]		dichotomous: OR 3.50 (95% CI 1.74–7.07)		dichotomous: OR 3.33 (95% CI 2.21–5.04)
Pighi et al., 2019 [74]		per point increase: OR 1.27 (95% CI 1.07–1.50)		dichotomous: OR 1.83 (95% CI 1.33–2.50)
Sathananthan et al., 2019 [37]				per point increase: OR 1.72 (95% CI 1.39–2.14)
Skaar et al., 2018 [75]				HR 1.36 (95% CI 0.87–2.21)
Bern scale				
Afilalo et al., 2017 [13]	score ≥ 3/7	dichotomous: OR 3.29 (95% CI 1.53–7.07)		dichotomous: OR 2.57 (95% CI 1.69–3.91)
Eichler et al., 2017 [12]				not predictive
Schoenenberger et al., 2018 [55]				per IQR increase of 3 points: HR 3.29 (95% CI 1.98–3.91)
Schoenenberger et al., 2012 [14]			linear: OR 1.73 (95% CI 1.36–2.20) dichotomous: OR 1.69 (95% CI 1.32–2.16)	
Stortecky et al., 2012 [9]		per point increase; OR 2.18 (95% CI 1.32–3.61) dichotomous: OR 8.33 (95% CI 0.99–70.48)		per point increase: OR 1.80 (95% CI 1.31–2.47) dichotomous: OR 3.68 (95% CI 1.21–11.19)

3.1. Single Markers of Frailty

Gait speed (Table 1) was the most commonly used single marker of frailty [17–39], with short-term mortality assessed in *n* = 4 prospective [17,20,32,33] (9474 patients) and *n* = 6 retrospective [18,19,21,31,34,35] (62,880 patients) investigations presenting conflicting information. Kiani et al. [19] showed in their retrospective analysis (36,242 participants) that slower gait speed or being unable to walk were predictive of death rate at 30 days. Similarly, Afilalo et al. [17] and Alfredsson et al. [20] found a higher risk of mortality in participants for slow walking speed. However, six authors [21,31–35] stated that slow gait speed was not associated with mortality. Long-term mortality was assessed in *n* = 7 prospective [22,24–26,28,37,39] (2360 patients) and *n* = 9 retrospective [18,19,21,23,27,29,30,34,38] (44,222 patients) investigations and was associated with results of 5-mWT [18,19,22–30].

Serum albumin level was the second most commonly used single marker of frailty and was associated with short-term mortality in *n* = 6 retrospective studies [18,19,21,34,35,40]. Long-term mortality was investigated in *n* = 4 prospective [22,39,43,46] (3845 patients) and *n* = 10 retrospective [18,19,21,23,34,38,41,42,44,45] (44,062 patients) studies and the majority of them found an inverse association between levels of serum albumin and risk of death at 1 year [23,34].

Activities of Daily Living (ADL) were evaluated in *n* = 3 prospective [47,51,52] (825 patients) and *n* = 4 retrospective [18,21,48,49] (9822 patients) studies with conflicting results. Two retrospective investigations [48,49], of 6339 and 2624 patients reported up to a twofold higher risk of mortality for a Katz [76] score < 6. However, this was not confirmed in three other studies [21,51,52] with smaller sample sizes. Long-term mortality was assessed in *n* = 9 prospective [24–26,39,47,50–53] (2531 patients) and *n* = 6 retrospective [18,21,23,38,48,49] (4069 patients) investigations and contradictory information was found.

Handgrip strength was assessed in *n* = 2 prospective [32,51] (1428 patients) and *n* = 3 retrospective [18,21,34] (4546 patients) studies, whereas decreased strength values (BMI normalized/sex stratified) were not predictive of short-term mortality. Long-term mortality was assessed in *n* = 4 prospective [24–26,39] (561 patients) and *n* = 5 retrospective [18,21,23,34,38] (5132 patients) investigations showing conflicting information. Five authors [18,23–26] found lower handgrip strength to be an independent predictor of mortality. In contrast, Steinvil et al. [21] and Hermiller et al. [34] showed that lower handgrip values were not predictive of relative mortality 1 year after intervention in 498 and in a larger cohort of 3687 participants, respectively.

Instrumental Activities of Daily Living (IADL) [77] were assessed in *n* = 9 prospective studies [9,12,14,22,33,50,51,54,55] (1972 patients). Most of these studies found that any impairment in the IADL scale was not predictive of short-term [9,33,51], intermediate [14,54] or long-term [9,12,22,55] mortality. Only two prospective investigations [50,51] of relatively small cohorts (116 and 213 patients) identified a higher risk of intermediate mortality for patients that presented at least two impairments.

The Mini-Mental State Examination questionnaire [78] was used in *n* = 3 prospective [9,33,51] studies with relatively small cohorts (89 to 213 participants) to predict short-term mortality. Only Storteky et al. [9] showed a higher relative risk of mortality with a decrease in cognitive capacity. Long-term mortality was investigated in *n* = 5 prospective [9,12,22,51,55] (1498 patients) and *n* = 1 retrospective [40] (1542 patients) studies, with most of the studies reporting no association with MMSE scores. Only *n* = 2 studies [9,55] with small sample sizes found that pre-interventional lower MMSE results were associated with mortality. Intermediate mortality was investigated in two prospective [14,54] studies (119 and 150 patients) that showed divergent results.

Psoas muscle area index (PMAi) was investigated in only *n* = 2 prospective studies [56,57] with conflicting evidence for short-term mortality. Kofler et al. [56] found that higher PMAi values were predictive of a lower relative risk of mortality, whereas van Mourik et al. [57] stated no association between PMAi and death rates. Long-term mortality was investigated in *n* = 5 prospective [25,56–58,60] (2172 patients) and *n* = 3 retrospective [44,45,59] (2515 patients) studies. The majority of these studies showed that lower PMAi seems to be associated with a negative post-interventional prognosis.

