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Prediction of outcome in patients with severe aortic stenosis treated with transcatheter aortic valve implantation

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Cover: His Majesty The King, Harald V by Solveig Konst. Elected among several honourable contributions by the collegiate at the Department of Gastrointestinal Surgery

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For king and country.

List of papers

This thesis is based on the following papers:

I. Kjønås D, Dahle G, Schirmer H, Malm S, Eidet, J, Aaberge L, Steigen T, Aakhus S, Busund R, Rösner A: **Predictors of early mortality after transcatheter aortic valve implantation**: *Open Heart*. 2019; 6(1):e00936

II. Kjønås D, Dahle G, Schirmer H, Malm S, Eidet J, Aaberge L, Steigen T, Aakhus S, Busund R, Rösner A: **Risk scores for prediction of 30-day mortality after transcatheter aortic valve implantation: Results from a two-center study in Norway:** *Health Science Reports.* 2021; 4:e283

III. Kjønås D, Schirmer H, Aakhus S, Eidet J, Malm S, Aaberge L, Busund R, Rösner A: **Clinical and echocardiographic parameters predicting 1-and-2-year mortality after transcatheter aortic valve implantation**. *Frontiers in Cardiovascular Medicine - Heart Valve Disease*. 2021; 8(1730)

Selected abbreviations

AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
HF	Heart failure
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVGLS	Left ventricular global longitudinal strain
MR	Mitral regurgitation
PAD	Peripheral artery disease
PHT	Pulmonary hypertension
RV	Right ventricle
SAVR	Surgical aortic valve replacement
SPAP	Systolic pulmonary artery pressure
STE	Speckle tracking echocardiography
TAVI	Transcatheter aortic valve implantation
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography

1 Summary

Aortic stenosis (AS) is the most common valvular heart disease in the western world. Symptomatic severe AS carries a dismal prognosis if left untreated. Surgical aortic valve replacement has since its introduction in the 1960`s been the gold standard for treating patients with this condition. However, many patients were previously not offered surgical treatment due to high age or unacceptable surgical risk estimated by surgical risk scores.

Transcatheter aortic valve implantation (TAVI) has in the last decade emerged as a less invasive treatment modality where the valve is implanted using a catheter, thus omitting the need for heart-lung machine and invasive open surgery. Initially reserved for patients not eligible for open surgery, TAVI is now performed in patients with intermediate and even low risk for open surgery.

Despite expanding indications to include lower risk patients, one of the main challenges in clinical practice is evaluating patients not candidates for open surgery where the question arises whether or not they will tolerate and/or benefit from interventional treatment. Surgical risk scores have shown rather low accuracy predicting unfavourable outcome in patients treated with TAVI. Several TAVI specific risk scores have been developed, albeit none has been incorporated into routine clinical practice.

This thesis aims to explore if preoperative echocardiographic measures, including speckle-tracking analysis, in addition to clinical parameters could aid in the prediction of unfavourable early and mid-term outcome after TAVI in high-risk elderly patients with AS. Furthermore, it aims to evaluate how novel TAVI risk scores perform compared to established surgical risk scores in this population.

In our study we found both clinical and echocardiographic parameters to be predictive of short and mid-term mortality after TAVI. However, speckle-tracking analysis for left- and right ventricular functional assessment did not yield additional predictive value. Additionally, risk scores specific for patients treated with TAVI showed a trend toward better predictive accuracy compared to surgical risk scores.

A multimodal and multidisciplinary approach is needed when evaluating elderly high-risk patients for TAVI with no single clinical or echocardiographic parameter being the decisive factor. Risk scores provide a stronger foundation for informed consent rather than exclusion from interventional treatment.

2 Background

2.1 Aortic stenosis

2.1.1 Epidemiology and natural course

Aortic stenosis (AS) is the most common valvular heart disease in the western world with a growing prevalence due to an ageing population[1-3]. The most common aetiology of AS in this population is calcific AS which is a chronic progressive condition[3]. This process has traditionally been viewed as degenerative due to mechanical stress, but is now considered a complex and multifactorial pathobiological process characterised by progressive calcification and remodelling of the aortic valve (AV) leaflets causing gradual obstruction of cardiac outflow[4, 5]. This results in increased afterload, adaptive ventricular wall hypertrophy, decreased myocardial perfusion pressure, cardiac remodelling and fibrosis, systolic-and diastolic dysfunction, and eventually symptomatic heart failure. Dyspnoea, dizziness, angina and syncope are the most common symptoms of AS, and clinical presentation has been linked to hemodynamic patterns associated with AS[6]. Aortic valve replacement (AVR) is the only definite therapy for symptomatic severe AS which carries a dismal prognosis with average survival of 2-3 years without intervention[7-10].

2.1.2 Surgical treatment

Until the last decade, surgical AVR (SAVR) has been the gold standard in treating patients with symptomatic severe AS[11]. The procedure is invasive with the need for general anaesthesia, sternotomy, and cardiopulmonary bypass. SAVR has proven effectiveness on both survival and symptoms, and has low perioperative mortality in the absence of severe comorbidities[12-15]. However, approximately one third of patients with symptomatic severe AS were not offered surgical treatment due to high or unacceptable

operative risk and short life expectancy as result of advanced age and comorbid status[16-18].

2.2 Transcatheter aortic valve implantation

2.2.1 Procedure

Transcatheter aortic valve implantation (TAVI) is a less invasive treatment modality where a catheter is used to insert and position a balloon-or self-expanding valve inside the calcified native aortic valve. Common vascular access sites used are the femoral artery (TF-TAVI), subclavian artery (SC-TAVI), carotid artery (TC-TAVI), through the cardiac apex (TA-TAVI), or ascending aorta via a small sternotomy (TAo-TAVI). Access site used are determined by the patients' vascular anatomy and comorbid status. The transfemoral approach is the preferred modality as it is the least invasive, can be done in local anaesthesia, performed percutaneously, and is associated with lower risk[19, 20].

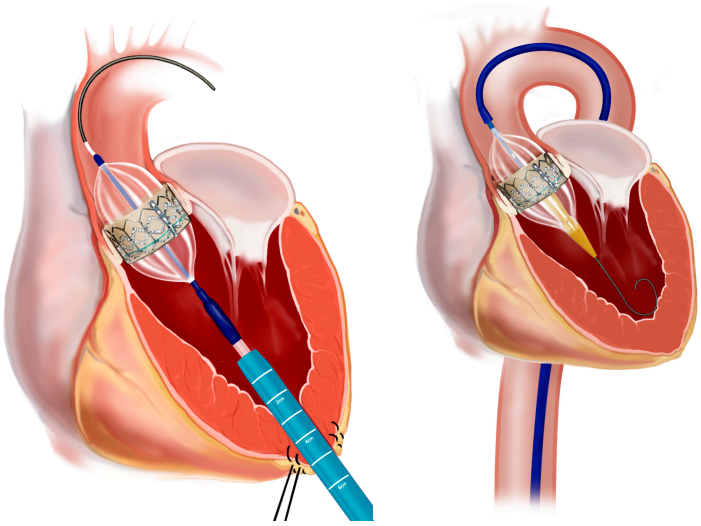

Figure 1: Transcatheter aortic valve implantation through the cardiac apex (left) and via the ascending aorta through transfemoral access (right). Source: Edwards Lifesciences.

2.2.2 From experimental to standard therapy

Henning Ruud Andersen published the first successful proof of concept for TAVI in animals in 1992 and in 2002 Cribier et al. published the first procedure in a human patient performed in April the same year[21, 22]. The initial feasibility, efficacy, and safety trials showed promising results in patients not candidates for SAVR due unacceptable risk[23-29]. The PARTNER (Placement of Aortic Transcatheter Valves) trial was the first multicentre randomised controlled trial (RCT) comparing TAVI with a balloon expandable valve vs. SAVR in patients with high operative risk (PARTNER A) and TAVI vs. standard therapy in patients with unacceptable risk (PARTNER B). The PARTNER A cohort consisted of 699 patients from 25 centres randomized to either SAVR (n=351) or TAVI (n=348), with the TAVI group being further randomized to TF-TAVI (n=244) or TA-TAVI (n=104). The PARTNER B cohort consisted of 358 patients from 21 centres randomized evenly between TF-TAVI and standard therapy. The study showed that TAVI was non-inferior compared to SAVR and superior to medical therapy with respect to 1-year all-cause mortality[30, 31]. Data from another multicentre RCT using a self-expandable prosthesis published shortly after the PARTNER trial showed similar results[32]. Results from subsequent follow-up studies and registry data displayed sustained efficacy and safety of TAVI over time compared to SAVR[33-41]. As a consequence, TAVI as a treatment option was incorporated into European and US practice guidelines in 2012 and 2014 respectively[42, 43]. In Norway, the first TAVI procedure was performed at Feiringklinikken in Oslo in the spring of 2008, and implemented as a treatment option at the University Hospital of North Norway (UNN) Tromsø in September the same year. Oslo University Hospital (OUS) Rikshospitalet and St. Olavs Hospital in Trondheim began treating patients with TAVI in 2009, and Haukeland University Hospital in Bergen the following year resulting in TAVI being

offered as a treatment option at all the major university hospitals in Norway. As a man of his people, His Majesty King Harald V was treated with TAVI at OUS Rikshospitalet in October 2020.

2.2.3 Current practice

Since the introduction of TAVI into routine clinical practice there has been an exponential growth in the number of procedures performed annually, a rapid development in catheter and valve technology, and a marked reduction in procedure related morbidity and mortality[44]. The indications for TAVI have expanded to include intermediate-and recently even low-risk patients including various vascular approaches and valve types[19, 45-49]. A Cohrane review from 2019 found, in the short-term, moderate-certainty evidence for little or no differences between all-cause mortality and major cardiovascular events in low-risk patients treated with TAVI or SAVR[50]. Although there are still unresolved issues regarding TAVI in younger patients, such as valve durability, it has become a standard treatment modality for a majority of elderly patients with symptomatic AS.

2.3 Echocardiography

2.3.1 Evaluation and diagnosis of aortic stenosis

Transthoracic echocardiography (TTE) is the most important diagnostic tool for the diagnosis of AS, estimation of its severity, and evaluation of cardiac function. Doppler echocardiography is the preferred method for the quantification of AS and is done by measuring mean transvalvular pressure gradient, maximum transvalvular velocity, and calculating aortic valve area (AVA)[51, 52]. Severe AS is generally defined as mean pressure gradient ≥ 40 mmHg, AVA ≤ 1.0 cm^2, or maximum velocity ≥ 4 m/s.[51]. Severe AS might still be present despite the criteria not being met as both pressure gradients and

velocities, and thus AVA estimate, are flow dependent. Therefore, echocardiographic measures for estimating degree of AS have to be considered together with functional and anatomical parameters for accurate diagnosis and classification of disease severity[49, 51].

2.3.2 Left ventricular systolic and diastolic function

The most commonly used echocardiographic parameter for estimation of left ventricular (LV) systolic function is ejection fraction (EF). LVEF is currently the only echocardiographic measure of LV function incorporated in the treatment algorithms for patients with symptomatic AS [49, 53, 54]. Reduced LVEF (<50%) is common in patients with AS, but data on the impact of reduced EF alone on survival after TAVI are somewhat equivocal[55-58]. The estimation of LVEF can be affected by small cavity size, due to concentric hypertrophy secondary to compensatory mechanisms in response to high afterload, in addition to loading conditions. This might result in an incomplete or incorrect estimate of LV function. Elevated intraventricular pressure in AS leads to LV diastolic dysfunction manifested by LV relaxations disturbances, which may result in increased end-diastolic pressure. Increased diastolic pressure is in turn associated with increased pulmonary artery pressure, which might increase mitral-or tricuspid regurgitation. Both of these parameters, as well as diastolic dysfunction, have been linked to adverse outcome after TAVI[59-61].

2.3.3 Low-flow states

Low trans-aortic flow in patients with severe AS has been identified as an important prognostic factor of mortality after TAVI[58, 62, 63]. Low-flow low-gradient (LF-LG) AS can be seen with both reduced and preserved LVEF. Reduced LVEF in this setting can be due to increased afterload, as in AS, or other causes such as myocardial ischemia or

cardiomyopathy[64]. Dobutamin stress-echocardiography can be performed to differentiate between these clinical conditions, where increase in flow indicates afterload dependent LV dysfunction. The presence of flow reserve in patients with LF-LG AS has prognostic implications in patients treated with SAVR, however the implications for patients treated with TAVI are less clear[65, 66]. First described in 2007, LF-LG AS with preserved EF is characterised by concentric hypertrophy and myocardial fibrosis causing restrictive filling and small ventricular size[67]. This results in intrinsic LV systolic dysfunction and reduced longitudinal shortening despite apparent normal EF. The condition is more common with advanced age, concomitant hypertension, in addition to cardiac amyloidosis, and indicates advanced fibrosis and disease stage associated with a poor prognosis[64, 68]. In patients with LF-LG AS, especially with preserved EF, the degree of myocardial fibrosis corresponds to impaired longitudinal function, but not EF, and has been associated with poor outcome[69, 70]. In this setting, contractile reserve cannot be sufficiently challenged by dobutamine-stress. Therefore, in patients with severe AS, especially in low-flow states, the estimation of LV systolic function solely based on EF is suboptimal. In this setting the evaluation of longitudinal function by tissue Doppler imaging, mitral annular peak systolic excursion (MAPSE), and/or longitudinal strain as a measure of LV systolic function may be more appropriate.[64]

2.3.4 Mitral regurgitation

Concomitant mitral regurgitation (MR) is common in patients with AS[71]. In patients treated with TAVI, MR has been shown to predict both early and late mortality, but whether it is an independent predictor or if the association is related to other pre-existing comorbidities is unknown[72-75]. MR can be primary or secondary, with the latter being caused by altered LV geometry due to compensatory mechanisms in response to

AS mediated increase in afterload. If present, MR improves in approximately 50% of patients treated with TAVI and its aetiology, severity, and presence post-TAVI might be of prognostic importance[73].

2.3.5 Right ventricular function

Right ventricular (RV) dysfunction is common in patients with AS evaluated for TAVI, however RV function is usually maintained in AS except in advanced disease or presence of concomitant pathology[76-78]. RV dysfunction may be secondary to pressure overload due to LV failure and increased pulmonary artery pressure, volume overload from fluid retention or concomitant tricuspid regurgitation (TR), myocardial ischemia, or intrinsic myocardial processes[78]. RV dysfunction has been associated with adverse outcome in patients treated with SAVR[79, 80]. In patients treated with TAVI these findings are still unclear. Results from three meta-analyses, the most recent published in 2020, indicate that RV systolic dysfunction (RVSD) were predictive of 1-year mortality after TAVI. Two meta-analyses showed additional effect of RV size and moderate to severe TR[81-83]. However, the studies included have a high-degree of heterogeneity in terms of the number of echocardiographic RV functional parameters used, the number of patients in each study, and predictors identified[84-89]. Cardiac Magnetic Resonance Imaging (MRI) is the gold standard for non-invasive measurement of RV function, but is impractical in daily clinical practice. Compared to the LV, the echocardiographic evaluation of RV volumes and EF is more challenging due to non-elliptical RV shape, complex geometry, trabeculated myocardium, retrosternal position, and marked load dependence[90]. These factors limit the echocardiographic quantification RV systolic function to surrogate markers including tricuspid annular peak systolic excursion (TAPSE), tricuspid annular systolic velocity (TASV) by Doppler, and RV fractional area change (FAC)[91]. Thus, the

optimal assessment of RV dysfunction, its cause and consequences, prognostic value of individual measures, and their implications regarding outcome in the TAVI population warrants further evaluation.

2.3.6 Tricuspid regurgitation and RV dilatation

Moderate to severe TR and RV dilation have been associated with increased mortality after TAVI although, as with RV dysfunction, these results are equivocal[85, 86, 92]. In patients with severe AS, LV failure increases pulmonary venous (post-capillary) pressure resulting in pulmonary hypertension (PHT) and subsequent increase RV afterload. The consequences of altered loading conditions are RV remodelling, dysfunction and dilatation resulting in larger tricuspid annular diameter. This causes a negative cycle of progressive RV dilation, worsening of TR, an increase in preload, and further deterioration of RV function[93].

