Postoperative Outcomes in SAVR/TAVR Patients With Cognitive Impairment: A Systematic Review

Betty M. Luan Erfe, MD,[*] J. Mark Erfe, MD, MPH,[†] Ethan Y. Brovman, MD,[‡] Jacqueline Boehme, MD,[‡] Angela M. Bader, MD, MPH,[,‡] and Richard D. Urman, MD, MBA[‡]*

To assess the predictive value of preoperative cognitive impairment on postoperative in-hospital, short-term, and mid-term outcomes among patients undergoing surgical or transcatheter aortic valve replacement. The review was conducted according to PRISMA guidelines. Articles were identified in EMBASE, Medline, and PubMed. Eligible articles compared the outcomes of patients with and without preoperative cognitive impairment who underwent aortic valve replacement and were published in English between January 1, 1997 and November 1, 2017. The quality of included observational studies was evaluated using the Newcastle-Ottawa scale. The strength of the body of evidence was also assessed. A total of 6163 abstracts were screened by 2 independent reviewers and 31 full-text articles were reviewed. Eight studies met inclusion criteria. The studies included 1 case-control, 5 prospective cohort, and 2 retrospective cohort studies. Given the paucity and heterogeneity of studies, meta-analysis was not possible. Five studies were of good quality. Preoperative cognitive impairment is a risk factor for postoperative delirium in 2 studies, increased mid-term mortality in 2 studies, and increased length of stay, risk of discharge to a health-care facility or progressive disability in 1 study. However, given the paucity and methodological flaws of the included studies, the body of evidence on the predictive value of preoperative cognitive impairment on postoperative outcomes remains weak. This systematic review highlights the need for more good quality studies to provide evidence regarding the incidence of cognitive impairment and associations with poor outcomes after aortic valve replacement.

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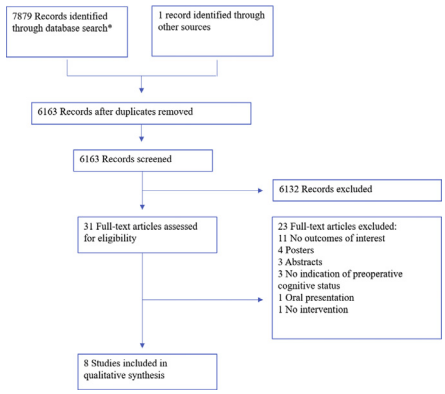
Keywords: Cognitive impairment, Delirium, Postoperative, Screening, Outcomes, Surgery



Eight studies assessed postoperative outcomes in AVR patients with cognitive impairment.

Central Message

There is a paucity of studies and weak body of evidence relating to outcomes of patients with cognitive impairment undergoing aortic valve replacement.

Perspective Statement

A small number of both good and poor-quality studies examined the association between preoperative cognitive impairment and postoperative outcomes. Given the increasing age of aortic valve replacement candidates and the prevalence of cognitive impairment among elderly patients, more studies focusing on the predictive value of preoperative cognitive impairment on postoperative outcomes are needed.

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass graft; CI, confidence interval; EFT, Essential Frailty Toolset; FIM, functional independence measure; HVLT, Hopkins Verbal Learning Test; LOS, length of stay; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; OR, odds ratio; POD, postoperative delirium; RR, relative risk; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TMT-B, Trail Making Test Part B.

*Harvard Medical School, Boston, Massachusetts
†Yale School of Medicine, New Haven, Connecticut
‡Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts

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Address reprint requests to Richard Urman MD, MBA, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA 02115. E-mail: rurman@bwh.harvard.edu

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INTRODUCTION

The surgical patient population is aging, increasing demand for less invasive surgeries that can reduce perioperative risk for this higher risk patient population. According to the US Census, the population aged 65 and over was 43.1 million in 2012, which is estimated to double by 2050.[1] The prevalence of mild cognitive impairment (MCI) in this age group is estimated to be as much as 28.3%.[2] The aging aortic valve replacement (AVR) patient population mirrors the aging population in the United States. One study estimated that transcatheter AVR (TAVR) patients are generally older than surgical AVR (SAVR) patients (75.3 vs 61.6 years).[3] Another study showed that the average age of SAVR patients has increased from 69 to 74 between 2009 and 2011.[4] With the increasing age of AVR candidates and an overall aging population in the United States, MCI will continue to be prevalent among AVR candidates.

Given the prevalence of MCI in the AVR surgical patient population, it is important to understand the predictive value of preoperative cognitive impairment on postoperative outcomes. Several studies indicate that preoperative MCI is a risk factor for poor outcomes among patients undergoing AVR. One study found that a score on the Mini-Mental Status Examination (MMSE) of less than 24 predicted progressive disability 1 year after TAVR.[5] Another study concluded that MMSE <27 is associated with all-cause mortality at 30 days and at 1 year after TAVR.[6] There are currently no recommendations for preoperative cognitive assessment for AVR patients, because it is still unclear whether cognitive impairment impacts postoperative short- and long-term recovery for this patient population.