The Timed Up-and-Go test (TUG) was used in *n* = 7 prospective studies [9,12,14,33,51, 54,55] with cohorts ranging from 89 [33] to 344 [12] patients. Storteky et al. [9] found linear (each 5 sec increase) and dichotomized ($\geq$20 versus <20 s) results on the TUG, predictive of short- and long-term mortality in 100 patients. Similarly, Eichler et al. [12] found that a longer time needed to complete the TUG ($\geq$10 to <20 versus <10 s) was predictive of up to a fivefold relative risk of mortality in 344 patients. However, Goudzwaard et al. [51] concluded that only linear values were predictive of 1-year mortality, but not over the short-term, and only when results were dichotomized (>20 versus $\leq$20 s).

3.2. Multidimensional Frailty Scales

The Clinical Frailty Scale (CFS) [79] was used in *n* = 9 studies [13,32,37,40,61–65]. Short-term mortality was considered in *n* = 2 prospective [13,32] (2235 patients) and *n* = 1 retrospective [40] (1542 patients) studies, with contradictory results. While two investigations [32,40] showed higher risk of 1-year mortality in patients with higher CFS scores, Afilalo et al. [13] demonstrated no association between CFS $\geq$ 5 and relative risk of mortality. Long-term mortality was investigated in *n* = 4 prospective [13,37,62,64] (3387 patients) and *n* = 4 retrospective [40,61,63,65] (2269 patients) studies, presenting divergent results.

The Canadian Study of Health Aging scale (CSHA) [79] was not predictive for short-term mortality [48,49,52]. Long-term mortality was assessed in *n* = 3 prospective [24–26] (402 patients) and *n* = 2 retrospective [48,52] (2936 patients) studies, that showed conflicting evidence.

3.3. Composite Indices

A 4-item index was used in *n* = 4 prospective [13,38,39,66] (1498 patients) and *n* = 3 retrospective [23,67,68] (650 patients) analyses. Afilalo et al. [13] found that dichotomized results predicted a more than twofold higher relative risk of short-term mortality. Similarly, Chauhan et al. [23] showed, for scores $\geq$ 3, a threefold higher risk of 1-year mortality in a cohort of 342 participants.

A 5-item index was used in *n* = 5 prospective [13,69–72] (2653 patients) and *n* = 1 retrospective [21] (498 patients) studies. Rogers et al. [69] found in a cohort of 544 patients that index values $\geq$ 3 corresponded to a fivefold increase in the relative risk of mortality at 30 days and up to a twofold increase at 1 year post-TAVI. Further, two authors [13,21] stated that higher scores on the index were predictive of long-term mortality.

The Elderly Frailty Toolset (EFT) was used in *n* = 4 prospective [13,37,74,75] (2676 patients) and *n* = 1 retrospective [73] (723 patients) studies. Three authors [13,73,74] found higher scores of the EFT predictive of short-term mortality. Four investigations [13,37,73,74] found higher scores of the EFT to be predictive of 1-year mortality, showing up to a threefold higher risk of death in frail patients [13].

The Bern scale was used in *n* = 5 investigations [9,12–14,55], all of a prospective design (1913 patients). Afilalo et al. [13] found scores $\geq$ 3 to be predictive of up to a threefold higher relative risk of mortality over the short-term. Similarly, Storteky et al. [9] found a threefold higher risk of death in a cohort of 100 patients per each point increase of the index and for dichotomized results.

4. Discussion

Besides a distinct heterogeneity of frailty definitions and assessments used across the included studies, the main finding of our systematic review is that single markers of frailty are the most frequently used tools to identify frailty in older TAVI patients, especially parameters of physical functionality (gait speed) and malnutrition (serum albumin level). Patients with a slower walk speed ($\geq$6 s) measured by the 5-mWT showed a higher relative risk of 1-year mortality. Pre-interventional lower levels ($\leq$3.5 g/dL) of serum albumin were associated with a worse long-term prognosis as well. Further, higher scores of composite indices (5-item, EFT, Bern scales) were associated with higher mortality risk over the short and long term after intervention.

A great number of studies (*n* = 23) investigated gait speed with the 5-mWT and found an association with higher 1-year mortality in older TAVI patients. Slower gait speed is largely used to evaluate impaired health conditions, especially among the elderly [80], and to assess the prevalence of frailty among the general population in a primary care setting [81]. Moreover, it is advocated as a reliable and valid tool to investigate frailty in patients with cardiovascular disease [6]. Gait speed is the result of neuromuscular control, cardiopulmonary condition, physical activity level, patient health status and sensorial pattern interactions, properly expressing the general physical functionality of older patients [82]. According to the physical frailty concept (physical phenotype), slower gait speed is considered a valid clinical indicator of frailty and sarcopenia [7]. Generally, TAVI patients who need $\geq$6 s ($\geq$0.85 m/s) to perform the 5-mWT are considered frail. However, several investigations advocate that patients' stratification into "slower/slow/normal" might be more appropriate, with the slowest walkers showing the highest risk of long-term mortality [20,39].

Besides physical functionality, malnutrition was mainly assessed as an indicator of frailty considering pre-interventional levels of serum albumin. In the majority of studies, a level of $\leq$3.5 g/dL was associated with a worse long-term prognosis. Albumin is a protein synthetized in the liver, and a serum concentration under 3.5 g/dL is considered representative of malnutrition [83]. Alteration of serum concentration levels is influenced by vascular injury, renal injury or various cytokine levels, and has been associated with increased risk of mortality in patients with cardiovascular disease [46]. In TAVI patients, serum albumin levels are routinely assessed pre-interventionally [46] and are often used for

retrospective analysis. Especially in older and very old patients, malnutrition is a common problem correlated to several factors, such as appetite reduction, physiological changes, altered hormonal responses, mental impairments and chewing or swallowing problems [7]. An impaired nutritional intake contributes to a worsened physical functionality as well as to the process of muscle wasting and sarcopenia, which are closely related to frailty syndrome [84].

Composite indices were developed as measurement tools with the intent to assess several patient components involved in the clinical condition of frailty. Depending on the index, patients with three or more impaired components are considered frail. In our review, several studies found that the assessment of frailty according to composite indices was predictive of 30-day and 1-year mortality in older TAVI patients, in particular the EFT and the 5-item index. Our findings are in line with the recommendation made by the International Conference on Frailty and Sarcopenia Research (ICFSR) [85]. Initially, Fried et al. [86] recommended the evaluation of frailty according to the frail phenotype, an index based on the assessment of slowness, weakness, low physical activity, exhaustion and shrinking. These components were measured according to gait speed, handgrip strength, calculation of kilocalories expended per week, self-reported exhaustion (questionnaire) and >5 kg unintentional weight loss. Several authors revised Fried's index and used alternative measurements tools. Thus, analysis of serum albumin levels as an expression of malnutrition was used to investigate the shrinking component [39]. Further, other indices (EFT, Bern scale) [9,13] were applied to the physical and nutritional component assessments of cognition (MMSE) and disability scales (BADL, IADL).