2.3.7 Pulmonary hypertension

PHT frequently coexist with severe AS and the severity of PHT estimated by systolic pulmonary artery pressure (SPAP) is linked to adverse outcome after TAVI[94-98]. Isolated LV mediated PHT and its negative effects on the RV may improve after TAVI. However, increased pulmonary venous pressure can also be secondary to non-cardiac mediated (pre-capillary) PHT. The distinction between pre-and-post-capillary PHT has been shown to have prognostic implications with pre-capillary PHT, or combined PHT, being associated with worse outcome but data are limited[99, 100]. Invasive hemodynamic measurements are needed to differentiate between these entities. Therefore, its implementation in routine clinical practice is likely neither feasible nor cost-effective. The presence and severity of PHT, regardless of pre-or-post-capillary aetiology, and its

effects on RV function evaluated by echocardiography might provide additional prognostic information.

2.4 Myocardial deformation

2.4.1 Strain and speckle tracking echocardiography

Myocardial strain is a measure of the degree of deformation of the myocardium occurring as a response to an applied force or stress. Strain is expressed as fractional length change of the myocardium between time points during the cardiac cycle, and is usually measured as peak value between end-diastole (reference point) and end-systole[101]. Strain can be measured as deformation in three dimension; longitudinally, radially, and circumferentially. Speckle tracking echocardiography (STE) is a quantitative technique based on measuring the displacement of speckles (ultrasound-interference patterns) between image frames in standard 2-D sonograms. STE time-curves can be used to measure segmental (regional) and global myocardial strain, and is relatively angle-independent and less affected by cardiac motion compared to tissue Doppler strain.

2.4.2 Left-and right ventricular longitudinal strain

LV global longitudinal strain (LVGLS) has been shown to be a more reproducible measure of LV function compared to EF and a better predictor of mortality in patients with heart failure (HF) compared to other echocardiographic parameters[102, 103]. Strain allows for a more direct measurement of systolic function of the myocardium compared to traditional volume-based parameters such as EF. It can detect impairment of myocardial function despite normal EF and is associated with poor prognosis in patients with AS and adverse outcome after SAVR, especially in LF-LG states[104-107]. Reduced LVGLS is common in patients treated with TAVI and has been linked to increased risk of

mortality[108-110]. LVGLS is a measure of reduced longitudinal deformation corresponding to degree of myocardial fibrosis, and its ability to detect impairment of myocardial function in the setting of normal volume-based parameters could likely infer prognostic value.

RV function is mostly attributed to longitudinal shortening of the RV free wall that can be challenging to measure by conventional echocardiographic parameters due to angle dependency and complex geometry[90]. Reduced RV free wall longitudinal strain has been shown to be a predictor of mortality in patients with heart failure and preserved EF, and associated with mortality in high-risk patients treated with TAVI[111-113]. Despite standard TTE being invaluable in the diagnostic work-up of patients with AS the modality does have limitations, especially in the presence of compensatory changes secondary to cardiac damage influencing conventional measures of cardiac function. In this setting STE might provide additional information and possible predictive value when evaluating high-risk patients for TAVI.

2.5 Risk assessment and predictors of mortality

2.5.1 Risk scores and patient selection

Risk scores have been developed and validated to estimate the risk of perioperative mortality in patients treated with SAVR. The STS PROM (Society of Thoracic Surgeons Patient Related Outcome Measure) score and different iterations of the EuroSCORE (European System for Cardiac Operative Risk Evaluation) are incorporated into clinical practice guidelines and used to roughly categorise patients as low, intermediate, or high risk for surgical treatment[15, 114-116]. In general, SAVR is still the recommended treatment modality in younger low risk patients without clinical, anatomical, or technical aspects favouring TAVI. For patients with intermediate risk for SAVR the evaluation of

treatment modality should be individualised for each patient. In patients with prohibitive risk for SAVR, TAVI is only considered if there is an expected clinical benefit of interventional treatment, life expectancy >12 months, and the absence of contraindications[49, 54]. Both European and American guidelines for the treatment of AS recommend that a "heart team", comprised of a cardiologist and a cardiothoracic surgeon as a minimum, should determine patients' suitability for TAVI. Aided by risk scores, the multidisciplinary team should take into consideration the individual patients' comorbid and functional status, technical feasibility of TAVI including access site selection, and expected benefit in terms of clinical improvement and survival. Although risk scores are useful in the risk stratification of patients candidates for both treatment modalities, surgical risk scores have shown limited predictive accuracy and overestimate risk of mortality when applied to patients treated with TAVI[117-121]. Risk scores are only applicable to the patient population and procedure for which they were originally developed. As a result, several TAVI specific risk scores have been proposed based on national registry studies, but none are currently externally validated in large series or included in clinical practice guidelines[96, 97, 122-125]. Validated risk scores for identifying patients where TAVI might be futile in terms of clinical non-improvement and mortality is still lacking[54]. The continuous development, validation, and improvement in clinical decision tools are important in order to aid in treatment decisions, especially for high-risk patients in order to provide a better foundation for informed consent.

2.5.2 Risk factors for 30-day mortality

Several risk factors of 30-day mortality in patients treated with TAVI have been identified and described based on large national registry studies, which reflect clinical

practice compared to RCTs with strict inclusion criteria and cohort studies with no external validation[96, 97, 122-125]. Factors identified in these registry studies include both clinical and echocardiographic measures, are both cardiac and non-cardiac in origin and include, but are not limited to; access site, age, body mass index (BMI), chronic obstructive pulmonary disease (COPD), renal failure, peripheral artery disease (PAD), heart failure, reduced LV systolic function, and high systolic pulmonary artery pressure (SPAP). The heterogeneity of the comorbid profiles of TAVI patients over time, possible unknown clinically relevant covariates not included, in addition to the difference in recorded variables across registries might in part explain the variability in risk factors identified. Only moderate discriminative accuracy has been seen in TAVI specific risk scores developed from these studies.

2.5.3 Risk factors for mortality beyond 30-days

The results from follow-up studies of the initial trials comparing TAVI to SAVR in high-risk patients showed that survival rates in patients treated with TAVI were favourable, but the residual mortality remained significant[33, 34]. This finding is also seen in registry studies on similar patients populations[41, 126-129]. Both pre-existing conditions, including clinical and echocardiographic measures, and procedure related complications have been identified as predictors of mortality beyond the immediate postoperative period. The risk factors identified differ between studies and the differences are more pronounced compared to predictors of early mortality. This might be due to the additional uncertainties associated with the natural prognosis of pre-existing conditions and possible adverse events related to treatment. Prediction models aimed at prediction of mortality at 1-year have not yet shown adequate discrimination nor been externally validated[130 131]. The estimated risk of unfavourable outcome beyond the first

year would likely have less impact on patient selection, but rather give a better foundation for informed consent when opting for treatment or not.

3 Objectives

This thesis aims to explore if echocardiographic measures of the left and right ventricle, including strain by speckle-tracking analysis, in addition to clinical parameters could aid in the prediction of early and mid-term mortality after TAVI in high-risk patients. Furthermore, it aims to evaluate how novel TAVI risk scores perform compared to established surgical risk scores in patients treated with TAVI.

4 Materials and methods

4.1 Study populations

4.1.1 Prospective observation cohort (Paper I, II, and III)

The prospective observational cohort study included 227 patients with severe symptomatic AS treated with TAVI at UNN Tromsø and OUS Rikshospitalet from February 2010 through June 2013. At the time, this cohort comprised the majority of patients treated with TAVI in Norway. The patients were pooled from two separate studies, one from each centre, evaluating echocardiographic measures pre-TAVI on outcome following treatment. The multidisciplinary heart team at each centre determined the patient suitability for TAVI considering cognitive function and comorbid status as well as technical feasibility. Patients with inability to give informed consent, life expectancy less than 12 months, and low motivation for treatment were not offered TAVI. Mortality and complications were prospectively registered and retrospectively classified according to the Valve Academic Research Consortium (VARC) 2 criteria[132]. These patients constituted the derivation cohort in paper II. All patients gave written informed consent. The study was approved by the Regional Ethics Committees for Medical Research Ethics, North and South East Norway.

4.1.2 Retrospective cohorts (Paper II and III)

Paper II included an additional 241 consecutive patients treated with TAVI at UNN Tromsø between June 2010 and April 2017 constituting the validation cohort. These patients were included in order to evaluate the discriminative accuracy of the logistic model based on the predictors of 30-day mortality identified from the prospective observational cohort study. Selected patient demographics, clinical characteristics, and 30-day mortality were extracted retrospectively from the patients` electronic records in order to calculate surgical and TAVI specific risk scores. The inclusion of these patients was approved by the local Data Protection Office. Patients from OUS was not included in this cohort as it was defined as local quality control exceptive of prolonged ethical committee approvals.

In paper III, the specific predictors identified as predictors of mortality were assessed in a separate and more recent cohort consisting of 258 patients treated with TAVI at the University Hospital of North Norway Tromsø from January 2017 through September 2019. The local Data Protection Office approved the evaluation of our original results.

4.2 TAVI procedure

4.2.1 Prospective observational cohort

In the prospective observational cohort, the procedures were performed at UNN Tromsø and OUS Rikshospitalet. All TAVI procedures were done in general anesthesia using the first generation self-expanding Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota, USA) or either the first-or second generation Edwards SAPIEN-SAPIEN XT balloon expandable valve (Edwards Lifesciences, Irvine, California, USA) via TF, TA, or TAo access.

4.2.2 Retrospective cohorts

In the retrospective cohorts all procedures were done at UNN Tromsø. The procedure was done in general anesthesia only when TA, SC, TC, or TAo access was used. In paper II either a first, second, or third generation Edwards SAPIEN - SAPIEN XT - SAPIEN 3 balloon-expandable valve (Edwards Lifesciences, Irvine, California) or one of two types of self-expanding valves; first –or second generation Medtronic CoreValve - EvolutR (Medtronic Inc., Minneapolis, Minnesota) or the St. Jude Portico (St. Jude Medical, Minnesota, USA) was used. In paper III, a fourth generation Edwards SAPIEN 3 Ultra balloon-expandable valve and a third generation Medtronic Evolut Pro self-expanding valve was also employed.

4.3 Echocardiography

4.3.1 Technical aspects and evaluation of valve pathology

TTE was performed in all patients by an experienced operator using either an iE33 (S5-1 probe, Philips Medical systems, Andover, MA) or a Vivid E9 (GE Vingmed, Horten, Norway) scanner. Two-dimensional grey-scale images were obtained in the parasternal long-and short axis and apical four-, two-, and three-chamber views, with an adjusted four-chamber view at the largest transversal diameter of the RV for assessment of RV geometry and function. The degree of AS was estimated by measuring mean-and peak transvalvular pressure gradient and maximum velocity of the Doppler flow across the AV. The AVA was calculated from left ventricular outflow tract (LVOT) diameter, LVOT velocity time integral (VTI), and VTI across the AV using the continuity equation. LVOT and LVOT VTI were also used for calculating stroke volume and cardiac output. The degree of aortic regurgitation (AR) was estimated from the size of the regurgitation area by colour Doppler, pressure half time, and diastolic velocity in descending aorta

measured by Doppler-flow signal. The severity of mitral regurgitation (MR) was estimated by measurement and visual assessment of colour Doppler images, vena contracta, and proximal isovelocity surface area. The presence of mitral stenosis was evaluated by measuring mean gradients over the mitral valve in addition to pressure half time and valve area.

4.3.2 Evaluation of systolic and diastolic function

LV systolic function was estimated by EF and longitudinal function. LVEF was derived from the Simpson`s biplane method. MAPSE in the septal and lateral mitral ring in the apical four-chamber view was used for estimation of longitudinal function. LV diastolic function was assessed by E/A ratio, E/ e' ratio, and E deceleration time. LV stroke volume (SV) and cardiac output (CO) was derived from the LVOT diameter and LVOT VTI. Atrial volumes were measured in the apical four-chamber view at end-systole. Intraventricular septum thickness was measured during diastole in M-mode in parasternal long-axis view. RV function was evaluated in an adjusted four-chamber view at the largest transversal diameter of the RV. Systolic RV function was assessed by tricuspid annular peak systolic excursion (TAPSE) and tissue Doppler derived peak tricuspid annular systolic velocity (TASV) in the basal RV free wall. RV fractional area change (RV FAC) was calculated from RV end-diastolic (RVEDA) and end-systolic areas. Systolic pulmonary artery pressure (SPAP) was derived from continuous wave Doppler measurements of tricuspid regurgitation (TR) adding an estimate of right atrial pressure derived from respiratory variation of the diameter of the inferior vena cava. The degree of TR was estimated from visual assessment of the regurgitant signal. When TR was estimated as moderate or larger, continuous systolic reversal of the hepatic flow served as indicator for large TR.

4.4 Strain analysis

4.4.1 Strain measurement

All strain analyses were performed using speckle-tracking software VVI 7 (Siemens, Mountain View, CA, USA). LV longitudinal endocardial strain was obtained from standard high-resolution 2-D sonograms in the apical four-, two-, and three-chamber views (figure 2). LV GLS was defined as the average of three peak strain values of the three views. Longitudinal RV strain was attained from an adjusted four-chamber view including only segments of the lateral wall (figure 2). Continuous Doppler registration of the aortic flow was used to measure the time point of aortic valve closure. GLS values were extracted from strain-curves by defining the systolic time interval between the R-wave and the time-point of AV closure. In the presence of atrial dysrhythmia strain from three cycles, if available, was obtained and averaged. Strain curves with artefacts due to noise, reverberation, air, missing wall segments or insufficient tracking were discarded based on subjective visual assessment. If there were inadequate tracking of more than one of 6 segments per view (LV)), GLS measurement was not performed.

4.4.2 Estimation of measurement variability

Inter-and intra-observer variability of strain measurements was determined by randomly selecting strain recordings from 30 patients, which were reanalysed by another experienced observer. The main observer repeated the analysis of the same data after several months. Inter-and intra-observer variability was tested using Intra-class Correlation Coefficient.