Cognitive function of AVR candidates is typically not assessed preoperatively. Most often, candidates are given subjective frailty "eyeball tests," while their renal, pulmonary, cardiac, and hepatic functions are formally assessed.[7,8] Occasionally, candidates are evaluated using frailty scoring systems. However, not all frailty indices include a cognitive component.[9] Without routine preoperative cognitive assessment, the percentage of AVR surgical candidates with MCI is likely underestimated and the effect of MCI on postoperative outcomes is not understood.

To date, there has been no systematic review to evaluate whether preoperative cognitive impairment predicts poor postoperative outcomes in patients undergoing TAVR or SAVR with or without concomitant coronary artery bypass graft (CABG). By using established methodology, we reviewed observational studies that compared the postoperative outcomes of SAVR and TAVR patients with and without cognitive impairment. First, we hypothesized that patients with cognitive impairment have a more complicated in-hospital course, including higher risk of delirium, lengthier hospital stays, and discharge to a health-care facility. Second, we hypothesized that these patients have worse short-term (within 30 days of surgery) and mid-term (within 1 month to 2 years of surgery) prognosis, including higher rates of complications and mortality, and decreased functionality. Finally, we evaluated the strength of the body of evidence to recommend areas of further research.

METHODS

Protocol and Registration

The protocol for this systematic review was designed according to PRISMA guidelines. We enlisted the assistance of a research librarian and a statistician in developing the protocol. The protocol was registered with PROSPERO (registration number: CRD42017072154. Website: http://www.crd.york.ac.uk/PROSPERO).

We performed a literature search in several databases, including PubMed, Embase, and Medline on November 5, 2017 for literature published between January 1, 1997 and November 1, 2017. Database-specific search was completed using the following search term list (see Appendix A): *Alzheimer's, dementia, cognition, cognitive defects, cognitive deficits, cognitive disorders, cognitive dysfunction, cognitive function, cognitive impairment, cognitive status, memory defects, memory deficits, memory disorders, memory dysfunction, memory impairment*, or *mental function*; and *anesthesia, surgery, surgical procedure*, or *operation*; and *outcomes, outcome assessment, prognosis*, or *surgical outcomes*; not *children* or *pediatrics*.

We applied filters to narrow search results to human subjects, English-only, and by study type to exclude conference abstracts, case reports, comments, editorials, essays, letters, meta-analyses, reviews, and unpublished studies. Duplicates were removed. Any additional articles identified by other means were added.

Inclusion/Exclusion Criteria

We included studies between January 1, 1997 and November 1, 2017 of patients with cognitive impairment who received TAVR or SAVR with or without concomitant CABG. Cognitive impairment is defined by previously diagnosed dementia or through preoperative cognitive assessment. Studies included in this review had only adult patients (age > 18), had a comparator group of patients who did not have preoperative cognitive impairment, and were peer reviewed. Reasons for exclusion are listed in Figure 1. We were interested in in-hospital outcomes (delirium, length of stay, and discharge disposition), short-term outcomes (mortality and complications), and mid-term outcomes (mortality and functionality).

Study Selection and Data Extraction

The studies were selected through a 2-step process. In the first phase, 2 reviewers (BLE and JME) independently ran the search criteria in the databases and reviewed the titles and abstracts to determine eligibility. In the second phase, 1 reviewer (BLE) obtained full-text articles from the initial screen and independently determined if articles were to be included. A third reviewer (RU) assessed the validity of reasons for the excluded articles. Data were extracted from the final set of studies by the first reviewer (BLE) and verified by the third reviewer (RU). Extracted data included author name(s), publication year, location, study design, setting, population, size,