In this review, we provide a detailed overview of the frailty assessments most commonly utilized in clinical practice, divided by category and their ability to predict mortality risk. However, due to the remarkable heterogeneity of the included studies, meta-analyses of the study results were not indicated. Therefore, this review does not provide pooled effect sizes for the frailty assessments investigated, potentially limiting information for the clinician. Heterogeneity is notable especially in regard to the methodology of frailty measurements, study designs and statistical analyses. For example, seven different cut-off values were identified for gait speed. This variety of cut-off values might have influenced the estimation of patients considered as frail across the studies. For composite indices, different measurement approaches (different tools used to assess the same domain; diverse domain cut-off values) were evident across studies. Additionally, the lack of a general agreement on the definition of frailty [6] and the diversity of TAVI populations included in the studies contributed to the wide range and heterogeneity of the reviewed outcomes.

First of all, there are two fundamentally different approaches to conceptualizing frailty. On the one hand, Fried et al. (2001) describe frailty based on the phenotype, focusing on physical components (e.g., unintentional weight loss, muscle weakness, slow walking speed, low physical activity and exhaustion) [86]. One the other hand, the multidimensional concept developed by Rockwood and Mitnitski (2001) comprises psychological and social components, multi-morbidity, disability in addition to the physical impairments [79,87]. Against this background, several authors purposed a large number of frailty assessments operationalizing these frailty concepts. Recently (2019), the International Conference on Frailty and Sarcopenia Research (ICFSR) recommended the Fried method for the clinical assessment of frailty [85]. However, the majority of studies in this review are conducted and published before 2019.

Although frailty is a multidimensional syndrome among older adults characterized by a marked vulnerability and diminished capability to recover from stressors, a considerable number of single markers of frailty were used in the included studies. From the statistical point of view, in multivariable analyses of mortality, single parameters often show equivalent or stronger predictive effects than composite measures [12,88,89]. Therefore, the use of single frailty markers—also due to their good practicability—in clinical studies seems justified. Given the high complexity of frailty syndrome and frailty definition, for clinical decision-making, composite indices are more appropriate for the characterization

of a patient. The use of single parameters, despite being acceptable for clinical studies, is not recommended in this context.

For patients scheduled for TAVI and classified as frail, the effect of prehabilitation programs on morbidity and mortality is currently being investigated [90]. Taking into account the fact that aortic stenosis as well as frailty usually develop over years, the monitoring of malnutrition and physical function seems to be just as important in preventive cardiology as the assessment of aortic stenosis.

5. Conclusions

Frailty was most commonly assessed using single markers of frailty, especially based on measurements of gait speed (5-mWT) and pre-interventional levels of serum albumin. Slow gait speed (≥ 6 s) and a level of serum albumin ≤ 3.5 g/dL were predictive of a higher risk of 1-year mortality in older TAVI patients. Composite indices (5 items), considered as a comprehensive assessment of frailty, were associated with short- and long-term mortality. However, considerable heterogeneity was observed among the studies, and the methodology of each frailty assessment should be carefully considered.

References

1. Chłoń-Domińczak, A.; Kotowska, I.E.; Kurkiewicz, J.; Abramowska-Kmon, A.; Stonawski, M.; Sobczak, D. *Population Ageing in Europe: Facts, Implications and Policies*; EUROPEAN COMMISSION, Directorate-General for Research and Innovation: Bruxelles, Belgium, 2014.
2. Vigorito, C.; Abreu, A.; Ambrosetti, M.; Belardinelli, R.; Corrà, U.; Cupples, M.; Davos, C.; Hoefer, S.; Iliou, M.-C.; Schmid, J.-P.; et al. Frailty and cardiac rehabilitation: A call to action from the EAPC cardiac rehabilitation section. *Eur. J. Prev. Cardiol.* **2016**, *24*, 577–590. [CrossRef]
3. Hoogendijk, E.O.; Afilalo, J.; Ensrud, K.; Kowal, P.; Onder, G.; Fried, L.P. Frailty: Implications for clinical practice and public health. *Lancet* **2019**, *394*, 1365–1375. [CrossRef]
4. Morley, J.E.; Vellas, B.; Van Kan, G.A.; Anker, S.D.; Bauer, J.M.; Bernabei, R.; Cesari, M.; Chumlea, W.; Doehner, W.; Evans, J.; et al. Frailty Consensus: A Call to Action. *J. Am. Med. Dir. Assoc.* **2013**, *14*, 392–397. [CrossRef]
5. Clegg, A.; Young, J.; Iliffe, S.; Rikkert, M.O.; Rockwood, K. Frailty in elderly people. *Lancet* **2013**, *381*, 752–762. [CrossRef]
6. Afilalo, J.; Alexander, K.P.; Mack, M.J.; Maurer, M.S.; Green, P.; Allen, L.A.; Popma, J.J.; Ferrucci, L.; Forman, D.E. Frailty Assessment in the cardiovascular care of older adults. *J. Am. Coll. Cardiol.* **2013**, *63*, 747–762. [CrossRef]
7. Cruz-Jentoft, A.J.; Kiesswetter, E.; Drey, M.; Sieber, C.C. Nutrition, frailty, and sarcopenia. *Aging Clin. Exp. Res.* **2017**, *29*, 43–48. [CrossRef]
8. Morley, J.E.; Von Haehling, S.; Anker, S.D.; Vellas, B. From sarcopenia to frailty: A road less traveled. *J. Cachex-Sarcopenia Muscle* **2014**, *5*, 5–8. [CrossRef]
9. Stortecky, S.; Schoenenberger, A.W.; Moser, A.; Kalesan, B.; Jüni, P.; Carrel, T.; Bischoff, S.; Schoenenberger, C.-M.; Stuck, A.E.; Windecker, S.; et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc. Interv.* **2012**, *5*, 489–496. [CrossRef]
10. Eichler, S.; Hadzic, M.; Völler, H.; Salzwedel, A. Octogenarians in interventional cardiology: Feasibility and safety of functional and nutritional assessments for a new patient group in cardiac rehabilitation. *Eur. J. Prev. Cardiol.* **2020**, *27*, 2345–2347. [CrossRef]