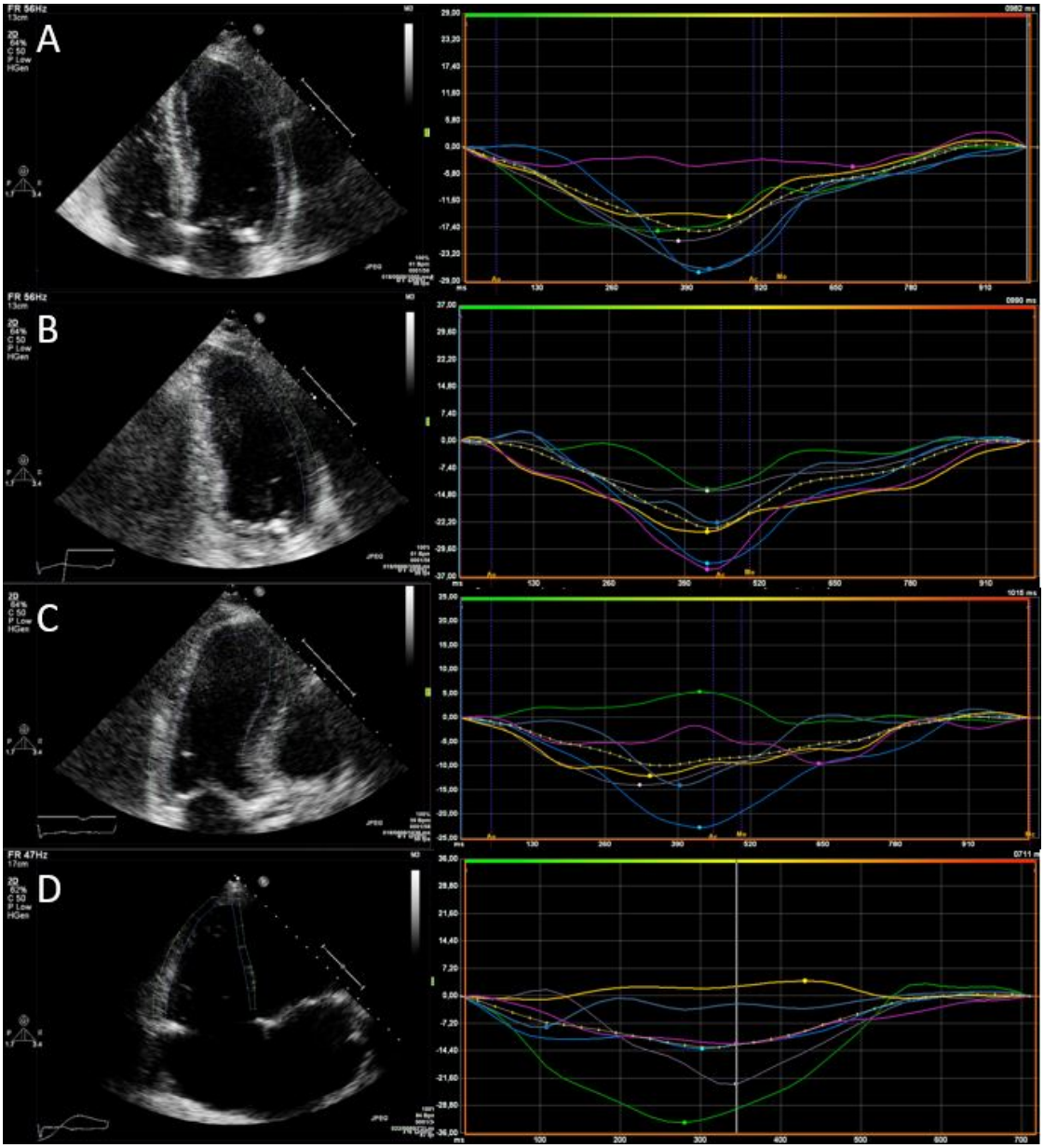

Figure 2: Examples of strain curves (right) generated by speckle tracking of the endocardial border (left) of the LV (A-C) in a four-chamber view (A), two-chamber view (B), and three-chamber view (C). Speckle tracking of the endocardium of the RV (D) with corresponding strain curves (right) where only segments of the lateral was extracted.

4.5 Risk scores (Paper II)

The surgical risk score evaluated in this study were the EuroSCORE, Logistic EuroSCORE, EuroSCORE II, and STS PROM (Society of Thoracic Surgeons) score[14, 15, 114, 115]. These scores were selected based on recommendations of clinical practice guidelines[49, 54].The calculations of these scores were done using validated publically available online calculators at euroscore.org and sts.org respectively. The TAVI specific risk scores evaluated were the FRANCE-2 (French Aortic National CoreValve and Edwards registry) score, IRRMA (Israeli TAVR Registry Risk Model Accuracy) score, German AV (German Aortic Valve) score, and OBSERVANT (Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic stenosis) score[96, 97, 122, 123]. These scores were selected because they had previously been evaluated and compared (with the exception of the IRRMA-score) in a separate study providing additional external validation of the discriminative accuracy for each score[97]. The calculation of each TAVI specific risk scores were done based on the respective original publications. All scores were calculated for both cohorts and compared to our own model based on the derivation cohort in paper I.

4.6 Statistical methods

The power calculation package in STATA version 12 was used for estimating the power of the study. A minimum detectable Hazard ratio of 1.25 for mortality for a 1-unit change for each echocardiographic variable with a power of 80% with a 5% probability of a false negative result was estimated. Clinical and- echocardiographic characteristics were in all papers presented as mean ± standard deviation, median (interquartile range), or numbers (percentages) as appropriate. Continuous variables were compared

using independent t-test or Mann-Whitney U test for normal and non-normal distributed data respectively. Categorical variables were compared using Pearson`s Chi-square test. In paper I and III univariable Cox regression analysis was performed for clinical and echocardiographic parameters where P<0.150 was considered statistically significant. Correlation, linearity, and interaction analysis was performed prior to multivariable analysis. A forward or backwards stepwise multivariable Cox regression analysis was performed depending on the absence or presence of statistically significant interactions respectively. The discriminative accuracy (C-statistic) for the logistic model for predictors of 30-day mortality was calculated from the predicted probabilities from binary logistic regression. In paper II, DeLong test was used to compare the C-statistic for risk scores, where P<0.05 was considered statistically significant. The Hosmer-Lemeshow test was used to evaluate calibration of each risk score. The Statistical analyses were performed using SPSS 24 with the exception of DeLong test that was performed using SAS statistical software version 9.4.

4.7 Author contributions

All data regarding patient demographics, clinical characteristics, perioperative results, and mortality were obtained by a thorough examination of the patients' electronic records at both OUS and UNN by the main author. This included data extraction and calculation of risk scores. Experienced operators at each centre performed all echocardiographic recordings with supplemental measurements on recorded images performed by the main author if needed. The author performed all strain analysis with Dr. Assami Rösner (main supervisor) performing additional analysis for the estimation of inter-and intra-observer variability. With the exception of power estimation the main author, under the guidance of supervisors, performed the statistical analysis.

5 Overview of results

5.1 Predictors of 30-day mortality after TAVI (Paper I)

Data from 218 patients treated with TAVI at the UNN Tromsø and OUS Rikshospitalet from February 2010 through June 2013 were included in the final analysis. All-cause 30-day mortality was 8.7% (n=19). Univariable and multivariable Cox regression analysis identified SPAP >60 mmHg (HR: 7.8, 95% CI 1.9-31.3, P=0.004), clinical signs of heart failure (HR: 2.9, 95% CI 1.1-7.8, P=0.03), TA access (HR: 3.8, 95% CI 1.3-11.2, P=0.015), PAD (HR: 5.9, 95% CI 1.9-17.9, P=0.002), and BMI (HR: 0.73, 95% CI 0.61-0.87, P<0.000) as predictors of 30-day mortality. A logistic model based on these predictors showed high discriminative accuracy in ROC-analysis with a C-statistic of 0.91 (95% CI 0.85-0.98). Despite a thorough preoperative echocardiographic evaluation, including strain analysis, the only echocardiographic predictor of early mortality identified was SPAP > 60 mmHg.

5.2 Risk scores (Paper II)

A logistic model (UNN/OUS) was developed from the prospective observational cohort (paper I). Selected surgical-and TAVI specific risk scores was calculated for all 218 patients. The same risk scores, including our own model, was calculated for a separate and more recent cohort consisting of 241 patients treated with TAVI between June 2010 and April 2017 at UNN Tromsø. The difference in discriminative accuracy between individual scores in each cohort was evaluated by DeLong test where P <0.05 was considered statistically significant. Our model showed statistically significant better accuracy than all other scores in the derivation cohort. In the validation cohort the FRANCE-2 had a significantly higher predictive accuracy compared to all previously

developed scores except the IRRMA -and STS score. Our model showed similar results. The TAVI specific IRRMA-and FRANCE-2 scores obtained a similar or higher discriminative accuracy in both cohorts compared to their originally published studies.

5.3 Predictors of mortality beyond 30-days after TAVI (Paper III)

All patients that died within 30-days after TAVI in the prospective observational cohort were excluded from the analysis with the aim to better identify risk factors not influenced by perioperative factors. The remaining 199 patients were included in the analysis. One-and two-year mortality was 12,1% (n=24) and 19,5% (n=39) respectively. Independent predictors of one-year mortality were lower BMI (HR: 0.88, 95% CI 0.80-0.98, P=0.018), previous myocardial infarction (HR; 2.69, 95% CI 1.14-6.32, P=0.023), and SPAP ≥60 mmHg (HR: 5.93, 95% CI 1.67-21.1, P=0.006). Predictors of two-year mortality were the presence of COPD (HR: 1.9, 95% CI 1.01-3.58, P=0.046), reduced eGFR (HR: 0.98, 95% CI 0.96-0.99, P=0.002), and moderate to severe MR (HR: 2.93, 95% CI 1.53-5.63, P=0.001). STE did not yield any additional predictive value. When evaluated in a more recent and less comorbid cohort, reduced eGFR remained the only significant predictor of mortality at 2-years.

6 Methodological discussion

6.1 Biases

The inclusion period of the prospective observational cohort study covered an early time period after the implementation of TAVI as a standard treatment option in Norway. These patients had high or unacceptable risk for SAVR defined by age and high preoperative risk estimated by surgical risk scores. Additionally, these patients were selected for TAVI at the discretion of the heart team and had the ability to consent for inclusion in a clinical study resulting in possible sampling-and selection bias. These biases are in part mitigated by a three-year inclusion period and the inclusion of patients from two separate centres. In paper III, patients with perioperative mortality within 30 days of TAVI were not included in the analysis in an attempt to more accurately identify preoperative conditions predictive of unfavourable outcome not influenced by peri-operative complications. Thus, there was a clear selection of patients based on a predefined time point that may result in omitting clinically relevant variables. In paper II, a single-centre cohort was evaluated reducing the external validity of the results.

6.2 Number of patients and missing data

The study cohorts were heterogeneous with a various composition of comorbidities, and differences in access site and valve type reflecting the TAVI population seen in clinical practice. Compared to large registry studies, we included a smaller number of patients with relatively few endpoints resulting in less power and higher uncertainty for each statistical outcome. In contrary to our study where multiple clinical and echocardiographic variables were evaluated, large registry studies have out of

practicality a limited number of variables that are investigated. This might result in missing the inclusion of factors that are potentially clinically relevant. In our studies, there were no patients lost to follow-up and echocardiographic measures, especially strain analysis, were the only aspects of the study where missing data occurred. This might contribute to the lack of possible associations between these parameters and the study endpoints observed in our study.

6.3 Statistical considerations

In paper I and III, a univariable Cox regression analysis was performed and a statistical level of significance of $P<0.15$ was selected resulting in several significant variables. However, reducing the level of significance in the univariable analysis could result in missing clinically relevant variables. After evaluation for possible correlations and interactions between variables, the result of multivariable stepwise Cox regression analysis, with a significance level of $P<0.05$, were highly significant. Thus stricter inclusion criteria in univariable analysis would not necessarily have changed the final result. A statistical level of significance of $P<0.20$ did not change the final results. In paper I, a logistic regression model was generated from the P-value-based stepwise selection of the predictors of 30-day mortality identified in the prospective observational cohort. Despite all variables identified being highly significant and the use of a forward multivariable analysis considering relevant covariates, the model was likely overfittet. This is because of a relatively small cohort, few endpoints compared to number of variables included, and the model reflected the results from the cohort from where it was derived. Consequently, the model was tested in a separate and more recent cohort of new patients from the same site, although an independent cohort would have been more optimal. The discriminative accuracy of the model was evaluated by

calculating the C-statistic obtained form Receiver Operating Characteristics (ROC) analysis of the predicted probabilities from the logistic model. There are several methods for evaluating discriminative accuracy. C-statistics is a global measure of diagnostic accuracy and facilitate general assessment and comparison of prediction models, but does not provide information regarding specific cut-off values.

7 Discussion

TAVI has in the last decade revolutionised the treatment of severe symptomatic AS in patients that were previously considered to have high or unacceptable risk for SAVR, a patient population for which the treatment was originally intended[30-32]. Despite the expanding indications for TAVI including patients that have previously been candidates for SAVR, one of the main challenges in clinical practice is to identify patients with high- or unacceptable risk even for TAVI. In this subgroup of patients in the current TAVI population, the aim of treatment is primarily relief of symptoms and eventually survival beyond what optimal medical treatment can provide. Factors associated with increased risk of mortality after TAVI in this population warrant improved patient selection and most importantly provide a better foundation for informed consent.

7.1 Echocardiographic measures and mortality

7.1.1 Left ventricular function

Echocardiography is an essential part in the diagnostic evaluation of patients with AS, although the definite prognostic impact of its individual parameters on both short-and long term mortality in high-risk patients is still unclear. Several echocardiographic parameters, including measures of both LV and RV function, have been associated with short-and long-term mortality[56, 57, 83]. In our study we included a wide array of echocardiographic variables for univariate analysis, albeit the only echocardiographic predictors of mortality identified were elevated SPAP and moderate to severe MR for 30-day -and 1-year mortality and 2-year mortality respectively. As mentioned in section 2.3.2, LVEF is currently the only anatomical and functional echocardiographic measure of LV function included in the treatment algorithms for AS despite unequivocal data on its prognostics implications and its inherent limitations. We found that neither LVEF nor

reduced longitudinal function, including evaluation of LVGLS, differed significantly between survivors and non-survivors at any time point. Reduced longitudinal function and deformation is associated with degree of myocardial fibrosis and impaired LV function regardless of EF[69, 70]. However, preliminary results from the TOPAS (True or Pseudo Severe Aortic Stenosis) study show that patients with low-flow states regardless of flow reserve treated with TF-TAVI have favourable outcomes, both in terms of mortality and functional improvement[133]. The conflicting data regarding the impact of reduced LV function on mortality and possible positive effects of TAVI in terms of survival, regardless of gradient or flow reserve, suggest that measures of LV function as a the sole echocardiographic parameter in risk stratification is not sufficient.

7.1.2 Right ventricular function, size, and tricuspid regurgitation

Despite a thorough evaluation of RV function including longitudinal strain of the RV free wall, no echocardiographic RV parameters differed preoperatively between survivors and non-survivors at any time point in our study. As noted in section 2.3.5, the cause of RV dysfunction can be multifactorial with RV function in AS usually being maintained unless concomitant pathology or advanced disease. Together with the inherent limitations of echocardiographic evaluation of RV function, uncertainties regarding impact of RV function on survival, and possibly more significant effect of other risk factors on mortality might explain the lack of association between RV function and mortality in our study. There was a significant difference in preoperative RVEDA and moderate to severe TR between survivors and non-survivors at 1-year post TAVI. However these parameters were not significant when adjusted for elevated SPAP. Both TR and RV size have been associated with adverse outcome and their presence likely

reflects adaptive responses to increased RV afterload secondary to PHT, but whether they alone predict outcome is still uncertain[81, 83, 85, 86].

7.1.3 Pulmonary hypertension

Marked elevated SPAP was a strong predictor of both 30-day and 1-year mortality in our study. The presence of PHT has been shown to be predictive of outcome after both TAVI and SAVR and incorporated into risk algorithms[96, 97, 114, 115]. As previously mentioned, the underlying cause of PHT can be pre-or-post-capillary or a combination of these two entities, with post-capillary or combined PHT being associated with worse outcome[99]. This is likely due to the possible reversibility of post-capillary PHT secondary to hemodynamic changes post TAVI. In our study we did not distinguish between pre-and-post capillary PHT. Regardless of underlying cause, we found the severity of PHT to be a predictor of unfavourable outcome in conformity with several previously published studies[96-98, 122, 123]. Severe PHT could indicate an irreversible condition less amenable to improvement after TAVI, although a significant proportion of patients with PHT do improve after treatment[98]. The cause of PHT, its severity, and possible reversibility seems to impact prognosis and is an important factor to consider when evaluating patients deemed high-risk even for TAVI [56, 95, 98-100, 114, 115, 134, 135]. However, its singular presence should not exclude patients from treatment as the benefits of TAVI likely outweigh the apparent risk in the presence of PHT. Whether efforts should be made to distinguish the cause of PHT in patients evaluated for TAVI is still uncertain.

7.1.4 Mitral regurgitation

Moderate to severe MR was in our study found to be an independent predictor of 2-year mortality and was more prevalent among non-survivors at 30-days and 1-year post TAVI. MR improves in a majority of patients after TAVI likely due to a reduction in LV

afterload, but residual moderate-to severe MR have been associated with increased risk of mortality[74, 75, 136-138]. Chronic MR itself is associated with poor prognosis, but there are currently no evidence suggesting operative management of secondary MR improve survival[54, 139]. With the development of catheter-based treatments for MR this might change in the future. Although the presence of significant MR seems to convey worse prognosis after TAVI, the definite prognostic implications of MR are still not clearly defined and its presence alone should currently not exclude patients for treatment with TAVI[73-75, 140].