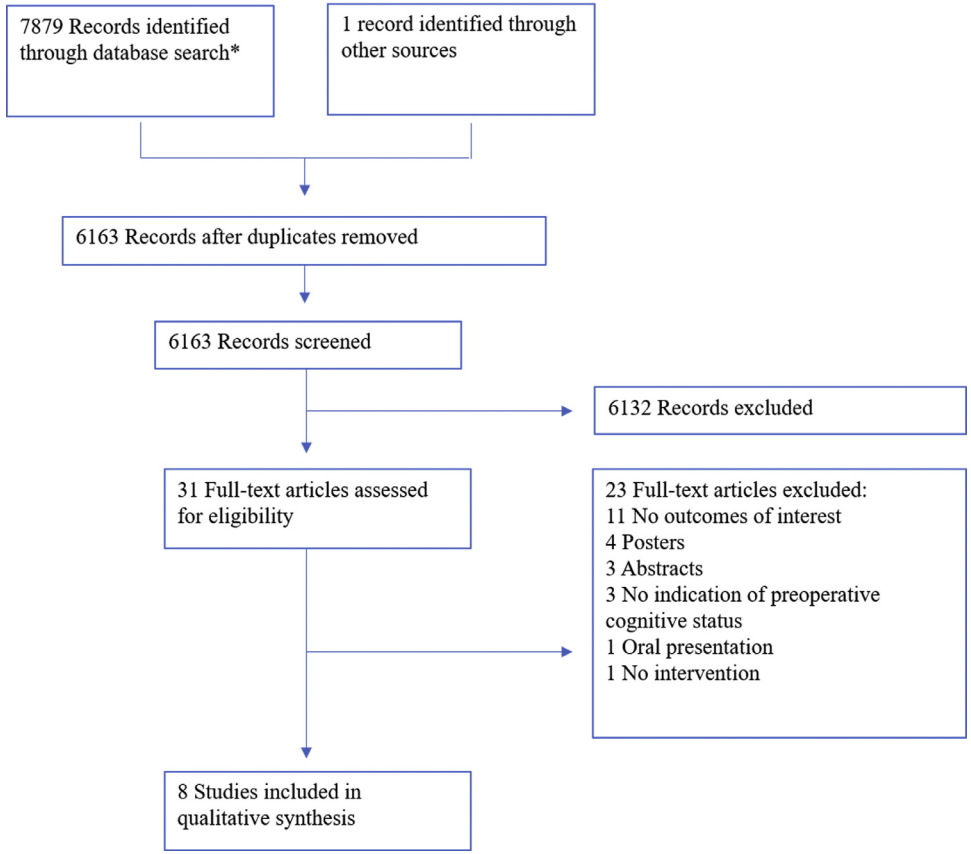

Figure 1. Flowchart for systematic literature search and screening.
*Articles were identified from PubMed (*n* = 4242) and EMBASE/Medline (*n* = 3637).

First Author, Year, Location	Design, Setting	Population	*n*	Intervention	Cognitive Assessment	Criteria for Cognitive Impairment	Cognitive Impairment Prevalence	Associations
Ryomoto, 2017 (Japan)	Case-control, single site	>65 years, severe stenosis	85	SAVR	FIM	None	Not reported	Strong evidence that lower cognitive scores on preoperative FIM were not associated with hospitalization >30 days or discharge to health-care facility.
Afilalo, 2017 (Canada)	Prospective cohort, multisite	≥70, symptomatic stenosis	1020	TAVR, SAVR	MMSE as part of Fried+ frailty and EFT scales	MMSE <24	18% (179/1020)	Strong evidence that cognitive impairment as part of frailty scale predicts mortality and

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First Author, Year, Location	Design, Setting	Population	*n*	Intervention	Cognitive Assessment	Criteria for Cognitive Impairment	Cognitive Impairment Prevalence	Associations
								progressive disability at 1 year. However, the independent effect of cognitive impairment is unclear.
Rudolph, 2006 (United States)	Prospective cohort, multisite	Patients age ≥60 without preoperative delirium	80	CABG, CABG-SAVR	MMSE, HVLT, TMT-B	None	Not reported	Strong evidence that preoperative cognitive impairment, specifically impaired executive function and not memory impairment, is a risk factor for postoperative delirium.
Jodati, 2013 (Iran)	Prospective cohort, single site	All patients receiving open heart surgery	329	SAVR, CABG	Preexisting diagnosis	Preexisting	14% (48/328)	Possibly no association between preexisting dementia and postoperative delirium.
Schoenenberger, 2013 (Switzerland)	Prospective cohort, single site	≥70 with severe symptomatic stenosis	119	TAVR	MMSE	MMSE <27	32.8% (39/119)	Possibly an association between preoperative cognitive impairment with functional decline or death at 6 months postoperatively.
Stortecky, 2012 (Switzerland)	Prospective cohort, single site	≥70 with severe symptomatic stenosis	100	TAVR	MMSE	MMSE <27	32.0% (32/100)	Possibly an association between preoperative cognitive impairment with all-cause mortality at 30 days and at 1 year postoperatively.
Eleid, 2015 (United States)	Retrospective cohort, single site	≥18 with preserved EF	1120	TAVR, SAVR	Preexisting diagnosis	Preexisting	Not reported	Strong evidence that preoperative cognitive impairment is a risk factor for midterm mortality.
Tse, 2014 (Canada)	Retrospective cohort, single site	All patients undergoing TAVR.	122	TAVR	Preexisting diagnosis	Preexisting	30.7% (36/117)	Strong evidence that preexisting cognitive impairment is a risk factor for postoperative delirium.

intervention, method of cognitive assessment, criteria for cognitive impairment, outcome measures, and results.

Data Analysis

We performed a qualitative analysis of the included studies. Given the paucity of studies and heterogeneity of the patient population, we were not able to perform a meta-analysis. In our qualitative analysis, we summarized the study characteristics, measures used to assess cognitive impairment, and the associations found.