11. Kappetein, A.P.; Head, S.J.; Généreux, P.; Piazza, N.; van Mieghem, N.M.; Blackstone, E.H.; Brott, T.G.; Cohen, D.J.; Cutlip, D.E.; van Es, G.-A.; et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *J. Thorac. Cardiovasc. Surg.* **2013**, *145*, 6–23. [CrossRef]

12. Eichler, S.; Salzwedel, A.; Harnath, A.; Butter, C.; Wegscheider, K.; Chiorean, M.; Völler, H.; Reibis, R. Nutrition and mobility predict all-cause mortality in patients 12 months after transcatheter aortic valve implantation. *Clin. Res. Cardiol.* **2017**, *107*, 304–311. [CrossRef]

13. Afilalo, J.; Lauck, S.; Kim, D.H.; Lefèvre, T.; Piazza, N.; Lachapelle, K.; Martucci, G.; Lamy, A.; Labinaz, M.; Peterson, M.D.; et al. Frailty in older adults undergoing aortic valve replacement. *J. Am. Coll. Cardiol.* **2017**, *70*, 689–700. [CrossRef]

14. Schoenenberger, A.W.; Stortecky, S.; Neumann, S.; Moser, A.; Jüni, P.; Carrel, T.; Huber, C.; Gandon, M.; Bischoff, S.; Schoenen-berger, C.-M.; et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur. Heart J.* **2012**, *34*, 684–692. [CrossRef] [PubMed]

15. Hayden, J.A.; van der Windt, D.A.; Cartwright, J.L.; Côté, P.; Bombardier, C. Assessing bias in studies of prognostic factors. *Ann. Intern. Med.* **2013**, *158*, 280–286. [CrossRef] [PubMed]

16. Wells, G.A.; Shea, B.; Higgins, J.; Sterne, J.; Tugwell, P.; Reeves, B.C. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. *Res. Synth. Methods* **2013**, *4*, 63–77. [CrossRef] [PubMed]

17. Afilalo, J.; Eisenberg, M.J.; Morin, J.-F.; Bergman, H.; Monette, J.; Noiseux, N.; Perrault, L.P.; Alexander, K.P.; Langlois, Y.; Dendukuri, N.; et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J. Am. Coll. Cardiol.* **2010**, *56*, 1668–1676. [CrossRef] [PubMed]

18. Forcillo, J.; Condado, J.F.; Ko, Y.-A.; Yuan, M.; Binongo, J.N.; Ndubisi, N.M.; Kelly, J.J.; Babaliaros, V.; Guyton, R.A.; Devireddy, C.; et al. Assessment of commonly used frailty markers for high- and extreme-risk patients undergoing transcatheter aortic valve replacement. *Ann. Thorac. Surg.* **2017**, *104*, 1939–1946. [CrossRef] [PubMed]

19. Kiani, S.; Stebbins, A.; Thourani, V.H.; Forcillo, J.; Vemulapalli, S.; Kosinski, A.S.; Babaliaros, V.; Cohen, D.; Kodali, S.K.; Kirtane, A.J.; et al. The effect and relationship of frailty indices on survival after transcatheter aortic valve replacement. *JACC Cardiovasc. Interv.* **2020**, *13*, 219–231. [CrossRef]

20. Alfredsson, J.; Stebbins, A.; Brennan, J.M.; Matsouaka, R.; Afilalo, J.; Peterson, E.D.; Vemulapalli, S.; Rumsfeld, J.S.; Sha-Hian, D.; Mack, M.J.; et al. gait speed predicts 30-day mortality after transcatheter aortic valve replacement: Results from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry. *Circulation* **2016**, *136*, 1351–1359. [CrossRef]

21. Steinvil, A.; Buchanan, K.D.; Kiramijyan, S.; Bond, E.; Rogers, T.; Koifman, E.; Shults, C.; Xu, L.; Torguson, R.; Okubagzi, P.G.; et al. Utility of an additive frailty tests index score for mortality risk assessment following transcatheter aortic valve replacement. *Am. Heart J.* **2018**, *200*, 11–16. [CrossRef]

22. van der Wulp, K.; van Wely, M.H.; Schoon, Y.; Vart, P.; Rikkert, M.G.O.; Morshuis, W.J.; van Royen, N.; Verkroost, M.W.; Gehlmann, H.R.; Van Garsse, L.A.; et al. Geriatric assessment in the prediction of delirium and long-term survival after transcatheter aortic valve implantation. *J. Thorac. Cardiovasc. Surg.* **2020**, *161*, 2095–2102. [CrossRef]

23. Chauhan, D.; Haik, N.; Merlo, A.; Haik, B.J.; Chen, C.; Cohen, M.; Mosenthal, A.; Russo, M. Quantitative increase in frailty is associated with diminished survival after transcatheter aortic valve replacement. *Am. Heart J.* **2016**, *182*, 146–154. [CrossRef] [PubMed]

24. Kleczynski, P.; Dziewierz, A.; Bagienski, M.; Rzeszutko, L.; Sorysz, D.; Trebacz, J.; Sobczynski, R.; Tomala, M.; Stapor, M.; Dudek, D. Impact of frailty on mortality after transcatheter aortic valve implantation. *Am. Heart J.* **2017**, *185*, 52–58. [CrossRef] [PubMed]

25. Kleczynski, P.; Tokarek, T.; Dziewierz, A.; Sorysz, D.; Bagienski, M.; Rzeszutko, L.; Dudek, D. Usefulness of psoas muscle area and volume and frailty scoring to predict outcomes after transcatheter aortic valve implantation. *Am. J. Cardiol.* **2018**, *122*, 135–140. [CrossRef] [PubMed]