7.2 Clinical parameters and mortality

7.2.1 Heart failure and ischemic heart disease

In our study we defined heart failure (HF) as physician-documented clinical signs of heart failure in the form of unusual dyspnea on light exertion, orthopnea, fluid retention, rales on auscultation, or pulmonary edema on chest X-ray less than two weeks prior to TAVI. New York Heart Association (NYHA) functional class IV has been linked to worse short term prognosis in patients treated with TAVI[96, 97, 122, 123, 141]. An objective assessment is needed in addition to patient reported symptoms as these are subjective, correlate poorly with ventricular function, and may be exacerbated by other disorders[53, 142, 143]. We found clinical signs of heart failure less than two weeks prior to TAVI to be an independent predictor of 30-day mortality. NYHA class IV or class ≥III did not statistically differ between survivors and non-survivors at 30-days, and neither NYHA class nor heart failure were predictive of mortality beyond 30-days. In patients with HF, there is clear relationship between severity of HF and survival[53, 144]. In elderly high-risk patients the classical self-reported symptoms of HF may be absent due to immobility or other concomitant comorbidity. Although we did not register data regarding ongoing

medical treatment for HF, and therefore did not evaluate its possible impact on outcome, patients with symptomatic HF may benefit from optimization of medical therapy prior to intervention. The most common cause of HF in general is ischemic heart disease that may still be present as myocardial scarring despite normal coronary angiogram[53]. Accordingly, we found previous myocardial infarction (MI) to be a predictor of 1-year mortality. CAD is frequent among patients evaluated for TAVI, but complete revascularization prior to treatment is not necessarily a prerequisite for favorable outcome[30, 32, 145, 146]. The implications of CAD on outcome likely depend on previous ischemic events, complexity of disease, extent of myocardial scarring, and the impact on cardiac function rather than its mere presence[147, 148].

7.2.2 Renal impairment

Impaired renal function is a common finding in elderly patients with severe AS evaluated for TAVI and has in several single-and multicentre studies and national registries been identified as a predictor of both short-and long-term all-cause-and cardiovascular mortality after TAVI[125, 128, 149-151]. The reason for this finding is likely multifactorial as patients with renal impairment are older, have a higher comorbid burden, and a higher incidence of peri-procedural stroke and complications[152, 153]. In our study there were statistically significant reduced eGFR between non-survivors and survivors 1-and 2-years post TAVI (P=0.011 and P=0.004 respectively), and an independent predictor of 2-year mortality. Additionally, eGFR was borderline significant between survivors and non-survivors at 30-days after TAVI (P=0.055). We did not divide the degree of renal impairment into stages and eGFR was analysed as a continuous variable supporting the importance of incremental worsening renal impairment as a prognostic factor[153]. Although patients with AS and impaired renal

function have increased risk of unfavourable outcome after TAVI, these patients still have considerably improved survival compared to patients treated conservatively[154]. Thus, the benefit of interventional treatment likely outweighs the risks.

7.2.3 Body mass index

We found lower body mass index to be an independent predictor of both 30-day and 1-year mortality, and the difference between survivors and non-survivors at 2-years was borderline significant (P=0.085). Although analysed as a continuous variable, the cut-off for BMI were found to be in the upper limit of normal range. This finding, termed the "obesity paradox", was first seen and described in patients undergoing percutaneous coronary intervention (PCI), but has also been observed in patients treated with SAVR and in patients treated with TAVI[155-158]. Data suggest that the relationship between BMI and outcome is not linear with increased mortality in very underweight and extremely obese patients, but overweight seems to convey favourable outcome compared to normal weight[159-161]. In our study there were too few patients at the extremes of BMI categories to stratify, but our results suggest improved short-and midterm survival with increased BMI. Several mechanisms behind the apparent paradoxical positive effect of high BMI on survival have been suggested including younger age, higher metabolic reserve, more intense follow-up for concomitant comorbidities resulting in earlier diagnosis, and less advanced disease stage[157, 159, 160, 162, 163]. In our study there were no difference in age between survivors and non-survivors at any time point and there was no clear difference in disease stage besides a higher comorbid burden among the non-survivors. Nonetheless, the exact mechanism behind the apparent paradoxical benefit of high BMI on survival has not yet been established. BMI is a measure derived from the patients` height and weight. It does not describe or reflect body composition nor fat

composition or distribution. The presence of low BMI alone does not necessarily indicate worse prognosis, and if present singularly should not exclude patients for treatment[164]

7.2.4 Chronic obstructive pulmonary disease

The presence of chronic obstructive pulmonary disease has been linked to unfavourable short-and long term outcome after TAVI in terms of mortality, postoperative respiratory complications, and clinical benefit[125, 165-167]. However in high-risk patients this association may in part be dependent on functional capacity, mobility, and low BMI[168]. The incidence of COPD in our study did not differ between survivors and non-survivors at 30-days, but were significantly more prevalent among non-survivors at 1-year and found to be an independent predictor of mortality at 2-years. The result was significant even though we did not stratify patients based on disease severity. Despite probability of worse outcome, patients with AS and impaired respiratory function treated with TAVI have improved survival compared to medical therapy[168]. In addition, discerning AS and COPD on symptoms might be challenging, including interpretation of pulmonary functional tests, making prediction of treatment effect difficult[169]. With most procedures now being performed via TF access in local anaesthesia and sedation, patients should be considered ineligible for treatment only in an advanced stage of disease and after a careful multidisciplinary evaluation.

7.2.5 Peripheral artery disease and access site

There are relatively few absolute contraindications for TAVI, but a prerequisite is suitable vascular access facilitating insertion of a catheter of adequate dimension for valve placement in the aortic annulus. Although the data are not completely unambiguous, there seems to be a clear association between access site and outcome in

favour of TF access[170-172]. In the presence of highly calcified narrow femoral and/or tortious pelvic vessel an alternative access site must be used. Despite that 95% of patients are now treated with TF-TAVI, alternative access options are still needed[173]. In our study we identified TA access as an independent predictor of 30-day mortality in line with results from registry studies[96, 97, 174]. There are still uncertainties whether the increased risk of mortality seen in TA-TAVI is a consequence of procedure related factors associated with access site or a result of increased comorbid burden often seen in these patients[175, 176]. The presence of PAD is an important factor in selection of access site, but its presence does not preclude TF access and was found to be an independent predictor of 30-day mortality in our study. This might be due to factors related to the procedure itself, a consequence of patient selection, or both, and its presence has been associated with both adverse outcome and increased risk of vascular complications[177]. As both TA-TAVI and TAo-TAVI require general anaesthesia and are performed via a mini-thoracotomy or mini-sternotomy respectively, these methods are considerably more invasive which likely infer additional stress on a patient already at risk as a result of pre-existing comorbidities. Although not used in our study, SC-TAVI and TC-TAVI are alternative vascular access sites where the former has been shown to be non-inferior to TF-TAVI and can be done percutaneously[178]. There are currently no RCTs comparing different access options. With the current success of TF-TAVI across all risk groups, such a study will not likely be performed. Different access options have unique features and technical aspects, and can be performed safely provided thorough assessment of technical feasibility for each individual patient. Therefore, the choice of access site depends on patient characteristics and local expertise requiring multidisciplinary cooperation in the preoperative evaluation and treatment.

7.2.6 Risk scores

Risk scores are intended to provide an estimate of the risk of an outcome from a pre-specified intervention. Ideally, risk scores should incorporate all variables associated with outcome related to the intervention. Estimated risk from these scores depends on variable composition, number of variables included, and weight assigned to each variable. Therefore, risk scores only reflect the patients' registered comorbid burden assumed to have an impact on outcome. Additionally, each risk score should be applicable to all populations receiving the same intervention. Surgical risk scores are still used in clinical practice to roughly estimate risk. Compared to patients treated with SAVR, the TAVI population is more heterogeneous for two main reasons: Firstly, there are numerous access options each with its unique features, technical challenges, and complications; Secondly, the TAVI population spans across a broader range of risk profiles from very low to unacceptable high risk due to a diverse comorbid spectrum. Incorporating all these factors into one unifying score is a tall order. With the exception of STS-PROM score we found in our study a clear trend towards better discriminative accuracy for two of the TAVI specific risk scores (FRANCE-2 score and IRRMA score), in addition to our own model. These two previous scores obtained a similar or higher discriminative accuracy in both our study cohorts compared to the studies from which they were derived[96, 97]. Interestingly the FRANCE-2 score obtained a higher discriminative accuracy in the more recent cohort with a C-statistic of 0.82, the same as our model, which is the threshold for clinical use. Both the FRANCE-2 score and IRRMA score have several common features with our own model, which might indicate the importance of these factors in the high risk TAVI population. However, the majority of patients are now being treated with TF-TAVI and procedure related morbidity and mortality are declining[173]. With decreasing morbidity and mortality following TAVI risk

scores should not necessarily be used to exclude patients from treatment, but rather strengthen the foundation for informed consent.

7.2.7 Frailty

Frailty can be described as an age-related syndrome characterized by physiological decline and vulnerability to adverse health events and has been associated with unfavourable outcome after TAVI [179-184]. However, there is no clear consensus on one definition of this clinical syndrome or how to best measure it in various clinical settings[185, 186]. Additionally, the prevalence of frailty in the TAVI population and its predictive value depends on how it is measured[180]. In our study we did not use a specific score to evaluate frailty. We included BMI and poor mobility, which are frequent parameters in frailty assessments[186]. In our study we defined poor mobility as severe impairment of mobility secondary to musculoskeletal or neurologic dysfunction. Poor mobility has been shown to predict unfavourable outcome after TAVI, but we found no difference in this parameter between survivors and non-survivors at any time point[183, 184]. Data suggest that frailty is an important factor to consider in elderly high-risk patients evaluated for TAVI and the incorporation of frailty measures into future risk scores might improve their accuracy. Identifying which factors that have an impact on outcome are important, as several might be amenable for optimisation prior to treatment. The on-going PERFORM-TAVR (Protein and Exercise to Reverse Frailty in OldeR Men and women undergoing Transcatheter Aortic Valve Replacement) trial is a multicenter RCT that aims to evaluate whether nutritional support and exercise could improve outcome in elderly frail TAVI patients. Until the prognostic value of specific frailty measures for the TAVI population is defined, a careful multidisciplinary evaluation of patients deemed at risk should be performed.

7.3 Ethical considerations

In addition to objectively considering the risk-benefit and benefit-cost trade-offs when evaluating patients for TAVI, shared decision-making with the patient regarding potential risks and expected outcome is equally important. Current guidelines define futility of TAVI as mortality within one year after treatment or lack of functional improvement[49, 54]. However, guideline-defined futility does not necessarily correspond to patient reported outcome. Subjectively, perceived effects of treatment are not necessarily reflected in the current outcome-based definition of futility[187]. In the elderly, the importance of potential improved quality of life after interventional treatment often supersedes the expected quantity[188]. There is an apparent discrepancy in the definition of futility between patients and health care providers. With TAVI now being a standard treatment option for patients with symptomatic AS with low procedural morbidity and mortality, the decision regarding treatment should likely be based on each patient's preferences based on information regarding expected outcome, possible risks, and potential residual impairment.

8 Conclusions

In elderly comorbid patients the effects of AS on cardiac function differ depending on disease stage, concomitant cardiac disease, extent of ventricular remodelling and fibrosis, and concomitant valvular disease. Because of the possible effects of AS on all cardiac functional parameters, a multimodal evaluation rather than a single parameter of cardiac function are likely needed for clarification of its prognostic implications in addition to patients` comorbid burden and symptoms.

In high-risk patients with symptomatic AS the estimation of risk of mortality is feasible. However, no single clinical parameter or risk score should alone be the decisive factor when evaluating patients for TAVI. A multidisciplinary holistic approach needs to be undertaken for each individual patient considering comorbid profile, technical aspects, and patients' functional status and expectations of treatment outcome.

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Paper I

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Predictors of early mortality after transcatheter aortic valve implantation

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ABSTRACT

Objectives To investigate whether preoperative echocardiographic evaluation of ventricular function, especially right ventricular systolic and diastolic parameters including speckle-tracking analysis, could aid in the prediction of 30-day mortality after transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis.

Methods This is a prospective observational cohort study including 227 patients accepted for TAVI at the University Hospital of North Norway and Oslo University Hospital from February 2010 through June 2013. All patients underwent preoperative transthoracic echocardiography with retrospective speckle-tracking analysis. Primary endpoint was all-cause 30-day mortality.

Results All-cause 30-day mortality was 8.7 % (n = 19). Independent predictors of 30-day mortality were systolic pulmonary arterial pressure (SPAP) > 60 mm Hg (HR: 7.7, 95% CI: 1.90 to 31.3), heart failure (HR: 2.9, 95% CI: 1.1 to 7.78), transapical access (HR: 3.8, 95% CI: 1.3 to 11.2), peripheral artery disease (HR: 6.0, 95% CI: 2.0 to 18.0) and body mass index (HR: 0.73, 95% CI: 0.61 to 0.87). C-statistic for the model generated was 0.91 (95% CI: 0.85 to 0.98). Besides elevated SPAP, no other echocardiographic measurements were found to be an independent predictor of early mortality.

Conclusion Except for elevated systolic pulmonary artery pressure, our data suggests that clinical rather than echocardiographic parameters are useful predictors of 30-day mortality after TAVI.

Key questions

What is already known about this subject?

- Prediction of early mortality after transcatheter aortic valve implantation (TAVI) is still imprecise.

What does this study add?

- Despite a thorough preoperative echocardiographic evaluation of left and right ventricular function, including speckle-tracking analysis, our data suggest that clinical parameters are more useful than echocardiographic measurements as predictors of early mortality after TAVI.

How might this impact clinical practice?

- When evaluating patients for TAVI, our data suggest that clinical rather than echocardiographic parameters are more useful in predicting early mortality. Whether this remains the case in today's TAVI population, which is younger and with fewer comorbidities, has yet to be determined.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become a treatment option for a growing number of patients with aortic stenosis (AS) with intermediate to high risk for surgical aortic valve replacement (SAVR).[1] However, there are still uncertainties about risk factors of early mortality for these patients. Identifying predictors of early mortality is important in order to improve patient selection and to give patients a better basis for informed consent. TAVI is now performed in patients with intermediate risk for SAVR[2] and there are ongoing studies even in low-risk patients (NOTION-2/NCT02825134, PARTNER 3/NCT02675114, Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients/NCT02701283). These patients are still candidates for open surgery where the risk factors are better identified and incorporated into validated risk algorithms. Despite the development of novel TAVI-specific risk algorithms,[3–6] risk factors specific for TAVI are currently not fully understood. Both established surgical and novel TAVI-specific risk algorithms are comprised primarily of clinical parameters with the exception of systolic pulmonary arterial pressure (SPAP) and ejection fraction (EF). While the evaluation of left ventricular (LV) function on the outcome after TAVI has been extensively studied,[7 8] the knowledge of the impact of right ventricular (RV) function on periprocedural outcome is still limited. RV dysfunction is linked to adverse outcome in several cardiovascular conditions including AS and heart failure.[9 10] The aim of our study was to investigate whether preoperative echocardiographic evaluation of ventricular function, especially RV systolic and diastolic parameters including speckle-tracking analysis, in

addition to clinical parameters could aid in the prediction of unfavourable early outcome after TAVI.

METHODS

Study population

From February 2010 through June 2013, 227 patients from the University Hospital of North Norway Tromsø and Oslo University Hospital Rikshospitalet with severe symptomatic AS accepted for TAVI were included in the study. A multidisciplinary heart team determined the patient suitability for TAVI considering cognitive function and comorbid status of the patient as well as technical feasibility. Patients with inability to give informed consent, life expectancy less than 12 months and low motivation for treatment were not offered TAVI. Primary endpoint was all-cause 30-day mortality classified according to the Valve Academic Research Consortium (VARC)-2 criteria.[11] The study was approved by the Regional Ethical Committees for Medical Research Ethics, North and South East Norway. All patients gave written informed consent.