Quality Assessment

The quality of observational studies was assessed using the Newcastle-Ottawa scale, which is a quality evaluation tool for nonrandomized studies that evaluates studies based on the domains of selection, comparability, and outcome.[10] Any study scoring 3−4, 1−2, and 2−3 in the selection, comparability, and outcome/exposure domains, respectively, were considered "good quality." A study scoring 2, 1−2, and 2−3 in these domains were "fair quality." Otherwise, the study was considered "poor quality."

We attempted to minimize study selection bias by having a predefined inclusion and exclusion criteria, dual review, and documentation of reasons for excluding studies. No studies were excluded based on how cognitive impairment was defined, study quality or size. We then used the GRADE approach in assessing the strength of the body of evidence based on the number and quality of studies, and consistency of results.[11]

RESULTS

Literature Search

A total of 6163 unique articles were identified and screened. Of the 31 full-text articles that were reviewed, 23 articles were excluded for reasons listed in Figure 1. Eight articles fulfilled selection criteria and were included in this review.

Study Characteristics

Individual study characteristics are listed in Table 1. All studies assessed its participants for cognitive impairment and evaluated its effects on postoperative outcomes. Half of the studies were conducted in either Canada or the United States. The remaining half were from Switzerland, Japan, and Iran. All but one were published after 2012. Study design included 1 case-control, 5 prospective cohort, and 2 retrospective cohort studies. The studies involved a total of 2975 patients. Two studies involved patients undergoing either TAVR or SAVR, 3 were TAVR-only, and the remaining were SAVR-only, SAVR or CABG, and CABG or CABG-SAVR. Given the limited number of studies, studies that included CABG surgeries were not excluded if the study also had SAVR or SAVR-CABG.

Measures of Cognitive Impairment

Three studies assessed for cognitive impairment based on preexisting diagnosis and 5 used cognitive evaluation tools (Table 1). All but one study included the MMSE in their assessment toolbox. MMSE is a paper-based test with a score range of 1−30, with lower scores indicating greater cognitive impairment (Appendix B1). Sensitivity and specificity of MMSE in detecting dementia are 0.85 and 0.90, respectively.[12] Ryomoto utilized the functional independence measure (FIM) only.[13] The FIM has a cognitive portion with a score range of 5−35 (Appendix C1). However, no systematic review demonstrates the accuracy of FIM to detect cognitive impairment. In addition to MMSE, Afilalo utilized the Bern scale, while Rudolph utilized the Hopkins Verbal Learning Test (HVLT) and Trail Making Test Part B (TMT-B).[5,14] Participants memorize and recall a 12-word list in HVLT and trace consecutive numbers in TMT-B. Of the 5 studies that used cognitive evaluation tools, 2 analyzed cognitive impairment as a linear variable, while others defined impairment at specific cut-off values. Seven studies investigated the independent association between preoperative cognitive impairment and postoperative outcomes, while 1 did not investigate the impact of cognitive impairment independent of a composite frailty score.

Association of Cognitive Impairment With In-Hospital Outcomes

Three studies investigated the impact of preoperative cognitive impairment on postoperative delirium (POD). These included 2 prospective cohort studies and 1 single-site retrospective cohort study, with a combined total of 531 participants. All but one study were of good quality. The good quality studies consistently found that preoperative cognitive impairment was a risk factor for POD.[14,15] For example, Rudolph showed in a multivariable model that lower scores on MMSE, working memory, fluency, naming, and memory were each independently associated with greater risk for developing POD. The study then grouped the above scores into composite memory and executive function scores. Poor preoperative performance on executive function was associated with delirium risk (RR = 0.49, 95% CI = 0.19−1.25), while memory impairment was not after adjusting for executive function performance. Using multivariable analysis, Tse similarly showed that preexisting dementia was associated with POD (OR = 6.5, 95% CI = 1.8−23.2, P = 0.004). Contrarily, Jodati showed using univariable analysis that there was no correlation between preexisting dementia and POD.[16] However, Jodati did not specify how the cohort was derived, how cognitive impairment was assessed, and did not demonstrate that delirium was not present preoperatively. This study also did not control for age, sex, and comorbidities.