26. Dziewierz, A.; Tokarek, T.; Kleczynski, P.; Sorysz, D.; Bagieński, M.; Rzeszutko, L.; Dudek, D. Impact of chronic obstructive pulmonary disease and frailty on long-term outcomes and quality of life after transcatheter aortic valve implantation. *Aging Clin. Exp. Res.* **2017**, *30*, 1033–1040. [CrossRef] [PubMed]

27. Green, P.; Cohen, D.J.; Généreux, P.; McAndrew, T.; Arnold, S.V.; Alu, M.; Beohar, N.; Rihal, C.S.; Mack, M.J.; Kapadia, S.; et al. Relation between six-minute walk test performance and outcomes after transcatheter aortic valve implantation (from the PARTNER trial). *Am. J. Cardiol.* **2013**, *112*, 700–706. [CrossRef] [PubMed]

28. Altisent, O.A.-J.; Puri, R.; Regueiro, A.; Chamandi, C.; Rodriguez-Gabella, T.; del Trigo, M.; Campelo-Parada, F.; Couture, T.; Marsal, J.R.; Côté, M.; et al. Predictors and association with clinical outcomes of the changes in exercise capacity after transcatheter aortic valve replacement. *Circulation* **2017**, *136*, 632–643. [CrossRef] [PubMed]

29. Dvir, D.; Waksman, R.; Barbash, I.M.; Kodali, S.K.; Svensson, L.G.; Tuzcu, E.M.; Xu, K.; Minha, S.; Alu, M.C.; Szeto, W.Y.; et al. Outcomes of patients with chronic lung disease and severe aortic stenosis treated with transcatheter versus surgical aortic valve replacement or standard therapy. *J. Am. Coll. Cardiol.* **2013**, *63*, 269–279. [CrossRef]

30. Kano, S.; Yamamoto, M.; Shimura, T.; Kagase, A.; Tsuzuki, M.; Kodama, A.; Koyama, Y.; Kobayashi, T.; Shibata, K.; Tada, N.; et al. Gait speed can predict advanced clinical outcomes in patients who undergo transcatheter aortic valve replacement. *Circ. Cardiovasc. Interv.* **2017**, *10*, e00508. [CrossRef]

31. Arnold, S.V.; O'Brien, S.M.; Vemulapalli, S.; Cohen, D.J.; Stebbins, A.; Brennan, J.M.; Shahian, D.M.; Grover, F.L.; Holmes, D.R.; Thourani, V.H.; et al. Inclusion of functional status measures in the risk adjustment of 30-day mortality after transcatheter aortic valve replacement. *JACC Cardiovasc. Interv.* **2018**, *11*, 581–589. [CrossRef]

32. Shimura, T.; Yamamoto, M.; Kano, S.; Kagase, A.; Kodama, A.; Koyama, Y.; Tsuchikane, E.; Suzuki, T.; Otsuka, T.; Kohsaka, S.; et al. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. *Circulation* **2017**, *135*, 2013–2024. [CrossRef]

33. Assmann, P.; Kievit, P.; van der Wulp, K.; Verkroost, M.; Noyez, L.; Bor, H.; Schoon, Y. Frailty is associated with delirium and mortality after transcatheter aortic valve implantation. *Open Heart* **2016**, *3*, e000478. [CrossRef]

34. Hermiller, J.B.; Yakubov, S.J.; Reardon, M.J.; Deeb, G.M.; Adams, D.H.; Afilalo, J.; Huang, J.; Popma, J.J. Predicting early and late mortality after transcatheter aortic valve replacement. *J. Am. Coll. Cardiol.* **2016**, *68*, 343–352. [CrossRef]

35. Patel, J.N.; Ahmad, M.; Kim, M.; Banga, S.; Asche, C.; Barzallo, M.; Mungee, S. Relation of frailty to cost for patients undergoing transcatheter aortic valve implantation. *Am. J. Cardiol.* **2019**, *125*, 469–474. [CrossRef]

36. Saji, M.; Lim, D.S.; Ragosta, M.; LaPar, D.J.; Downs, E.; Ghanta, R.K.; Kern, J.A.; Dent, J.M.; Ailawadi, G. Usefulness of psoas muscle area to predict mortality in patients undergoing transcatheter aortic valve replacement. *Am. J. Cardiol.* **2016**, *118*, 251–257. [CrossRef]

37. Sathananthan, J.; Lauck, S.; Piazza, N.; Martucci, G.; Kim, D.H.; Popma, J.J.; Asgar, A.W.; Perrault, L.P.; Lefèvre, T.; Labinaz, M.; et al. Habitual physical activity in older adults undergoing TAVR. *JACC Cardiovasc. Interv.* **2019**, *12*, 781–789. [CrossRef]

38. Green, P.; Arnold, S.V.; Cohen, D.J.; Kirtane, A.J.; Kodali, S.K.; Brown, D.L.; Rihal, C.S.; Xu, K.; Lei, Y.; Hawkey, M.C.; et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). *Am. J. Cardiol.* **2015**, *116*, 264–269. [CrossRef] [PubMed]

39. Green, P.; Woglom, A.E.; Genereux, P.; Daneault, B.; Paradis, J.-M.; Schnell, S.; Hawkey, M.; Maurer, M.S.; Kirtane, A.J.; Kodali, S.; et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis. *JACC Cardiovasc. Interv.* **2012**, *5*, 974–981. [CrossRef] [PubMed]

40. Shimura, T.; Yamamoto, M.; Kano, S.; Hosoba, S.; Sago, M.; Kagase, A.; Koyama, Y.; Tsujimoto, S.; Otsuka, T.; Tada, N.; et al. Patients Refusing Transcatheter Aortic Valve Replacement Even Once Have Poorer Clinical Outcomes. *J. Am. Heart Assoc.* **2018**, *7*, e009195. [CrossRef] [PubMed]

41. Grossman, Y.; Barbash, I.M.; Fefer, P.; Goldenberg, I.; Berkovitch, A.; Regev, E.; Fink, N.; Ben-Zekry, S.; Brodov, Y.; Kogan, A.; et al. Addition of albumin to Traditional Risk Score Improved Prediction of Mortality in Individuals Undergoing Transcatheter Aortic Valve Replacement. *J. Am. Geriatr. Soc.* **2017**, *65*, 2413–2417. [CrossRef]