Patient characteristics

Patient demographics, clinical characteristics, periprocedural mortality and complications were obtained from the patients' electronic records. Chronic obstructive pulmonary disease (COPD) was classified according to the global initiative for chronic obstructive lunge disease (GOLD) classification. Patients with COPD of unknown grade were classified as having grade 1. Previous cerebrovascular events comprised both previous strokes and transient ischaemic attacks. Chronic and paroxysmal atrial fibrillation/flutter was grouped as one variable. Heart failure was defined as physician-documented clinical signs of heart failure in the form of unusual dyspnoea on light exertion, orthopnoea, fluid retention, rales on auscultation or pulmonary oedema on chest X-ray less than 2 weeks prior to TAVI. Peripheral artery disease (PAD) was defined as claudication, previous amputation due to vascular insufficiency, previous reconstructive surgery or percutaneous intervention, abdominal aortic aneurism and/or >50% stenosis in a peripheral artery diagnosed by CT or angiographic imaging.

Echocardiography

All patients underwent preoperative transthoracic echocardiographic evaluation with either an iE33 (S5-1 probe, Philips Medical systems, Andover, MA) or a Vivid E9 (GE Vingmed, Horten, Norway) scanner using a 2.5–3.5 MHz transducer in the left lateral decubital position. Conventional two-dimensional grey-scale images were obtained in the parasternal long-axis and short-axis view, as well as the apical four-chamber, two-chamber and three-chamber views. Left ventricular EF (LVEF) was derived from the Simpson's biplane method. The same two views served to calculate left atrial volumes at end-systole. LV longitudinal function was assessed by mitral annular plane systolic excursion in the septal and lateral mitral ring in the apical four-chamber view. Intraventricular septum thickness in diastole was measured in M-mode images in the parasternal long-axis view. Diastolic LV function was assessed by E/A ratio, E/e′ ratio and E deceleration time. The degree of AS was derived from the mean and peak gradient of the Doppler flow across the aortic valve, as well as the aortic valve area derived by the continuity equation. LV stroke volume, cardiac output and cardiac index were derived from the LV outflow tract (LVOT) diameter and LVOT velocity time integral. The degree of aortic regurgitation was estimated by the size of the regurgitation area by colour Doppler, pressure half-time and diastolic velocities in descending aorta by Doppler-flow signal. The degree of mitral regurgitation (MR) was based on measurement and visual assessment of colour Doppler images, vena contracta and proximal isovelocity surface area.

RV geometry and function were evaluated in an adjusted four-chamber view at the largest transversal diameter of the RV. Systolic RV function was assessed by tricuspid annular peak systolic excursion (TAPSE) and tissue velocity imaging derived tricuspid annular systolic velocity in the basal RV free wall. RV areas were measured in end-diastole and end-systole and used for calculating fractional area change. RV longitudinal diameter in diastole was measured as the distance from the RV apex to the middle of the RV annulus. RV mediolateral diameter in diastole was measured from the intraventricular septum to the RV free wall at the widest part of the RV cavity. SPAP was derived from continuous wave Doppler measurements of tricuspid regurgitation (TR) and respiratory variation of the diameter of the inferior vena cava. When TR gradient was not recorded, SPAP was considered being <30 mm Hg if TR was described by visual assessment as trivial or mild, and 30–60 mm Hg when TR was described as moderate.

Strain analyses

Strain analyses were performed using speckle-tracking software VVI7 (Siemens, Mountain View, CA, USA). Longitudinal LV strain was obtained by analyses of the LV in the apical four-chamber, two-chamber and three-chamber views. Longitudinal RV strain was obtained from an apical four-chamber view including segments of the lateral wall only (figure 1). The time point of the aortic valve closure was measured in continuous Doppler registrations of the aortic flow. Global strain peak longitudinal strain values were extracted from strain curves by defining the systolic time interval between R-wave and the time point of aortic valve closure. Strain curves with artefacts due to reverberation, air artefact or insufficient tracking were discarded based on subjective visual assessment. In patients with atrial arrhythmia, strain from three cycles, if available, was obtained and averaged.

TAVI procedure

All TAVI procedures were performed under general anaesthesia with transfemoral (TF), transaortic (TAo) or transapical (TA) access using either first-generation

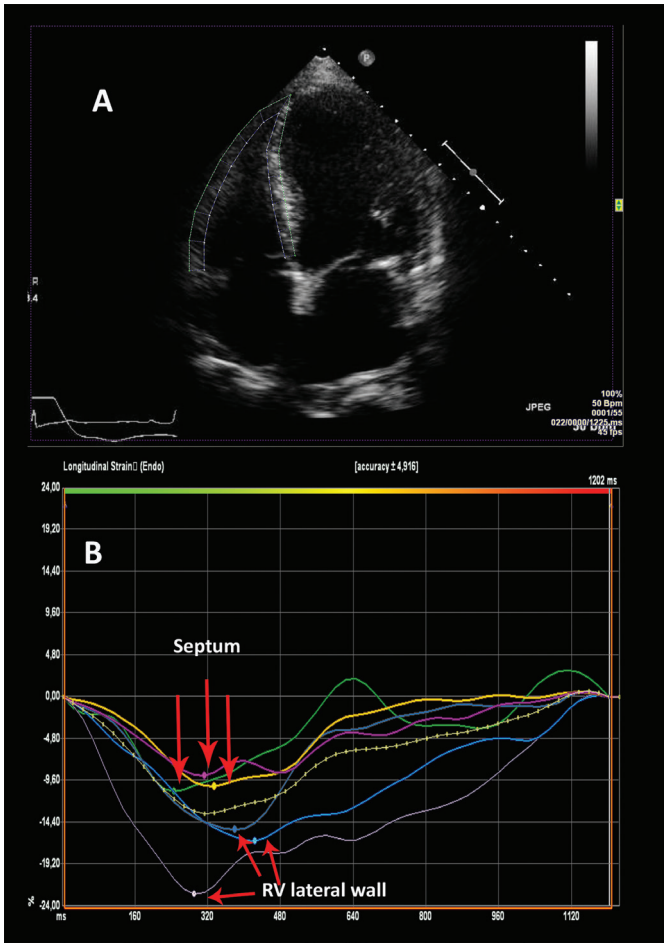

Figure 1 Example of how the RV strain curves are generated from a two-dimensional four-chamber view. RV, right ventricular.

self-expanding Medtronic CoreValve (Medtronic, Minneapolis, MN, USA) or either first- or second-generation Edwards SAPIEN-SAPIEN XT balloon-expandable valve (Edwards Lifesciences, Irvine, CA, USA). Valve size was determined from the aortic annular diameter measured by CT scan reconstruction and/or transesophageal echocardiography. TF access was the preferred modality. TA access was used in the presence of highly calcified and tortious pelvic vessels given acceptable LV and respiratory function. In the presence of inaccessible peripheral vessels and reduced LVEF or COPD, TAo access was used.

Statistical analysis

The power of the study was calculated using the power calculation package in STATA V.12. We estimated a minimum detectable HR of 1.25 for mortality for a 1-unit change for each echocardiographic variable with a power of 80% with a 5% probability of a false-negative result. Data are presented as number (%) or mean±SD as appropriate. Variables between groups were compared using Pearson χ^2 or independent t-test for percentages and continuous variables, respectively. Univariable Cox regression analysis was performed for all-cause 30-day mortality. Variables with p<0.15 and deemed clinically relevant were selected and tested for interaction and co-linearity prior to forward and backward multivariable Cox regression analysis. When the interaction terms in the backwards analysis were non-significant, the forward model was used. No imputation for missing data was performed and multivariable analyses performed on all available patients for each analysis. The final model was based on 213 patients. P<0.05 in multivariable analysis was considered significant. C-statistic for predicted 30-day mortality in our cohort was obtained from receiver operating characteristic (ROC) analyses of the predicted probabilities generated from binary logistic regression. All statistical analysis was done using SPSS V.24 (SPSS, Chicago, IL, USA).

Reproducibility

To determine the interobserver and intraobserver variability of longitudinal strain measurements, recordings from 30 patients were selected at random and another experienced observer repeated the analysis. The same data were reanalysed by the main observer after several months. Intraclass correlation coefficient was used to test interobserver and intra-observer variability.

RESULTS

The patients' demographics, clinical characteristics and periprocedural results are listed in table 1 and echocardiographic parameters in table 2. Nine patients were excluded from final analysis including three patients who did not undergo TAVI, five cases where preoperative echocardiographic images were not accessible and one patient with aortic insufficiency and not stenosis. The remaining 218 patients were included in the final analysis. All-cause mortality at 30 days was 8.7% (n=19). Six (32%) of these patients died peroperatively. Postoperatively, 12 (63%) died of cardiovascular causes where three (16%) were due to myocardial infarction, five (26%) secondary to cerebrovascular event and one (5%) from either bleeding, worsening heart failure, procedure related or death of unknown cause. One (5%) died of non-cardiovascular cause due to subarachnoid haemorrhage secondary to trauma. These patients had significantly lower body mass index (BMI), higher peripheral vascular disease burden, more TA procedures and a higher percentage of patients with SPAP >60 mm Hg. The difference in the presence of moderate to severe MR and heart failure was borderline significant between the groups. There was no interaction between variables in our data consequently a forward multivariable regression analysis was performed. All clinically significant variables with p<0.15 in univariable analysis and the result of multivariable analysis are shown in table 3. All variables included in the final model were highly significant in univariable analysis and maintained significance after multivariable analysis. Figure 2 displays the Kaplan-Meier curves for each independent predictor of all-cause 30-day mortality.

Table 1 Baseline demographics, clinical characteristics and periprocedural results stratified according to 30-day mortality

Variable	Survivors (n=199)	Dead (n=19)	P value
Age, years	82±7	80±8	0.330
Female	89(45)	9 (47)	0.825
Body surface area, m^2	1.8±0.2	1.7±0.1	0.005
Body mass index, kg/m^2	26±5	22±3	0.001
STS score	5.9±3.9	8.3±4.4	0.012
Euroscore 2	9.4±7.2	11.3±8.8	0.300
NYHA class			0.527
II	29(15)	2 (11)	
III	120(60)	10(53)	
IV	50(25)	7 (37)	
Heart failure	84(42)	12(63)	0.079
Hypertension	133(67)	15(79)	0.280
Atrial dysrhythmia	89(45)	11(58)	0.271
Previous myocardial infarction	76(38)	6 (32)	0.570
Previous PCI	78(39)	9 (47)	0.487
Previous cardiac surgery	93(47)	5 (26)	0.087
LBBB	18(9)	2 (11)	0.831
Peripheral artery disease	66(33)	14(74)	<0.000
Porcelain aorta	21(11)	5 (26)	0.043
Cerebrovascular disease	52(26)	6 (32)	0.608
Previous cerebrovascular event	46(23)	6 (32)	0.408
Immunocompromised	24(12)	4 (21)	0.263
Diabetes	59(30)	3 (1.5)	0.201
COPD	70(35)	8 (42)	0.547
eGFR, ml/min/1.73 m^2	54±20	50±24	0.055
Previous radiation therapy	8 (4)	1 (5)	0.795
Access			0.001
Transfemoral	117(59)	5 (26)	
Transaortic	27(14)	1 (5)	
Transapical	55(28)	13(68)	
Valve type			0.206
Edwards Sapien	153(77)	17(89)	
CoreValve	46(23)	2 (11)	
Periprocedural results			
Intraoperative mortality	–	6 (2.8)	
Myocardial infarction	3 (1.5)	3 (16)	<0.000
Cerebrovascular event	6 (3)	7 (37)	<0.000
Major or life-threatening bleeding	5 (2.5)	5 (26)	<0.000
PVL moderate to severe	18(9)	2 (10.5)	0.085
Permanent PM postoperatively	17 (8.5)	0 (0)	–

Values are mean±SD or *n* (%)
COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block;NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; PVL, paravalvular leakage; STS, society of thoracic surgeons; eGFR, estimated glomerular filtration rate; eGFR, estimated glomerular filtration rate.

SPAP >60 mm Hg was the only independent echocardiographic predictor of early mortality and was present in 21 (9.6%) of the patients. In all, 14 (67%) of these had clinical signs of heart failure prior to surgery, 11 (52%) had COPD and 6 (29%) had both. Out of the 21 patients with SPAP >60 mm Hg, five (24%) died within 30 days after treatment, with three having concomitant clinical signs of heart failure, two had COPD and one had both. Heart failure was present in 12 (63%) patients with early mortality compared with 96 (44%) in the whole cohort. Neither New York Heart Association (NYHA) IV nor NYHA III and IV combined were identified as risk factors by univariable analysis. TA access with concomitant PAD was present in 12 (63%) patients who died within 30 days compared with 22 (11%) of the survivors. All of these patients died of cardiovascular causes. BMI was analysed as a continuous variable and was still statistically significant as a predictor of early mortality even when patients with BMI <20 kg/m^2 (n=17) were excluded from analyses (HR: 0.79, 95% CI: 0.649 to 0.97, p=0.025). C-statistic for the model generated from multivariable regression analysis in our cohort was 0.91 (95% CI: 0.85 to 0.98).

Reproducibility

Intraclass correlation coefficient for longitudinal strain measurement was 0.799 (95% CI 0.695 to 0.868) and 0.924 (95% CI 0.885 to 0.950) for interobserver and intraobserver variability, respectively.

DISCUSSION

All-cause 30-day mortality rate was 8.7% which is similar to registry data from the same period.[12] All but one patient died of cardiovascular causes as defined by the VARC-2 criteria.[11] In our study, we identified SPAP >60 mm Hg, heart failure, TA access, PAD and BMI as independent predictors of 30-day mortality after TAVI and the model showed high accuracy in ROC analysis correctly allocating 91% as cases or controls.

Despite a thorough preoperative echocardiographic evaluation, especially of RV systolic and diastolic functional parameters, we did not identify any echocardiographic marker for early mortality except for SPAP >60 mm Hg.

Table 2 Preoperative echocardiographic parameters stratified according to 30-day mortality

Variable*	Survivors (n=199)	Dead (n=19)	P value
LVEF %, (n=212)			0.751
≥50	100(50)	10(53)	
31–49	72(36)	7 (37)	
≤30	22(11)	1 (5)	
LVLS, (n=198)	−11.1±3.8	−10.9±3.6	0.783
MAPSE septal, cm (n=212)	0.70±0.27	0.67±0.31	0.691
MAPSE lateral, cm (n=212)	0.99±0.32	1.0±0.31	0.844
IVSDd, cm (n=202)	1.2±0.3	1.3±0.3	0.158
AVA, cm^2 (n=215)	0.63±0.21	0.58±0.20	0.407
AVA index, cm^2/m^2 (n=215)	0.34±0.11	0.34±0.11	0.802
AV gradient max, mm Hg (n=215)	84±24	77±20	0.189
AV gradient mean, mm Hg (n=215)	52±15	47±12	0.202
AV max velocity, m/s (n=216)	453±67	430±58	0.162
SV LVOT index, ml/m^2 (n=216)	37±11	35±12	0.559
LVOT diameter, cm	2.1±0.25	2.1±0.23	0.348
E/é (n=148)	19.2±8.1	18.1±9.7	0.644
E/A (n=147)	1.1±0.6	0.8±0.5	0.159
MV deceleration time, ms (n=215)	227±92	221±89	0.769
MV E, cm/s (n=215)	96±34	89±39	0.454
LA volume index, mL/m^2 (n=204)	53±20	53±22	0.995
MR moderate to severe (n=209)	38(20)	7 (37)	0.079
AR moderate to severe (n=213)	35(18)	3 (16)	0.777
Mitral stenosis	9 (5)	1 (5)	0.816
SPAP, mm Hg (n=215)			0.033
>60	16(8)	5 (26)	
30–60	120(60)	10(53)	
<30	63(32)	4 (21)	
TAPSE, cm (n=204)	1.6±0.5	1.7±0.5	0.405
TASV, cm/s (n=133)	9.5±3.2	10.9±3.3	0.140
FAC, % (n=197)	36±13	37±9	0.655
RVEDA, cm^2 (n=197)	20±5	21±5	0.469
RVESA, cm^2 (n=197)	13±5	13±3	0.872
TR moderate to severe (n=213)	40(21)	5 (26)	0.562
RVLS, % (n=171)	−16±7	−16±6	0.888

Continued

Table 2 Continued

Variable*	Survivors (n=199)	Dead (n=19)	P value

Values are mean±SD or n(%).
*Numbers in brackets indicate the number of cases where the measurement was available.
AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; FAC, fractional area change; IVSDd, intraventricular septum diameter in diastole; LA, left atrium; LVLS, left ventricular longitudinal strain; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAPSE, mitral annular plane systolic excursion; MR, mitral regurgitation; MV, mitral valve; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVLS, right ventricular longitudinal strain; SPAP, systolic pulmonary arterial pressure; SV, stroke vol; TAPSE, tricuspid annular peak systolic excursion; TASV, tricuspid annular systolic velocity; TR, tricuspid regurgitation.