Only 1 other study investigated the impact of cognitive impairment on length of stay and postdischarge disposition. Ryomoto used case-controls with a total of 85 patients to evaluate the efficacy of FIM in assessing frailty, and to investigate associations between frailty and discharge status.[13] Ryomoto

Table 1. Characteristics of Included Studies

First Author, Year, Location	Design, Setting	Population	*n*	Intervention	Cognitive Assessment	Criteria for Cognitive Impairment	Associations
Ryomoto, 2017 (Japan)	Case-control, single site	>65 years, severe stenosis	85	SAVR	FIM	None	Strong evidence that lower cognitive scores on preoperative FIM were not associated with hospitalization >30 days or discharge to health-care facility.
Afilalo, 2017 (Canada)	Prospective cohort, multisite	≥70, symptomatic stenosis	1020	TAVR, SAVR	MMSE as part of Fried+ frailty and EFT scales	MMSE <24	Strong evidence that cognitive impairment as part of frailty scale predicts mortality and progressive disability at 1 year. However, the independent effect of cognitive impairment is unclear.
Rudolph, 2006 (United States)	Prospective cohort, multisite	Patients age ≥60 without preoperative delirium	80	CABG, CABG-SAVR	MMSE, HVLT, TMT-B	None	Strong evidence that preoperative cognitive impairment, specifically impaired executive function and not memory impairment, is a risk factor for postoperative delirium.
Jodati, 2013 (Iran)	Prospective cohort, single site	All patients receiving open heart surgery	329	SAVR, CABG	Preexisting diagnosis	Preexisting	Possibly no association between preexisting dementia and postoperative delirium.
Schoenenberger, 2013 (Switzerland)	Prospective cohort, single site	≥70 with severe symptomatic stenosis	119	TAVR	MMSE	MMSE <27	Possibly an association between preoperative cognitive impairment with functional decline or death at 6 months postoperatively.
Stortecky, 2012 (Switzerland)	Prospective cohort, single site	≥70 with severe symptomatic stenosis	100	TAVR	MMSE	MMSE <27	Possibly an association between preoperative cognitive impairment with all-cause mortality at 30 days and at 1 year postoperatively.
Eleid, 2015 (United States)	Retrospective cohort, single site	≥18 with preserved EF	1120	TAVR, SAVR	Preexisting diagnosis	Preexisting	Strong evidence that preoperative cognitive impairment is a risk factor for mid-term mortality.
Tse, 2014 (Canada)	Retrospective cohort, single site	All patients undergoing TAVR.	122	TAVR	preexisting diagnosis	preexisting	Strong evidence that preexisting cognitive impairment is a risk factor for postoperative delirium.

AVR, aortic valve repair; CABG, coronary artery bypass graft; CI, confidence interval; EF, ejection fraction; EFT, Essential Frailty Toolset; FIM, functional independence measure; HVLT, Hopkins Verbal Learning Test; MMSE, Mini-Mental Status Exam; RR, relative risk; SAVR, surgical aortic valve repair; TAVR, transcatheter aortic valve repair; TMT-B, Trail Making Test Part B.

found that among patients who had length of stay >30 days or were discharged to a health-care facility, FIM score was significantly lower (79 ± 32 vs 120 ± 9, $P < 0.01$), but the cognitive portion of FIM was not significantly different between the 2 groups.

Association of Cognitive Impairment With Short-Term Outcomes

Only 1 study investigated the impact of cognitive impairment on mortality within 30 days. Stortecky evaluated the ability of the multidimensional geriatric assessment to predict mortality after TAVR.[17] The study concluded that MMSE <27 was associated with all-cause mortality at 30 days (OR = 7.62, 95% CI = 1.44−40.19, $P = 0.01$). However, the study did not perform multivariable analysis to control for age, sex, or comorbidities.

No study investigated the impact of cognitive impairment on complications within 30 days.

Association of Cognitive Impairment With Mid-Term Outcomes

Four studies investigated the impact of cognitive impairment on mortality between 2 months and 2 years following surgery. This included 3 prospective cohort and 1 retrospective cohort studies. Two of the prospective cohort studies also investigated the impact of preoperative cognitive impairment on mid-term functionality. Studies by Afilalo and Stortecky consistently found that cognitive impairment was associated with increased rates of mid-term mortality and decreased functionality.[5,17] However, only half of these studies were good quality, and only 1 study used multivariable analysis to control for demographic variables and comorbidities.

Afilalo aimed to compare the predictive value of 7 different frailty scales for mortality and decreased functionality 1 year after TAVR and SAVR. Afilalo found that all aspects of frailty, including cognitive impairment, were more prevalent in patients with mortality or with progressive disability at 1 year. While the independent effect of cognitive impairment was not assessed in the multivariable model, the study found that the Essential Frailty Toolset scale, which is a composite frailty score that encompasses assessment of lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia, was the best predictor of mid-term mortality and functionality compared to other frailty assessment methods.

Stortecky and Schoenenberger also found that cognitive impairment was a risk factor for mortality and functional decline in the midterm.[6] Schoenenberger identified risk factors for functional decline and mortality in elderly patients 6 months after undergoing TAVR. Using univariable analysis, Schoenenberger found that cognitive impairment was associated with functional decline or death at 6 months (OR = 3.18, 95% CI = 1.38−7.29, $P = 0.01$). Stortecky similarly concluded that cognitive impairment is associated with all-cause mortality at 1 year (OR = 2.98, 95% CI = 1.07−8.31, $P = 0.03$). However, both studies are vulnerable to significant confounding effect because neither performed multivariable analysis to control for age, sex, or comorbidities.