42. Bogdan, A.; Barbash, I.M.; Segev, A.; Fefer, P.; Bogdan, S.N.; Asher, E.; Fink, N.; Hamdan, A.; Spiegelstein, D.; Raanani, E.; et al. Albumin correlates with all-cause mortality in elderly patients undergoing transcatheter aortic valve implantation. *EuroIntervention* **2016**, *12*, e1057–e1064. [CrossRef]

43. Berkovitch, A.; Barbash, I.M.; Finkelstein, A.; Assali, A.R.; Danenberg, H.; Fefer, P.; Maor, E.; Zhitomirsky, S.; Orvin, K.; Ben Zekry, S.; et al. Validation of cardiac damage classification and addition of albumin in a large cohort of patients undergoing transcatheter aortic valve replacement. *Int. J. Cardiol.* **2020**, *304*, 23–28. [CrossRef] [PubMed]

44. Michel, J.; Pellegrini, C.; Rheude, T.; von Scheidt, M.; Trenkwalder, T.; Elhmidi, Y.; Mayr, N.P.; Brecker, S.; Kasel, A.M.; Kastrati, A.; et al. The clinical impact of psoas muscle cross-sectional area on medium-term mortality after transcatheter aortic valve implantation. *Hear. Lung Circ.* **2019**, *29*, 904–913. [CrossRef]

45. Krishnan, A.; Suarez-Pierre, A.; Zhou, X.; Lin, C.T.; Fraser, C.D.; Crawford, T.C.; Hsu, J.; Hasan, R.K.; Resar, J.; Chacko, M.; et al. Comparing frailty markers in predicting poor outcomes after transcatheter aortic valve replacement. *Innov. Technol. Tech. Cardiothorac. Vasc. Surg.* **2019**, *14*, 43–54. [CrossRef]

46. Koifman, E.; Magalhaes, M.A.; Ben-Dor, I.; Kiramijyan, S.; Escarcega, R.O.; Fang, C.; Torguson, R.; Okubagzi, P.; Negi, S.I.; Baker, N.C.; et al. Impact of pre-procedural serum albumin levels on outcome of patients undergoing transcatheter aortic valve replacement. *Am. J. Cardiol.* **2015**, *115*, 1260–1264. [CrossRef]

47. Puls, M.; Sobisiak, B.; Bleckmann, A.; Jacobshagen, C.; Danner, B.C.; Hünlich, M.; Beißbarth, T.; Schöndube, F.; Hasenfuß, G.; Seipelt, R.; et al. Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: Risk assessment by Katz Index of activities of daily living. *EuroIntervention* **2014**, *10*, 609–619. [CrossRef]

48. Martin, G.P.; Sperrin, M.; Ludman, P.F.; Debelder, M.A.; Gunning, M.; Townend, J.; Redwood, S.R.; Kadam, U.T.; Buchan, I.; Mamas, M. Do frailty measures improve prediction of mortality and morbidity following transcatheter aortic valve implantation? An analysis of the UK TAVI registry. *BMJ Open* **2018**, *8*, e022543. [CrossRef]

49. Martin, G.P.; Sperrin, M.; Ludman, P.F.; De Belder, M.A.; Redwood, S.R.; Townend, J.; Gunning, M.; Moat, N.E.; Banning, A.; Buchan, I.; et al. Novel United Kingdom prognostic model for 30-day mortality following transcatheter aortic valve implantation. *Heart* **2017**, *104*, 1109–1116. [CrossRef]

50. Bureau, M.-L.; Liuu, E.; Christiaens, L.; Pilotto, A.; Mergy, J.; Bellarbre, F.; Ingrand, P.; Paccalin, M.; Cruz-Jentoft, A.J.; Maggi, S.; et al. Using a multidimensional prognostic index (MPI) based on comprehensive geriatric assessment (CGA) to predict mortality in elderly undergoing transcatheter aortic valve implantation. *Int. J. Cardiol.* **2017**, *236*, 381–386. [CrossRef] [PubMed]

51. Goudzwaard, J.A.; de Ronde-Tillmans, M.J.; El Faquir, N.; Acar, F.; Van Mieghem, N.M.; Lenzen, M.J.; de Jaegere, P.P.; Mattace-Raso, F.U. The Erasmus Frailty Score is associated with delirium and 1-year mortality after Transcatheter Aortic Valve Implantation in older patients. The TAVI Care & Cure program. *Int. J. Cardiol.* **2018**, *276*, 48–52. [CrossRef] [PubMed]

52. Cockburn, J.; Singh, M.S.; Rafi, N.H.M.; Dooley, M.; Hutchinson, N.; Hill, A.; Trivedi, U.; De Belder, A.; Hildick-Smith, D. Poor mobility predicts adverse outcome better than other frailty indices in patients undergoing transcatheter aortic valve implantation. *Catheter. Cardiovasc. Interv.* **2015**, *86*, 1271–1277. [CrossRef] [PubMed]

53. Szekely, Y.; Finkelstein, A.; Bazan, S.; Halkin, A.; Younis, M.A.; Erez, J.; Keren, G.; Banai, S.; Arbel, Y. Red blood cell distribution width as a prognostic factor in patients undergoing transcatheter aortic valve implantation. *J. Cardiol.* **2019**, *74*, 212–216. [CrossRef] [PubMed]

54. Boureau, A.S.; Trochu, J.N.; Rouaud, A.; Hureau, R.; Jaafar, P.; Manigold, T.; Letocart, V.; Guerin, P.; Berrut, G.; De Decker, L. Predictors of health-related quality of life decline after transcatheter aortic valve replacement in older patients with severe aortic stenosis. *J. Nutr. Health Aging* **2017**, *21*, 105–111. [CrossRef] [PubMed]

55. Schoenenberger, A.W.; Moser, A.; Bertschi, D.; Wenaweser, P.; Windecker, S.; Carrel, T.; Stuck, A.E.; Stortecky, S. Improvement of risk prediction after transcatheter aortic valve replacement by combining frailty with conventional risk scores. *JACC Cardiovasc. Interv.* **2018**, *11*, 395–403. [CrossRef] [PubMed]

56. Kofler, M.; Reinstadler, S.J.; Mayr, A.; Stastny, L.; Reindl, M.; Dumfarth, J.; Dachs, T.M.; Wachter, K.; Rustenbach, C.J.; Friedrich, G.; et al. Prognostic implications of psoas muscle area in patients undergoing transcatheter aortic valve implantation. *Eur. J. Cardio-Thoracic Surg.* **2018**, *55*, 210–216. [CrossRef] [PubMed]