In a study based on 870 patients undergoing TAVI, Testa *et al* found that patients with TAPSE <10 mm had increased risk of mortality at 30 days[13] in contrast to two other studies where TAPSE was not found to predict early mortality.[14 15] Both RV dilation and reduced TAPSE have been linked to increased risk of long-term mortality.[13 14 16 17] Barvalia *et al* found TR to be an independent risk factor for early mortality after TAVI.[18] To the best of our knowledge, no other studies have identified any RV ventricular functional parameter as independent risk factor for early mortality besides elevated SPAP. The number of previous studies evaluating the effects of RV function on periprocedural outcome is low and the RV functional parameters included are often incomplete. Based on our results, the addition of speckle-tracking analysis did not yield any additional benefit in terms of evaluating the effect of RV nor LV function on early mortality.

Pulmonary hypertension

In all patients with pulmonary hypertension (PHT) in our cohort, we observed the two most common reasons for this condition; either COPD, heart failure or both. COPD has been identified as an important comorbid factor in patients undergoing TAVI with PHT.[19] In contrast to large registry studies, we did not identify COPD as an independent predictor for early mortality.[4–6] While mild PHT might be associated with reversible increased PAP in heart failure, markedly elevated PAP probably indicates an irreversible condition in patients with heart failure that might not improve after TAVI. Irreversible PHT causes reduced cardio-circulatory reserve resulting in impaired ability to increase stroke volume and cardiac output. As a consequence, patients undergoing TAVI might have inadequate circulatory compensatory mechanism during and after the intervention in response to rapid load changes, anaesthesia and rapid pacing. Our finding of marked PHT as an independent risk factor for early mortality after TAVI is in accordance with data from several registry studies.[3–6]

Table 3 Results of univariable and multivariable analysis for all-cause 30-day mortality

	Univariable			Multivariable		
Variable	P value	HR	95% CI	P value	HR	95% CI
Body mass index, kg/m^2	<0.000	0.78	0.68 to 0.90	<0.000	0.73	0.61 to 0.87
Heart failure	0.083	2.78	0.90 to 5.80	0.03	2.95	1.11 to 7.78
Access	0.004			0.017		
Transfemoral		Ref			Ref	
Transaortic	0.905	0.88	0.10 to 7.51	0.614	0.57	0.06 to 5.14
Transapical	0.011	4.98	1.78 to 13.99	0.015	3.8	1.29 to 11.16
SPAP, mm Hg	0.053			0.004		
<30		Ref			Ref	
30–60	0.737	1.22	0.38 to 3.89	0.688	1.28	0.39 to 4.14
>60	0.038	4.03	1.08 to 14.99	0.004	7.77	1.90 to 31.28
Peripheral artery disease	0.002	5.16	1.86 to 14.34	0.002	5.95	1.97 to 17.99
MR moderate to severe	0.091	2.24	0.88 to 5.68	NS	–	–
COPD	0.065	1.40	1.01 to 7.79	NS	–	–
Previous cardiac surgery	0.101	0.43	0.15 to 1.18	NS	–	–
eGFR ml/min/1.73 m^2	0.055	0.98	0.96 to 1.00	NS	–	–
Porcelain aorta	0.048	2.81	1.01 to 7.79	NS	–	–

COPD, chronic obstructive pulmonary disease; MR, mitral regurgitation;NS, non-significant; SPAP, systolic pulmonary arterial pressure; eGFR, estimated glomerular filtration rate.

Heart failure

Clinical signs of heart failure within 2 weeks prior to TAVI was an independent predictor of early mortality in our cohort. Opposed to physical and radiological signs of heart failure, the NYHA classification is based on limitations on physical activity. The majority of our patients were classified as NYHA III-IV. The distinction between classes III and IV is subjective and might in addition to cardiac have its origin in respiratory, musculoskeletal and mental causes, or a combination of these factors. This might suggest that in this setting objective clinical signs of heart failure could be more helpful than only functional limitation when evaluating symptom severity. Furthermore, it may also indicate that optimisation of medical heart failure treatment prior to surgery might be a key factor to improve outcome.

Access and PAD

Central access, especially TA access, has emerged as a significant risk factor for early mortality compared with TF access.[4 6] Compared with patients receiving TF-TAVI, these patients have a higher burden of comorbidities and higher preoperative risk based on preoperative surgical risk algorithms.[20–22] Central access is also more invasive and requires surgical access via a limited thoracotomy or sternotomy, which might impair postoperative respiratory effort secondary to pain. Our cohort had a low number of patients treated with TAo access, rendering to low power to assess if it is a significant risk factor. TF access depends on anatomical accessibility and adequate diameter of femoral and iliac vessels to facilitate instrumentation of introducer sheaths, but the presence of PAD does not necessarily result in a central access. If there are adequate diameter of access site vessels and satisfactory vascular anatomy proximally, TF access can be employed. Despite patients treated with central access having a higher burden of comorbidities, including PAD that might impact choice of access site, our data suggest that access and PAD are independent risk factors for early mortality. This might be due to factors related to the procedure itself, a consequence of patient selection or both. Whatever the reason, choice of access site is an important factor in risk evaluation when considering patients for TAVI as it seems to convey increased risk in itself. In addition to being a factor in the selection of access site, PAD reflects the patients' vascular disease burden and has been shown to increase the risk of TF-TAVI vascular complications,[23] which, in turn, has been associated with increased 30-day mortality.[24 25] A meta-analysis by D'Ascenzo *et al* showed that the extent of coronary artery disease and the results of percutaneous coronary intervention (PCI), evaluated by Syntax Score and residual Syntax Score, respectively, were predictive of 1-year but not 30-day mortality.[26] Despite not calculating Syntax Score in our cohort, we found no mortality difference between the groups with respect to previous myocardial infarction or PCI. In accordance with the aforementioned study, we found neither PCI nor previous myocardial infarction to be predictive of 30-day mortality. Although all patients in our cohort underwent TAVI under general anaesthesia, TF-TAVI is at present often

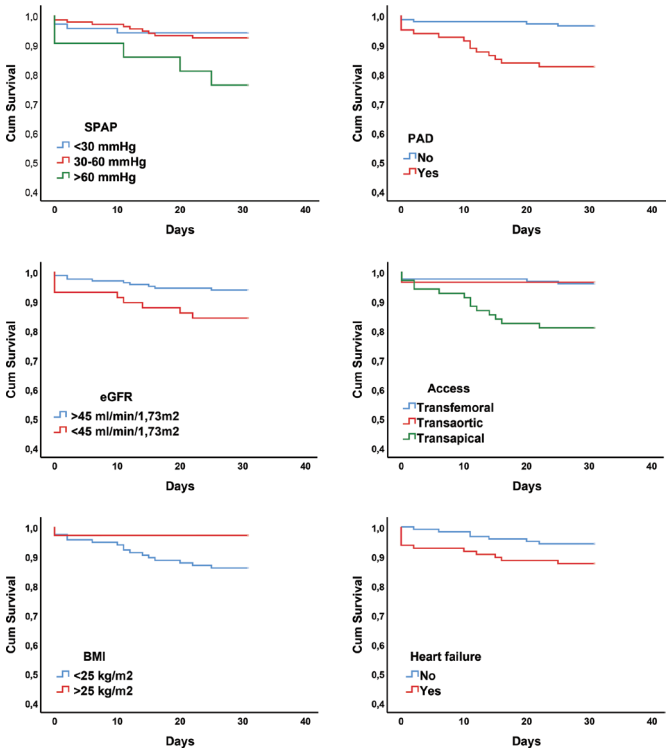

Figure 2 Kaplan-Meier curves for each independent predictor stratified according to 30-day all-cause mortality. Heart failure defined as clinical signs of heart failure in the form of unusual dyspnoea on light exertion, orthopnoea, fluid retention, rales on auscultation, or pulmonary oedema on chest X-ray less than 2 weeks prior to TAVI. BMI, body mass index; eGFR, estimated glomerular filtration rate; PAD, peripheral artery disease; SPAP, systolic pulmonary arterial pressure; TAVI, transcatheter aortic valve implantation,

done in local anaesthesia and sedation, which has been shown to reduce 30-day mortality after TAVI.[27] Although TA-TAVI being a valid option in clinical practice when TF access is not technically feasible, TF-TAVI should be considered the preferred modality.

BMI

The term 'obesity paradox' was first used to describe the increased early mortality after PCI in patients with low BMI[28] and has also been observed in patients treated with TAVI.[29–31] The VARC-2 consensus document states that frailty, where BMI<20 kg/m^2 is a component, is among the risk factors not captured by traditional surgical risk scores.[11] BMI might be a possible surrogate for frailty or cardiac cachexia in the TAVI population, but there are conflicting data whether low BMI confers risk in itself compared with the apparently protective effect of obesity.[32 33] In our cohort, BMI was analysed as a continuous variable and was still statistically significant even when patients with low BMI (<20 kg/m^2) were excluded. Although we had few patients that were morbidly obese, our data suggest better survival with increasing BMI supporting the obesity paradox.

Limitations

Compared with large registry studies, our study included patients from only two centres and was performed during an early stage after the implementation of TAVI as a treatment option. This makes our findings less generalisable at present, and the results may be affected by center-and operator experience in addition to improvements in operative technique and equipment. Our inclusion criteria were rather strict and patients with lower preoperative risk are now offered TAVI, which may alter the risk considerably. Our univariable regression analysis resulted in several significant variables with the risk of low power in a relatively small cohort. This in general could be viewed as a limitation. However, since a forward multivariable regression analysis was performed and all variables were highly significant, stricter inclusion criteria would not have changed the final model.

CONCLUSION

With the exception of elevated SPAP, our data suggest that clinical rather than echocardiographic parameters are more useful as predictors of 30-day mortality after TAVI. We identified SPAP >60 mm Hg, heart failure, TA access, PAD and BMI as independent predictors of 30-day mortality after TAVI. Our data suggest that these factors should be taken into consideration when evaluating high-risk patients for TAVI.

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Contributors AR, HS, RB and SA designed the protocol. AR, SA, GD, JE, SM, LA and RB collected the data. DK performed the data extraction and the offline calculations. DK did the statistical analysis and drafting of the first version of the manuscript in close cooperation with AR, HS, RB and SA. All authors contributed to the revision and all aspects of the final manuscript, and are guarantors of the study.

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Paper II

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RESEARCH ARTICLE

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Risk scores for prediction of 30-day mortality after transcatheter aortic valve implantation: Results from a two-center study in Norway

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Abstract

Objectives: Transcatheter aortic valve implantation (TAVI)-specific risk scores have been developed based on large registry studies. Our aim was to evaluate how both surgical and novel TAVI risk scores performed in predicting all cause 30-day mortality. In addition, we wanted to explore the validity of our own previously developed model in a separate and more recent cohort.

Methods: The derivation cohort included patients not eligible for open surgery treated with TAVI at the University Hospital of North Norway (UNN) and Oslo University Hospital (OUS) from February 2010 through June 2013. From this cohort, a logistic prediction model (UNN/OUS) for all cause 30-day mortality was developed. The validation cohort consisted of patients not included in the derivation cohort and treated with TAVI at UNN between June 2010 and April 2017. EuroSCORE, Logistic EuroSCORE, EurosSCORE 2, STS score, German AV score, OBSERVANT score, IRRMA score, and FRANCE-2 score were calculated for both cohorts. The discriminative accuracy of each score, including our model, was evaluated by receiver operating characteristic (ROC) analysis and compared using DeLong test where $P < .05$ was considered statistically significant.

Results: The derivation cohort consisted of 218 and the validation cohort of 241 patients. Our model showed statistically significant better accuracy than all other scores in the derivation cohort. In the validation cohort, the FRANCE-2 had a significantly higher predictive accuracy compared to all scores except the IRRMA and STS score. Our model showed similar results.

Conclusion: Existing risk scores have shown limited accuracy in predicting early mortality after TAVI. Our results indicate that TAVI-specific risk scores might be useful when evaluating patients for TAVI.

KEYWORDS
mortality, risk prediction, TAVI

1 | INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease requiring operative treatment and carries a dismal prognosis if left untreated.[1,2] Transcatheter aortic valve implantation (TAVI) is an established treatment option for patients with severe symptomatic aortic stenosis with intermediate or high risk for surgical aortic valve replacement (SAVR). While the risk factors for SAVR are known and incorporated into validated preoperative surgical risk scores,[3-6] they are not reliable in predicting early mortality after TAVI.[7,8] It is important to identify patients with unacceptable perioperative risk where the potential benefit of the procedure might be outweighed by unfavorable outcome and where conservative medical treatment alone might be more appropriate. Accordingly, several novel TAVI-specific risk scores have been developed,[9-12] but they have shown limited generalizability when applied in independent cohorts.[12,13] In a previously published study, we identified five independent risk factors of early mortality and created a model for predicting 30-day mortality after TAVI.[14] In the present study, we aimed to evaluate how our model, UNN/OUS (University Hospital of North Norway/Oslo University Hospital), performed compared to established surgical and previously published TAVI-specific risk scores. There has been a rapid development in the TAVI population with a trend toward treating lower risk patients.[15] Therefore, we wanted to explore the validity of our own model in a separate and more recent validation cohort.

2 | METHODS

2.1 | Derivation cohort

The derivation cohort is based on our previously published study which included patients with severe symptomatic AS that underwent TAVI at the University Hospital of North Norway (UNN) Tromsø and Oslo University Hospital (OUS) Rikshospitalet from February 2010 through June 2013.[14] All patients were found to have too high or unacceptable risk for SAVR based on surgical risk scores and evaluation by a cardiothoracic surgeon. A multidisciplinary heart team consisting of a cardiothoracic surgeon, cardiologist, and interventional cardiologist determined the patient suitability for TAVI considering cognitive function, comorbid status, and technical feasibility. Patients with life expectancy less than 12 months, low motivation for treatment, and/or inability to give informed consent were not offered TAVI. All procedures were done in general anesthesia via transfemoral (TF), transapical (TA), or transaortic (TAo) access. TF-TAVI was done via open access to the femoral artery, TA-TAVI was achieved through a small thoracotomy above the cardiac apex, and a small limited sternotomy were done to facilitate TAo-TAVI. Either the first-generation self-expanding Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota, USA) or either first-or second generation Edwards SAPIEN-SAPIEN XT balloon-expandable valve (Edwards Lifesciences, Irvine, California, USA) was used at the discretion of the TAVI team and implanted during rapid pacing. Patient demographics, clinical characteristics, and 30-day mortality were prospectively registered. All patients underwent preoperative transthoracic echocardiographic (TTE) evaluation. The aforementioned data were used for the calculation of risk scores. The surgical risk scores calculated were the EuroSCORE (European System for Cardiac Operative Risk Evaluation), Logistic EuroSCORE, EuroSCORE II, and STS (Society of Thoracic Surgeons) score.[3-6] The TAVI specific risk scores evaluated were the FRANCE-2 (French Aortic National CoreValve and Edwards registry) score, IRRMA (Israeli TAVR Registry Risk Model Accuracy) score, German AV (German Aortic Valve) score, and OBSERVANT (Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic stenosis) score.[9-12] The TAVI-specific risk scores were developed based on French, Israeli, German, and Italian registries, respectively. The study was approved by the Regional Ethical Committees of North and South Norway. All patients gave written informed consent.