Eleid et al followed patients for the longest duration of an average of 2.2 years.[18] They sought to identify predictors of post-AVR survival. After multivariable analysis, the study concluded that cognitive impairment was one of the predictors of post-AVR mortality due to noncardiac cause (RR = 3.30, 95% CI = 1.00−7.97, $P = 0.0496$). The other predictors in this multivariable model included age, serum creatinine and hemoglobin, right ventricular systolic pressure, and stroke volume index.

Quality of Included Studies and Risk for Bias

The grading scheme by domain for each article is specified in Table 2. Five articles were good quality, while 3 were poor quality. The poor-quality articles had a high risk of bias in comparability, because they performed only univariable analysis. The good quality articles had a low risk of bias in selection, variable risk of bias in comparability, and low risk of bias in outcome.

Strength of Evidence

Using the GRADE criteria, a scoring system based on the number and quality of studies and consistency of results, the body of evidence for the effect of cognitive impairment on in-hospital, short-term and mid-term outcomes were of low quality (Table 3). Population selection and group allocation in the included studies is shown in (Table 4).

Table 2. Newcastle-Ottawa Scale Assessment of Study Quality

First Author, Year	Selection	Comparability	Outcome	Total	Quality
Ryomoto, 2017	4	1	3	8	Good
Afilalo, 2017	4	2	3	9	Good
Rudolph, 2006	4	2	3	9	Good
Jodati, 2013	0	0	2	2	Poor
Schoenenberger, 2013	4	0	3	7	Poor
Stortecky, 2012	4	0	3	7	Poor
Eleid, 2015	4	2	3	9	Good
Tse, 2014	3	1	3	7	Good

Table 3. Outcome Measures Assessed in Studies Meeting Inclusion Criteria and the Strength of the Body of Evidence for Each Outcome Studied

First Author, Year	Delirium	Length of Stay	Discharge Disposition	Mortality	Complications	Mortality	Functionality
Ryomoto, 2017		X	X				
Afilalo, 2017						X	X
Rudolph, 2006	X						
Jodati, 2013	X						
Schoenenberger, 2013						X	X
Stortecky, 2012				X		X	
Eleid, 2015						X	
Tse, 2014	X						
Summary of level of evidence*	(2) level 2b, (1) level 4	(1) level 3b	(1) level 3b	(1) level 4	none	(2) level 2b, (2) level 4	(1) level 2b, (1) level 4
Quality of Body of Evidence†	low	low	low	low	N/A	low	low

*Level of evidence based on Oxford Centre for Evidence-based Medicine's "Levels of Evidence."
†Grading based on the Cincinnati Children's Hospital Medical Center Evidence Collaboration's.

Table 4. Population Selection and Group Allocation in Included Studies

First Author, Year	Population Selection	Group Allocation	Incidence	Univariable/ Multivariable Analysis	Ascertainment of Cognitive Impairment Diagnosis
Ryomoto, 2017	85 patients undergoing AVR from 1/2008 to 10/2015	All underwent SAVR	Not reported	Not reported	None
Afilalo, 2017	1020 patients undergoing SAVR/TAVR at 14 centers in 3 countries between 1/2012 and 12/2015	SAVR/TAVR depending on clinical need	18% (179/1020)	Not reported	MMSE <24
Rudolph, 2006	97 patients undergoing CABG/valve surgery at three hospitals	CABG/Valve surgery depending on need	Not reported	OR 1.25, 95% CI 1.01−1.55	None
Jodati, 2013	329 patients undergoing open heart surgery during 2008−2009 at 1 center	CABG/Valve surgery depending on need	14% (48/329)	Not reported	Preexisting
Schoenenberger, 2013	119 consecutive patients undergoing TAVR from 9/1/2009−3/31/2011	All underwent TAVR	32.8% (39/119)	OR 3.18, 95% CI 1.38−7.29	MMSE <27
Stortecky, 2012	100 consecutive patients undergoing TAVR between 9/1/2009 and 12/31/2010	All underwent TAVR	32.0% (32/100)	OR 2.98, 95% CI 1.07−8.31	MMSE <27
Eleid, 2015	1120 consecutive patients with AS from 2006−2011	All underwent AVR	Not reported	RR 3.30, 95% CI 1.00−7.97	Preexisting diagnosis
Tse, 2014	All patients undergoing TAVR from 2008 to 2009 at 1 center	Transfemoral vs transapical approach based on clinical routine	25% transfemoral vs 11% transapical	OR 6.5, 95% CI 1.8−23.2	Preexisting diagnosis

AVR, aortic valve repair; CABG, coronary artery bypass graft; OR, odds ratio; CI, confidence interval; SAVR, surgical aortic valve repair; TAVR, transcatheter aortic valve repair.