57. Van Mourik, M.S.; Janmaat, Y.C.; Van Kesteren, F.; Vendrik, J.; Planken, R.N.; Henstra, M.J.; Velu, J.F.; Vlastra, W.; Zwinderman, A.H.; Koch, K.T.; et al. CT determined psoas muscle area predicts mortality in women undergoing transcatheter aortic valve implantation. *Catheter. Cardiovasc. Interv.* **2018**, *93*, E248–E254. [CrossRef]

58. Mamane, S.; Mullie, L.; Piazza, N.; Martucci, G.; Morais, J.; Vigano, A.; Levental, M.; Nelson, K.; Lange, R.; Afilalo, J. Psoas muscle area and all-cause mortality after transcatheter aortic valve replacement: The Montreal-Munich study. *Can. J. Cardiol.* **2015**, *32*, 177–182. [CrossRef]

59. Foldyna, B.; Troschel, F.M.; Addison, D.; Fintelmann, F.J.; Elmariah, S.; Furman, D.; Eslami, P.; Ghoshhajra, B.; Lu, M.T.; Murthy, V.L.; et al. Computed tomography-based fat and muscle characteristics are associated with mortality after transcatheter aortic valve replacement. *J. Cardiovasc. Comput. Tomogr.* **2018**, *12*, 223–228. [CrossRef]

60. Garg, L.; Agrawal, S.; Pew, T.; Hanzel, G.S.; Abbas, A.E.; Gallagher, M.J.; Shannon, F.L.; Hanson, I.D. Psoas muscle area as a predictor of outcomes in transcatheter aortic valve implantation. *Am. J. Cardiol.* **2016**, *119*, 457–460. [CrossRef]

61. Honda, Y.; Yamawaki, M.; Shigemitsu, S.; Kenji, M.; Tokuda, T.; Tsutumi, M.; Mori, S.; Sakamoto, Y.; Kobayashi, N.; Araki, M.; et al. Prognostic value of objective nutritional status after transcatheter aortic valve replacement. *J. Cardiol.* **2019**, *73*, 401–407. [CrossRef]

62. Seiffert, M.; Sinning, J.-M.; Meyer, A.; Wilde, S.; Conradi, L.; Nicotera, M.; Ghanem, A.; Kempfert, J.; Hammerstingl, C.; Ojeda, F.M.; et al. Development of a risk score for outcome after transcatheter aortic valve implantation. *Clin. Res. Cardiol.* **2014**, *103*, 631–640. [CrossRef]

63. Miura, M.; Shirai, S.; Uemura, Y.; Jinnouchi, H.; Morinaga, T.; Isotani, A.; Watanabe, S.; Hayashi, M.; Kamioka, N.; Nagasawa, A.; et al. Early safety and efficacy of transcatheter aortic valve implantation for asian nonagenarians (from KMH Registry). *Int. Heart J.* **2017**, *58*, 900–907. [CrossRef]

64. Yokoyama, H.; Tobaru, T.; Muto, Y.; Hagiya, K.; Higuchi, R.; Saji, M.; Takamisawa, I.; Shimizu, J.; Takanashi, S.; Takayama, M.; et al. Long-term outcomes in Japanese nonagenarians undergoing transcatheter aortic valve implantation: A multi-center analysis. *Clin. Cardiol.* **2019**, *42*, 605–611. [CrossRef]

65. Saji, M.; Tobaru, T.; Higuchi, R.; Hagiya, K.; Takamisawa, I.; Shimizu, J.; Iguchi, N.; Takanashi, S.; Takayama, M.; Isobe, M. Cognitive assessment using the revised Hasegawa's dementia scale to determine the mid-term outcomes following transcatheter aortic valve replacement. *J. Cardiol.* **2019**, *74*, 206–211. [CrossRef] [PubMed]

66. Okoh, A.K.; Chauhan, D.; Kang, N.; Haik, N.; Merlo, A.; Cohen, M.; Haik, B.; Chen, C.; Russo, M.J. The impact of frailty status on clinical and functional outcomes after transcatheter aortic valve replacement in nonagenarians with severe aortic stenosis. *Catheter. Cardiovasc. Interv.* **2017**, *90*, 1000–1006. [CrossRef]

67. Okoh, A.K.; Kang, N.; Haik, N.; Fugar, S.; Chunguang, C.; Bruce, H.; Cohen, M.; Russo, M.J. Clinical and functional outcomes associated with age after transapical transcatheter aortic valve replacement. *Innov. Technol. Tech. Cardiothorac. Vasc. Surg.* **2019**, *14*, 151–158. [CrossRef]

68. Huded, C.P.; Huded, J.M.; Friedman, J.L.; Benck, L.R.; Lindquist, L.; Holly, T.A.; Sweis, R.N.; Ricciardi, M.J.; Malaisrie, S.C.; Davidson, C.J.; et al. Frailty status and outcomes after transcatheter aortic valve implantation. *Am. J. Cardiol.* **2016**, *117*, 1966–1971. [CrossRef] [PubMed]

69. Rogers, T.; Alraies, M.C.; Pacha, H.M.; Bond, E.; Buchanan, K.D.; Steinvil, A.; Gai, J.; Torguson, R.; Ben-Dor, I.; Satler, L.F.; et al. Clinical frailty as an outcome predictor after transcatheter aortic valve implantation. *Am. J. Cardiol.* **2018**, *121*, 850–855. [CrossRef] [PubMed]

70. Shi, S.; Afilalo, J.; Lipsitz, L.A.; Popma, J.J.; Khabbaz, K.R.; Laham, R.J.; Guibone, K.; Grodstein, F.; Lux, E.; Kim, D.H. Frailty phenotype and deficit accumulation frailty index in predicting recovery after transcatheter and surgical aortic valve replacement. *J. Gerontol. Ser. A Boil. Sci. Med. Sci.* **2018**, *74*, 1249–1256. [CrossRef]