2.2 | Validation cohort

The validation cohort consisted of patients treated with TAVI between June 2010 and April 2017 at the University Hospital of North Norway (UNN), Tromsø. All patients were found eligible for TAVI based on the same criteria as above. However, some patients with acceptable risk for SAVR were offered TAVI at the discretion of the heart team based on technical aspects favoring TAVI and patient preference. Valve implantation was done through TF, TA, or TAo. The procedure was done using either a first-, second-, or third-generation Edwards SAPIEN-SAPIEN XT-SAPIEN 3 balloon-expandable valve (Edwards Lifesciences, Irvine, California) or one of the two types of self-expanding valves; first- or second-generation Medtronic CoreValve-EvolutR (Medtronic Inc., Minneapolis, Minnesota) or the St. Jude Portico (St. Jude Medical, Minnesota, USA). The procedures were performed under either general anesthesia for TA- and TAo- TAVI or local anesthesia and sedation in selected cases for TF-TAVI. Patient demographics, clinical characteristics, and 30-day mortality data were extracted retrospectively from the patients' electronic records and used for the calculation of surgical and TAVI-specific risk scores. The validation cohort study was approved by UNN's Data Protection Office.

2.3 | Clinical characteristics and echocardiographic parameters

All clinical and echocardiographic parameters were obtained and measured during the preoperative evaluation for TAVI occurring within 3 months of planned treatment. The presence of chronic obstructive pulmonary disease (COPD) was evaluated by spirometry and defined according to the GOLD classification. Chronic and paroxysmal atrial fibrillation/flutter, diagnoses by ECG, was grouped as one variable. Heart failure was defined as physician-documented clinical signs of heart failure in the form of unusual dyspnea on light exertion, orthopnea, fluid retention, rales on auscultation, or pulmonary edema

on chest X-ray less than 2 weeks prior to TAVI. Peripheral artery disease (PAD) was defined as claudication, previous amputation due to vascular insufficiency, previous reconstructive surgery or percutaneous intervention, abdominal aortic aneurism, and/or >50% stenosis in a peripheral artery diagnosed by computed tomography (CT) or angiographic imaging. Previous cerebrovascular events comprised both previous strokes and transient ischemic attacks. Conventional two-dimensional grey-scale echocardiographic images were obtained in the parasternal long- and short-axis view, as well as the apical four-, two-, and three-chamber views. Left ventricular ejection fraction (LVEF) was derived from the Simpson's biplane method. The degree of aortic regurgitation (AR) was estimated by the size of the regurgitation area by color Doppler, pressure half time, and diastolic velocities in descending aorta by Doppler-flow signal. The degree of mitral regurgitation (MR) was based on measurement and visual assessment of color Doppler images, vena contracta, and proximal isovelocity surface area. Systolic pulmonary artery pressure (SPAP) was derived from continuous wave Doppler measurements of tricuspid regurgitation (TR) and respiratory variation of the diameter of the inferior vena cava.

2.4 | Outcome

The primary endpoint of this study was all-cause mortality 30-days after TAVI. We did not distinguish between in-house mortality and mortality after discharge. Data on mortality are registered in the patients' electronic records, which are linked and automatically updated from the Norwegian Cause of Death Registry. As a result, none of the patients were lost to follow-up.

2.5 | Statistical analysis

Continuous data were tested for normality using Shapiro–Wilk and Kolmogorov–Smirnov tests in addition to evaluation of histograms and normal Q-Q plot. Categorical variables are presented as numbers (%) and continuous variables as mean ± SD or median (interquartile range [IQR]) for normal and nonnormal distributed data, respectively. Continuous variables in the two cohorts were compared using independent *t*-test or Mann–Whitney *U* test as appropriate. Categorical variables were compared using Pearson's Chi-square test.

In the derivation cohort, univariable Cox regression analysis was performed for all-cause 30-day mortality. Variables with $P < .15$ were selected and tested for interaction and linearity. A forward stepwise multivariable Cox regression analysis was performed for the identification of independent predictors of all-cause 30-day mortality where $P < .05$ after multivariable adjustment was considered statistically significant. There was no imputation for missing data and multivariable analysis was performed on all available patients for each analysis. The final model was based on 213 patients. The predicted probabilities obtained from binary logistic regression were used in receiver operating characteristic (ROC) analysis to estimate the discriminative capacity (C-statistic) for the model and compare it to surgical and TAVI risk scores in the same cohort. In the validation cohort, the C-statistic for our model was calculated as above based on the independent predictors identified in the derivation cohort. The difference in discriminative capacity between each individual risk score was evaluated by DeLong test, where $P < .05$ was considered statistically significant. The Hosmer–Lemeshow test was performed to evaluate the calibration of our model in addition to the surgical and TAVI risk scores. All statistical analyses were performed using SPSS 24 (SPSS, Inc., Chicago, IL, USA) with the exception of DeLong test that was performed using SAS statistical software version 9.4.

3 | RESULTS

Patient demographics and clinical characteristics for both the derivation and validation cohort are shown in Table 1. Based on the derivation cohort consisting of 218 patients, we identified body mass index (BMI), SPAP above 60 mm Hg, PAD, TA-access, and heart failure as independent predictors of all-cause 30-day mortality.[14] Variables evaluated constituted both clinical and echocardiographic parameters. The logistic model generated from this cohort is shown in Table 2. Table 3 displays the respective C-statistics with 95% CI for each score, and Table 4 displays the results of DeLong test. The derivation cohort had a larger burden of comorbidities, more TA and TAo procedures, and higher 30-day mortality compared to the validation cohort (Table 1). The validation cohort consisted of 241 patients not included in the derivation cohort. Fourteen of these patients underwent intervention during the inclusion period of the derivation cohort. The remaining 227 patients underwent intervention after the inclusion period of the original study ended.

3.1 | Derivation cohort

Figure 1 shows the ROC curves for our model in addition to both surgical and TAVI risk scores. Our model showed statistically significant higher discriminative accuracy compared to all the other risk scores (Table 4). This, of course, is not unexpected since our model was developed from this cohort. The FRANCE-2 score, IRRMA score, and STS score had moderate-to-good discriminative accuracy when evaluating C-statistics alone (Table 3), but none of the risk scores demonstrated statistically significant better discriminative accuracy over the others. However, the difference in discriminative accuracy between the STS and IRRMA score and EuroSCORE 2, Logistic EuroSCORE, and EuroSCORE was borderline significant. Hosmer–Lemeshow test showed adequate calibration except for EuroSCORE ($P = .024$) and Logistic EuroSCORE ($P = .084$).

3.2 | Validation cohort

The ROC curves for the validation cohort are shown in Figure 1. Our model retained a high discriminative accuracy and the FRANCE-2

TABLE 1 Preoperative demographics and clinical characteristics for the derivation and validation cohort

Variable	Reference cohort (N = 218)	Validation cohort (N = 241)	*P* value
Age (y)	82 ± 7	81 ± 8	.43
Female gender, n (%)	98 (45)	111 (46)	.81
Body mass index, (kg/m^2)	26 ± 5	27 ± 5	.097
NYHA 4, n (%)	57 (26)	40 (17)	.012
HF < 2 wk, n (%)	96 (44)	87 (36)	.083
LVEF (%)	49 ± 12	51 ± 13	.22
AI2, n (%)	38 (17)	30 (12)	.09
MI2, n (%)	45 (21)	31 (13)	.019
Mean gradient (mm Hg)	52 ± 15	53 ± 15	.92
Atrial fibrillation/flutter, n (%)	100 (46)	89 (37)	.052
Hypertension, n (%)	148 (68)	138 (57)	.019
Porcelain aorta, *n* (%)	26 (12)	12 (5)	.007
Immunocompromised, *n* (%)	28 (13)	52 (22)	.014
Diabetes, *n* (%)	62 (28)	49 (20)	.043
SPAP			
<30 mm Hg	67 (31)	83 (34)	.40
30-60 mm Hg	130 (60)	126 (53)	.113
> 60 mm Hg	21 (9)	32 (13)	.222
Previous CABG, n (%)	95 (44)	70 (29)	.001
Previous SAVR, n (%)	9 (4.1)	4 (1.7)	.83
Previous PCI, n (%)	87 (40)	95 (39)	.92
Previous myocardial infarction, n (%)	82 (38)	77 (32)	.20
Previous cerebrovascular event, n (%)	52 (24)	35 (15)	.011
eGFR (ml/min)	54 ± 26	64 ± 24	<.001
COPD, n (%)	78 (36)	63 (26)	.025
Peripheral artery disease, *n* (%)	80 (37)	75 (31)	.21
Access, *n* (%)			
Transfemoral	122 (56)	209 (87)	<.000
Transaortic	28 (13)	10 (4)	.001
Transapical	68(31)	22(9)	<.000
Local anesthesia, n (%)	0 (0)	105 (44)	NA
STS score (6)	7.1 ± 4.5	6.3 ± 4.4	.68
EuroSCORE 2(5)	9.1 ± 7.5	8.1 ± 6.8	.031
Logistic EuroSCORE (4)	22 [19]	20 [22]	.210
EuroSCORE	11.0 ± 2.4	10.0 ± 2.5	.167
FRANCE-2 score (10)	3.4 ± 2.1	2.4 ± 1.8	<.000
IRRMA score (12)	0.8 ± 0.7	0.5 ± 0.6	<.000
OBSERVANT score (9)	3 [8]	0 [6]	.079
German AV score (11)	2.8 ± 0.8	2.7 ± 0.9	.124
Mortality, n (%)	19 (8.7)	10 (4.1)	.045

Note: Numbers are presented as n (%), mean ± SD, or median [IQR].

Abbreviations: AI2, aortic insufficiency grade 2 or above; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF < 2 wk, physician-documented clinical signs of heart failure less than 2 wk prior to surgery in the form of unusual dyspnea on light exertion, orthopnea, fluid retention, rales on auscultation, or pulmonary edema on chest X-ray; LVEF, left ventricular ejection fraction; MI2, mitral insufficiency grade 2 or above; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SPAP, systolic pulmonary artery pressure.

score had a higher discriminative accuracy than in the derivation cohort (Table 3). The FRANCE 2 score had statistically significant better discriminative accuracy compared to all other scores with the exception of our model, IRRMA score, and STS score (Table 4). Our model showed similar results, but the discriminative accuracy was only borderline significant compared to the German AV score. The discriminative accuracy between the STS and IRRMA score and EuroSCORE 2 and EuroSCORE was borderline significant. The IRRMA score had also borderline significant better discriminative accuracy than EuroSCORE 2. Based on Hosmer–Lemeshow test, all scores evaluated in this cohort displayed adequate calibration ($P > .15$).

TABLE 2 Logistic model for 30-d mortality based on the derivation cohort

	β coefficient	OR	95% CI
Body mass index (kg/m^2)[a]	−0.37	0.69	0.56-0.86
HF < 2 wk	1.37	3.93	1.1-14.25
SPAP			
<30 mm Hg			
30-60 mm Hg	0.45	1.57	0.36-6.86
> 60 mm Hg	2.84	17.18	2.39-123
Peripheral artery disease	2.17	8.72	2.12-35
Access[b]			
Transfemoral			
Transaortic	- 0.62	0.54	0.049-6.01
Transapical	2.8	5.09	1.34-19.31
Constant	5.64		

Abbreviations: HF < 2 wk, physician-documented clinical signs of heart failure less than 2 wk prior to surgery in the form of unusual dyspnea on light exertion, orthopnea, fluid retention, rales on auscultation, or pulmonary edema on chest X-ray; SPAP, systolic pulmonary artery pressure.
[a]Analyzed as a continuous variable.
[b]Analyzed as a categorical variable.

4 | DISCUSSION

Of the previously published risk scores evaluated in this study, the IRRMA and FRANCE-2 scores, both TAVI specific, obtained a similar or higher discriminative accuracy in both cohorts compared to the studies from which they were originally derived.[10,12] The FRANCE-2 score showed good discriminative accuracy in both cohorts and had statistically significant better discriminative accuracy compared to all but three scores (IRRMA score, STS score, and UNN/OUS) in the more recent validation cohort. Our model showed similar results and retained a high discriminative accuracy when applied to the validation cohort compared to the original and validated C-statistics of the surgical and TAVI risk scores evaluated in this study.

A study by Halkin et al[12] based on the Israeli TAVI registry including 1327 patients, from which the IRRMA score was derived, found that with the exception of the FRANCE-2 score, all risk scores had less predictive accuracy than in their original studies when applied to an independent cohort. None of the scores in this study attained a C-statistic >0.8. In contrast to our own model, which is based on a relatively low number of patients at only two centers, the FRANCE-2 score is derived from a national registry of 3833 patients. It has shown a better predictive accuracy than originally reported both in the IRRMA study and our cohort. Our model was developed from a wide range of clinical and echocardiographic parameters not incorporated in large registries, thus emphasizing the importance of the factors identified. Despite the differences in composition and number of risk factors included, our own model and FRANCE-2 scores share several common features indicative of factors important in predicting 30-day mortality after TAVI in elderly high-risk patients.

TABLE 3 C-statistic with 95% CI for surgical and TAVI risk scores and DeLong test for each risk score compared to our model (UNN/OUS)

	Derivation cohort		Validation cohort	
	C-statistic	95% CI	C-statistic	95% CI
UNN/OUS (14)	0.91	0.85-0.98	0.83	0.66-0.99
IRRMA score (12)	0.72	0.59-0.84	0.72	0.55-0.90
FRANCE-2 score (10)	0.69	0.57-0.80	0.82	0.69-0.95
STS score (6)	0.68	0.56-0.81	0.67	0.50-0.85
German AV score (11)	0.58	0.44-0.73	0.65	0.49-0.81
OBSERVANT score (9)	0.57	0.42-0.72	0.58	0.39-0.77
EuroSCORE 2(5)	0.56	0.42-0.70	0.53	0.37-0.70
EuroSCORE (3)	0.56	0.41-0.70	0.55	0.43-0.68
Logistic EuroSCORE (4)	0.55	0.41-0.70	0.55	0.40-0.70

Abbreviations: EuroSCORE, European System for Cardiac Operative Risk Evaluation; FRANCE-2, French Aortic National CoreValve and Edwards registry score; German AV, German Aortic Valve score; IRRMA, Israeli TAVR Registry Risk Model Accuracy score; OBSERVANT, Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic stenosis score; STS, Society of Thoracic Surgeons score; UNN/OUS, University Hospital of North Norway/Oslo University Hospital.

TABLE 4 Results of DeLong test comparing the C-statistic between each risk score in the derivation and validation cohort

	UNN/OUS	FRANCE-2	IRRMA	German AV	OBSERVANT	STS	EuroSCORE	Log EuroSCORE	EuroSCORE 2
UNN/OUS	-	*0.97*	*0.20*	*0.08*	*0.02*	*0.16*	*0.004*	*0.004*	*0.01*
FRANCE-2	<0.001	-	*0.16*	*0.03*	*0.009*	*0.11*	*<0.001*	*<0.001*	*0.003*
IRRMA	0.001	0.61	-	*0.43*	*0.03*	*0.63*	*0.06*	*0.05*	*0.07*
German AV	<0.001	0.26	0.20	-	*0.23*	*0.67*	*0.29*	*0.32*	*0.21*
OBSERVANT	<0.001	0.15	0.10	0.89	-	*0.17*	*0.82*	*0.79*	*0.63*
STS	0.003	0.92	0.70	0.17	0.16	-	*0.06*	*0.15*	*0.06*
EuroSCORE	<0.001	0.11	0.06	0.59	0.85	0.07	-	*0.90*	*0.74*
Log EuroSCORE	<0.001	0.10	0.06	0.55	0.84	0.06	0.89	-	*0.76*
EuroSCORE 2	<0.001	0.16	0.07	0.75	0.91	0.05	0.86	0.83	-

Note: Validation cohort displayed in the upper right-hand corner in *italic*. Derivation cohort in lower left-hand corner.
Abbreviations: EuroSCORE, European System for Cardiac Operative Risk Evaluation; FRANCE-2, French Aortic National CoreValve and Edwards registry score; German AV, German Aortic Valve score; IRRMA, Israeli TAVR Registry Risk Model Accuracy score; OBSERVANT, Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic stenosis score; STS, Society of Thoracic Surgeons score; UNN/OUS, University Hospital of North Norway/Oslo University Hospital.