DISCUSSION

This systematic review demonstrates that there are only 8 studies to date examining the association between cognitive impairment on postoperative outcomes among patients undergoing AVR. Three studies are of poor quality. Given the limited number of studies available and the poor quality of nearly half of these studies, there is low-quality evidence by GRADE standards that cognitive impairment predisposes patients undergoing TAVR and SAVR to worse in-hospital, short-term, and mid-term outcomes. Further investigation on each of these outcomes is needed. Below, we discuss each postoperative outcome separately.

Two good quality studies showed that cognitive impairment is a risk factor for POD (Tse and Rudolph). However, they used different methods of assessing for cognitive impairment. Given the paucity and heterogeneity of studies, there is weak evidence that either preexisting dementia or MCI is predictive of POD among AVR patients. MCI has been shown to be a predictor for POD in cardiac surgeries generally, but the effect among AVR patients is unclear. A systematic review found that among patients undergoing elective cardiac surgery, the most commonly reported risk factor for delirium included cognitive impairment.[19] However, this systematic review does not exclusively examine patients undergoing AVR, and results may be confounded by patients undergoing CABG. A more recent systematic review identified studies of patients undergoing on-pump cardiac surgeries and found strong evidence that POD was predicted by cognitive impairment among other risk factors.[20] However, this study did not focus solely on AVR nor did it include patients undergoing TAVR. Further research is needed as effective interventions against POD can be targeted to individuals at risk. According to one meta-analysis of cardiac and noncardiac surgeries, there is moderate-quality evidence that multicomponent interventions utilizing a combination of early mobilization, reorientation, attention to sensory deprivation, cognitive stimulation, sleep hygiene, a multidisciplinary team, etc., can reduce delirium in nonintensive care unit patients compared to routine care.[21]

In a recent Danish nationwide cohort study of patients who received heart valve surgery, the study found that as many as 26% of the cohort had an acute readmission and 8% died within 30 days.[22] While the research identified in our review on short-term outcomes is of low quality, MCI has been found to be a risk factor for short-term complications among surgical patients generally. In a systematic review that included gastrointestinal, cardiac, and orthopedic surgeries, cognitive impairment was found to be predictive of prolonged hospital stay, discharge to health-care facility, mortality, and decreased functional dependence.[23] However, many of the cardiac surgeries included were CABG or on-pump. Another systematic review found that hospitalized surgical and nonsurgical patients with dementia were more likely to have urinary tract infections, pressure ulcers, pneumonia, delirium, dehydration, and electrolyte balance.[24] They were also more likely to be readmitted. However, of the 11 studies included in the review, only 2 were surgical patients, and none were evaluated for MCI. Further research is needed to ascertain whether a routine cognitive assessment can predict which AVR patients may be at risk of a complicated postoperative course so that specific clinical pathways can be developed for these individuals.

In the same Danish study, 56% of patients who underwent SAVR and TAVR had a readmission rate of 2.4 per person within the first year, and 89% of whom had an acute readmission.[22] The study found that readmission was associated with self-reported low physical activity level and emotional quality of life. This study highlighted the need for long-term follow-up and rehabilitation, especially for individuals at risk for complications and functional decline. Two good quality studies in our review found that MCI was predictive of poor mid-term outcomes (Afilalo and Eleid). Despite these good quality studies, the body of evidence for cognitive impairment as a predictor for mid-term functionality and mortality is still of low quality. More studies are needed because cognitive impairment has been identified as a risk factor for poor mid-term outcomes in noncardiac surgeries. For example, a systematic review on patients undergoing hip surgery found that patients with cognitive impairment gained less functionality relative to patients without impairment even though the absolute gains were comparable.[25]

This is the first review to assess cognitive impairment as a prognostic factor for TAVR and SAVR patients. Previously, a systematic review by Anand evaluated frailty as a prognostic factor for TAVR patients and found that frailty was associated with early (≤30 days) or late (>30 days) mortality.[26] However, only 3 articles included in Anand's review assessed for cognitive function. Other systematic reviews evaluated cardiac and renal functions as possible predictors for outcomes after TAVR/SAVR, but not baseline cognitive function.[27,28]

With the initiation of TAVR in 2009, the population receiving AVR increased from an average age of 69 to 74 years at 1 institution.[27–29] Preexisting dementia and MCI is prevalent among this population. Dementia prevalence in persons over 70 in the United States in 2010 was estimated to be 14.7%.[30] In this systematic review, patients with MCI were as prevalent as 32.8%, 32.0%, and 30.7% in Schoenenberger, Stortecky, and Tse, respectively. Given the prevalence of MCI, we ought to understand the impact of MCI on patients' outcomes. Further studies need to elucidate how this impact may be different between TAVR and SAVR patients given the differing invasiveness of these procedures, and patients' surgical risk and coexisting medical conditions. The predictive value of cognitive impairment on postoperative recovery and prognosis should be thoroughly explored to target interventions to improve outcomes and minimize costs.[31]

Strengths and Limitations

Our systematic review has several strengths. First, we developed a protocol with dual reviewers, clear inclusion and exclusion criteria and good documentation for exclusion. Second, our literature search included a broad range of terms to ensure the inclusion of all relevant published literature. We included all qualified studies regardless of quality to minimize bias in the selection process.