71. Ewe, S.H.; Marsan, N.A.; Pepi, M.; Delgado, V.; Tamborini, G.; Muratori, M.; Ng, A.; van der Kley, F.; de Weger, A.; Schalij, M.J.; et al. Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis. *Am. Heart J.* **2010**, *160*, 1113–1120. [CrossRef] [PubMed]

72. Abramowitz, Y.; Chakravarty, T.; Jilaihawi, H.; Cox, J.; Sharma, R.P.; Mangat, G.; Nakamura, M.; Cheng, W.; Makkar, R.R. Impact of body mass index on the outcomes following transcatheter aortic valve implantation. *Catheter. Cardiovasc. Interv.* **2016**, *88*, 127–134. [CrossRef]

73. Drudi, L.M.; Ades, M.; Asgar, A.; Perrault, L.; Lauck, S.; Webb, J.G.; Rassi, A.; Lamy, A.; Noiseux, N.; Peterson, M.D.; et al. Interaction between frailty and access site in older adults undergoing transcatheter aortic valve replacement. *JACC Cardiovasc. Interv.* **2018**, *11*, 2185–2192. [CrossRef]

74. Pighi, M.; Piazza, N.; Martucci, G.; Lachapelle, K.; Perrault, L.P.; Asgar, A.W.; Lauck, S.; Webb, J.G.; Popma, J.J.; Kim, D.H.; et al. Sex-specific determinants of outcomes after transcatheter aortic valve replacement. *Circ. Cardiovasc. Qual. Outcomes* **2019**, *12*, e005363. [CrossRef]

75. Skaar, E.; Eide, L.S.P.; Norekvål, T.M.; Ranhoff, A.H.; Nordrehaug, J.E.; Forman, D.E.; Schoenenberger, A.W.; Hufthammer, K.O.; Kuiper, K.K.-J.; Bleie, O.; et al. A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation. *Eur. Heart J.-Qual. Care Clin. Outcomes* **2018**, *5*, 153–160. [CrossRef] [PubMed]

76. Katz, S.; Ford, A.B.; Moskowitz, R.W.; Jackson, B.A.; Jaffe, M.W. Studies of illness in the aged: The index of ADL: A standardized measure of biological and psychological function. *JAMA* **1963**, *185*, 914–919. [CrossRef]

77. Lawton, M.P.; Brody, A.E.M. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontology* **1969**, *9*, 179–186. [CrossRef]

78. Folstein, M.F.; Folstein, S.E.; McHugh, P.R. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **1975**, *12*, 189–198. [CrossRef]

79. Rockwood, K.; Song, X.; MacKnight, C.; Bergman, H.; Hogan, D.B.; McDowell, I.; Mitnitski, A. A global clinical measure of fitness and frailty in elderly people. *Can. Med. Assoc. J.* **2005**, *173*, 489–495. [CrossRef] [PubMed]

80. Jerome, G.J.; Ko, S.-U.; Kauffman, D.; Studenski, S.A.; Ferrucci, L.; Simonsick, E.M. Gait characteristics associated with walking speed decline in older adults: Results from the Baltimore longitudinal study of aging. *Arch. Gerontol. Geriatr.* **2015**, *60*, 239–243. [CrossRef]

81. Castell, V.; Sánchez, M.; Julián, R.; Queipo, R.; Martín, S.; Otero, A. Frailty prevalence and slow walking speed in persons age 65 and older: Implications for primary care. *BMC Fam. Pr.* **2013**, *14*, 86. [CrossRef]

82. Binotto, M.A.; Lenardt, M.H.; Rodríguez-Martínez, M.D.C. Fragilidade física e velocidade da marcha em idosos da comunidade: Uma revisão sistemática. *Rev. Esc. Enferm. USP* **2018**, *52*, e03392. [CrossRef] [PubMed]

83. Phillips, A.; Shaper, A.G.; Whincup, P. Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *Lancet* **1989**, *334*, 1434–1436. [CrossRef]

84. Al-Kassou, B.; Shamekhi, J.; Weber, M.; Germeroth, J.; Gillrath, J.; Feldmann, K.; Sedaghat, A.; Werner, N.; Treede, H.; Becher, M.U.; et al. Frailty, malnutrition, and the endocrine system impact outcome in patients undergoing aortic valve replacement. *Catheter. Cardiovasc. Interv.* **2021**, 1–13. [CrossRef]

85. Dent, E.; Morley, J.E.; Cruz-Jentoft, A.J.; Woodhouse, L.; Rodríguez-Mañas, L.; Fried, L.P.; Woo, J.; Aprahamian, I.; Sanford, A.; Lundy, J.; et al. Physical frailty: ICFSR international clinical practice guidelines for identification and management. *J. Nutr. Health Aging* **2019**, *23*, 771–787. [CrossRef]

86. Fried, L.P.; Tangen, C.M.; Walston, J.D.; Newman, A.B.; Hirsch, C.; Gottdiener, J.S.; Seeman, T.E.; Tracy, R.P.; Kop, W.J.; Burke, G.L.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. Ser. A Boil. Sci. Med. Sci.* **2001**, *56*, M146–M157. [CrossRef]

87. Mitnitski, A.B.; Mogilner, A.J.; Rockwood, K. Accumulation of deficits as a proxy measure of aging. *Sci. World J.* **2001**, *1*, 323–336. [CrossRef]

88. Studenski, S.; Perera, S.; Wallace, D.; Chandler, J.M.; Duncan, P.; Rooney, E.; Fox, M.; Guralnik, J.M. Physical performance measures in the clinical setting. *J. Am. Geriatr. Soc.* **2003**, *51*, 314–322. [CrossRef]

89. Guralnik, J.M.; Ferrucci, L.; Pieper, C.F.; Leveille, S.G.; Markides, K.S.; Ostir, G.V.; Studenski, S.; Berkman, L.F.; Wallace, R.B. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J. Gerontol. Ser. A Boil. Sci. Med. Sci.* **2000**, *55*, M221–M231. [CrossRef]

90. Boreskie, K.F.; Hay, J.L.; Kehler, D.S.; Johnston, N.M.; Rose, A.V.; Oldfield, C.J.; Kumar, K.; Toleva, O.; Arora, R.C.; Duhamel, T.A. Prehabilitation. *Clin. Geriatr. Med.* **2019**, *35*, 571–585. [CrossRef]