There are several limitations to our systematic review. Only 1 study focused on patients undergoing SAVR solely. We included articles that also had patients undergoing CABG-only or combined CABG-SAVR, which may introduce confounders. Patients who undergo CABG-SAVR or SAVR have lower rates of peripheral vascular disease, diabetes, prior myocardial infarction, and surgical urgency than CABG-only patients.[32] Additionally, patients undergoing both SAVR and CABG have higher risk of short-term mortality than SAVR alone.[32] This study is also limited by possible

confounding effects of including both SAVR and TAVR patients. While TAVR is less invasive, TAVR patients have more comorbidities that may impact recovery.[3,33] Furthermore, we included all studies regardless of type of anesthesia given. It is important to note that different types of anesthetic such as midazolam are associated with increased risk of POD.[34]

Finally, we included English-only studies, restricted our search to 3 databases, and excluded posters, abstracts, reviews, and meta-analysis so we may have excluded good quality data. There may also be publication bias. The body of evidence based on the included studies was low for all outcomes measured, so we were not able to draw any firm conclusion from the included studies.

CONCLUSION

We identified a small number of good- and a few poor-quality studies that evaluated cognitive impairment as a prognostic factor of postoperative in-hospital, short-term, and mid-term outcomes. The overall body of evidence is weak for these outcomes. This systematic review highlights the need for more good quality studies to provide evidence regarding the incidence of MCI and dementia and associations with poor outcomes after TAVR and SAVR.

APPENDIX A. SEARCH TERMS

PUBMED

(alzheimer's OR dementia OR cognition OR "cognitive defects" OR "cognitive deficits" OR "cognitive disorders" OR "cognitive dysfunction" OR "cognitive function" OR "cognitive impairment" OR "cognitive status" OR " memory defects" OR "memory deficits" OR "memory disorders" OR "memory dysfunction" OR "memory impairment" OR "mental function") AND (anesthesia OR surgery or "surgical procedure" OR operation) AND (outcomes OR "outcome assessment" OR prognosis OR "surgical outcomes")

EMBASE AND MEDLINE

("alzheimer disease"/exp OR "alzheimer disease" OR "dementia"/exp OR "dementia" OR "cognitive defect"/exp OR "cognitive defect" OR "memory disorder"/exp OR "memory disorder" OR "mild cognitive impairment"/exp OR "mild cognitive impairment" OR "thinking impairment"/exp OR "thinking impairment") AND ("anesthesiology"/exp OR "anesthesiology" OR "surgery"/exp OR "surgery") AND ("outcomes research"/exp OR "outcomes research" OR "outcomes"/exp OR "outcomes" OR "outcome assessment"/exp OR "outcome assessment" OR "prognosis"/exp OR "prognosis") AND ("cognition"/exp OR "cognition" OR "mental function"/exp OR "mental function" OR "dementia"/exp OR "dementia") AND [1997−2017]/py AND [humans]/lim AND [english]/lim NOT ("children" OR "child" OR "pediatric" OR "adolescent")

Appendix B1. Mini-Mental State Examination

Category	Instruction	Points
Orientation	Year, month, day, date, season.	5
	Country, county, town, hospital, clinic.	5
Registration	Examiner names 3 objects then patient repeats objects (1 point each).	3
Attention	Subtract 7 from 100 five times (Answers: 93, 86, 79, 72, 65) OR spell "world" backward (D LR O W). Score best performance on either.	5
Recall	Ask for names of the 3 objects.	3
Language	Name a pencil and a watch.	2
	Repeat "no ifs, ands, or buts."	1
	Give a 3-stage command. Score 1 for each stage.	3
	Ask patient to read and obey a written command on a piece of paper.	1
	Ask patient to write a sentence. Score correct if it contains a subject and verb.	1
Copying	Ask patient to copy intersecting pentagons. Score correct if they overlap and each has 5 sides.	1
		Total: 30

Appendix C1. Functional Independence Measure Cognitive Subscale

Communication	Scoring Levels
Comprehension	7 — Complete Independence
Expression	6 — Modified Independence
	5 — Supervision
Social cognition	4 — Minimal assistance
Social interaction	3 — Moderate assistance
Problem solving	2 — Maximal assistance
Memory	1 — Total assistance

"Grading the body of evidence."

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