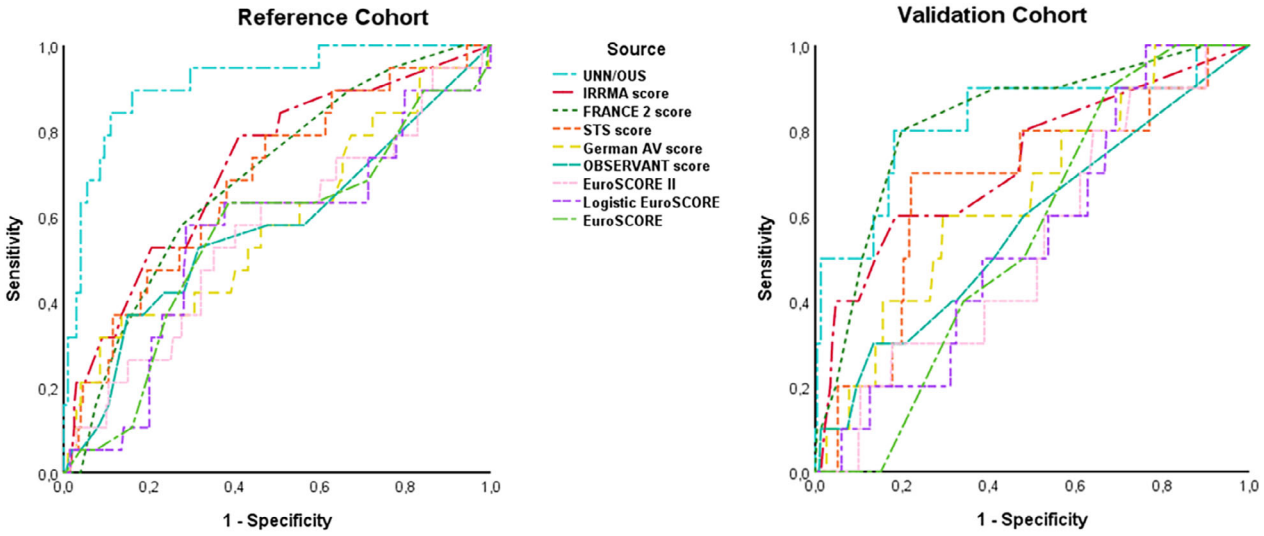

FIGURE 1 Receiver operating characteristic (ROC) curves for surgical and TAVI specific risk scores applied to the derivation and validation cohorts. EuroSCORE, European System for Cardiac Operative Risk Evaluation; FRANCE-2, French Aortic National CoreValve and Edwards registry score; German AV, German Aortic Valve score; IRRMA, Israeli TAVR Registry Risk Model Accuracy score; OBSERVANT, Observational Study of Appropriateness, Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic stenosis score; STS, Society of Thoracic Surgeons score; UNN/OUS, University Hospital of North Norway/Oslo University Hospital

Both American and European guidelines advocate for the use of surgical risk scores as part of the evaluation in patients considered for TAVI.[16,17] However, risk algorithms are accurate only for the population and treatment options for which they were developed and validated. Despite being a useful tool when considering patients for open surgery, they do not take into consideration the inherent differences between the two procedures in addition to the considerable diversity and severity of comorbidities often seen in the TAVI population. Our results support the previous findings that surgical risk scores are inaccurate in predicting early mortality after TAVI.[7,8]

Initially, TAVI was done primarily in patients with high or prohibitive risk for SAVR. This was the population from which the TAVI-specific risk scores evaluated in our study, including our own model, were developed. A limitation of existing risk scores, including our own model, is the lack of frailty measures, especially when considering patients with high or prohibitive risk for open surgery. TAVI is now performed in patients with intermediate risk for SAVR,[15] and results from the recently published PARTNER 3 and NOTION trials show promising results in low-risk patients.[18,19] However, the main challenge in clinical practice is evaluating patients with high comorbid burden that are not candidates for SAVR. In this setting, the question is

whether or not they will tolerate and/or benefit from interventional treatment. This might result in patients undergoing a procedure resulting in no additional benefit over medical therapy alone. These patients require a thorough multidisciplinary evaluation where objective risk scores are needed.

Expanding the indication for TAVI to include patients with intermediate or low surgical risk will make the comorbid burden more comparable to those currently treated with SAVR. However, due to the more invasive nature of the procedure and the use of general anesthesia and heart-lung machine, the inherent risks of surgical valve procedures will never be comparable with those of catheter-based interventions. In addition, there has been rapid development and improvement in valve and catheter technology as well as operator and center experience.[20] Therefore, continuous development, revision, and improvement in TAVI-specific risk scores are needed and must incorporate the heterogeneous comorbid profiles of these patients.

5 | LIMITATIONS

In contrast to larger registry studies, our model was based on relatively few patients treated with TAVI at only two centers, with a low number of clinical endpoints. The validity of our model is therefore uncertain and should serve as topic for further research prior to a conclusion of its clinical usefulness. As with previous existing risk scores, our model does not include frailty measures, which might have an impact on early mortality in the high-risk TAVI population. The validation cohort is not independent, since it was derived from new patients at one of the centers that generated the derivation cohort. Our primary endpoint was all cause 30-day mortality. In-hospital mortality beyond 30 days as well as postoperative morbidity was not evaluated in the current study.

6 | CONCLUSIONS

Existing risk scores have shown limited accuracy in predicting early mortality after TAVI. This study indicates that TAVI-specific risk scores may contribute to improving the preoperative evaluation of patients undergoing TAVI compared to surgical risk scores. Our results have the potential to aid in the further development of TAVI risk scores. Larger clinical studies and TAVI registries have to confirm their usefulness.

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CONFLICT OF INTEREST

Rolf Busund is a proctor for Edwards Lifesciences and has received speakers fee from Abbot. Lars Aaberge is a proctor for Edwards Lifesciences. These affiliations were not involved in design, data collection, analysis, data interpretation, or financial support of the current study.

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All authors have read and approved the final version of the manuscript.

All data used in the study are stored in an off-line central database with restricted access.

TRANSPARENCY STATEMENT

Dr. Didrik Kjønås affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspects of the study have been omitted.

DATA AVAILABILITY STATEMENT

The data used in our study can unfortunately not be shared, even upon request. The reason being that it contains sensitive information that could compromise patient anonymity and contain sensitive medical information. Law strictly regulates the access and distribution of such data.

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Paper III

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ORIGINAL RESEARCH
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Clinical and Echocardiographic Parameters Predicting 1- and 2-Year Mortality After Transcatheter Aortic Valve Implantation

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Background: Transcatheter aortic valve implantation (TAVI) has become a standard treatment option for patients with symptomatic aortic stenosis. Elderly high-risk patients treated with TAVI have a high residual mortality due to preexisting comorbidities. Knowledge of factors predicting futility after TAVI is sparse and clinical tools to aid the preoperative evaluation are lacking. The aim of this study was to evaluate if echocardiographic measures, including speckle-tracking analysis, in addition to clinical parameters, could aid in the prediction of mortality beyond 30 days after TAVI.

Methods: This prospective observational cohort study included 227 patients treated with TAVI at the University Hospital of North Norway, Tromsø and Oslo University Hospital, Rikshospitalet from February 2010 to June 2013. All the patients underwent preoperative echocardiographic evaluation with retrospective speckle-tracking analysis. Primary endpoints were 1- and 2-year mortality beyond 30 days after TAVI.

Results: All-cause 1- and 2-year mortality beyond 30 days after TAVI was 12.1 and 19.5%, respectively. Predictors of 1-year mortality beyond 30 days were body mass index [hazard ratio (HR): 0.88, 95% CI: 0.80–0.98, $p = 0.018$], previous myocardial infarction (HR: 2.69, 95% CI: 1.14–6.32, $p = 0.023$), and systolic pulmonary artery pressure $\geq$ 60 mm Hg (HR: 5.93, 95% CI: 1.67–21.1, $p = 0.006$). Moderate-to-severe mitral regurgitation (HR: 2.93, 95% CI: 1.53–5.63, $p = 0.001$), estimated glomerular filtration rate (HR: 0.98, 95% CI: 0.96–0.99, $p = 0.002$), and chronic obstructive pulmonary disease (HR: 1.9, 95% CI: 1.01–3.58, $p = 0.046$) were predictors of 2-year mortality.

Conclusion: Both the clinical and echocardiographic parameters should be considered when evaluating high-risk patients for TAVI, as both are predictive of 1-and 2-year mortality. Our results support the importance of individual risk assessment using a multidisciplinary, multimodal, and individual approach.

Keywords: TAVI, mortality, echocardiography, strain, risk assessment

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) for the treatment of symptomatic aortic stenosis (AS) was initially reserved for patients with high or prohibitive risk for surgical aortic valve replacement (SAVR) (1, 2). Although there has been an expansion of indication for TAVI, uncertainties still exist with respect to criteria when TAVI is futile in terms of survival (3–5). Clinical tools for identification of these patients are lacking and surgical risk scores have shown limited applicability in this patient group (5–7). TAVI in elderly high-risk patients with symptomatic AS has shown to improve symptoms and prolong life compared to medical therapy (1, 2). However, these patients have a high residual mortality as a result of preexisting comorbidities, both the cardiac and non-cardiac in origin (8, 9). Identification of factors that predict survival after TAVI is important in order to improve patient selection and form a better foundation for informed consent. The evaluation of these patients is complex and requires a multidisciplinary approach and individualized risk assessment to identify, if any of these risk factors are modifiable pre-TAVI. The aim of this study was to investigate, if clinical parameters, in addition to preoperative echocardiographic evaluation, including conventional and speckle-tracking analysis of the right and left ventricle, could aid in the identification of patients with increased risk of mortality beyond the perioperative period.

MATERIALS AND METHODS

Study Population

This study included 227 patients with severe symptomatic AS treated with TAVI at the University Hospital of North Norway, Tromsø and Oslo University Hospital, Rikshospitalet from February 2010 to June 2013. The patients were recruited continuously from the population offered TAVI during this study period at both the centers. Suitability of the patient for TAVI was determined by a multidisciplinary heart team considering comorbid status and cognitive function in conjunction with technical feasibility. Patients unable to give informed consent, low motivation for treatment, and life expectancy of $<$12 months were not offered TAVI. The primary endpoints of this study were to identify risk factors for 1- and 2-year mortality beyond 30 days after TAVI. This study was approved by the Regional Ethics Committees for Medical Research Ethics, North and South East Norway. All the patients gave a written informed consent.

Demographics, clinical characteristics, and postoperative mortality and complications of the patient were obtained from the electronic records of the patient. All the patients were offered outpatient follow-up at 6 and 12 months after TAVI and mortality data were obtained from the electronic records of the patient linked to the National Mortality Registry. Complications were classified according to the Valve Academic Research Consortium (VARC)-2 criteria (10). Peripheral artery disease (PAD) was defined as claudication, previous amputation due to vascular insufficiency, previous reconstructive surgery or percutaneous intervention, abdominal aortic aneurism, and/or $>$50% stenosis in a peripheral artery diagnosed by CT or angiographic imaging. Chronic obstructive pulmonary disease (COPD) was classified according to the GOLD classification. Patients with COPD of unknown grade were classified as having grade 1. Chronic and paroxysmal atrial fibrillation/flutter was grouped as one variable. Previous cerebrovascular events comprised both the previous strokes and transient ischemic attacks. Poor mobility was defined as severe impairment of mobility secondary to musculoskeletal or neuromuscular dysfunction.

The specific predictors identified were assessed in a separate and more recent cohort consisting of 258 patients treated with TAVI at the University Hospital of North Norway, Tromsø from January 2017 to September 2019. A local data protection officer approved the validation of our original results.

Echocardiography

Preoperative transthoracic echocardiogram (TTE) evaluation was performed in all the patients using either an iE33 (S5-1 probe, Philips Medical systems, Andover, Massachusetts, USA) or a Vivid E9 (GE Vingmed, Horten, Norway, UK) scanner with a 2.5–3.5 MHz transducer. In the left lateral decubitus position, two-dimensional grayscale images were obtained in the apical four-, two-, and three-chambers and parasternal short- and long-axis views. Simpson's biplane method was used for estimating left ventricular ejection fraction (LVEF) and left atrial volume at end-systole was obtained from the same views. LV longitudinal function was assessed by mitral annular plane systolic excursion (MAPSE) in the septal and lateral mitral rings in the apical four-chamber view or the mean-value of both (MAPSE average). Intraventricular septum thickness in diastole was derived from M-mode images in the parasternal long-axis view. Mitral flow E velocity, E/A ratio, E/e' ratio, and E deceleration time were used for the assessment of LV diastolic function. LV stroke volume index was calculated from the left ventricular outflow tract (LVOT) diameter and LVOT velocity time integral. The degree of AS was expressed by the mean and peak gradient and peak velocity of the Doppler flow across the aortic valve and the aortic valve area from the continuity equation and the indexed area. The degree of aortic regurgitation (AR) was estimated by the size of the regurgitation area by color Doppler, pressure half time, and diastolic velocities in descending aorta by Doppler-flow signal. The degree of mitral regurgitation (MR) was based on measurement and visual assessment of color Doppler images, vena contracta, and/or calculation of proximal isovelocity surface area. The presence of mitral stenosis was evaluated by measuring mean gradients over the mitral valve in addition to pressure half time and valve area.

Right ventricular (RV) function was evaluated in an adjusted four-chamber view at the largest transversal diameter of the RV. Systolic RV function was assessed by tricuspid annular peak systolic excursion (TAPSE) and tissue Doppler-derived peak tricuspid annular systolic velocity (TASV) in the basal RV free wall. RV fractional area change (RV FAC) was calculated from RV end-diastolic and end-systolic areas. Systolic pulmonary artery pressure (SPAP) was derived from continuous wave Doppler measurements of tricuspid regurgitation (TR) adding an estimate of right atrial pressure derived from respiratory variation of the diameter of the inferior vena cava. When TR gradient was not

recorded, SPAP was considered being < 30 mm Hg. Pulmonary arterial hypertension (PHT) was categorized into mild (<30 mm Hg), moderate (30–59 mm Hg), and severe (≥60 mm Hg).

Strain Analysis

Left ventricular longitudinal (myocardial) strain was estimated by analysis of the LV in the apical four-, two-, and three-chamber views. In this study, LV global longitudinal strain (LVGLS) was defined as the average of three peak strain values of the three views. RV longitudinal strain (RVLS) was estimated by analysis of the lateral RV wall only in an apical four-chamber view. The time point of the aortic valve closure was measured in continuous Doppler registrations of the aortic flow. GLS values were extracted from strain curves by defining the systolic time interval between R wave and the time point of aortic valve closure. Strain curves with artifacts due to reverberation, air artifact, or insufficient tracking were discarded based on subjective visual assessment. In patients with atrial dysrhythmia, strain from three cycles, if available, was obtained and averaged. All the strain analyses were performed using speckle-tracking software VVI7 (Siemens, Mountain View, California, USA).

Transcatheter Aortic Valve Implantation Procedure

All the procedures were performed in general anesthesia using a first-generation self-expanding Medtronic CoreValve (Medtronic Incorporation, Minneapolis, Minnesota, USA) or either first- or second-generation Edwards SAPIEN XT balloon-expandable valve (Edwards Lifesciences, Irvine, California, USA). Transfemoral (TF) access was the preferred modality. Transapical (TA) access was used in the presence of highly calcified and tortuous pelvic vessels given acceptable LV and respiratory function. In the presence of inaccessible peripheral vessels and reduced LVEF or COPD, transaortic (TAo) access was used. Valve size was determined from the aortic annular diameter measured by CT scan reconstruction and/or transesophageal echocardiography.

Statistical Analysis

Data are presented as mean ± SD or number (%) as appropriate. The Pearson's chi-squared test for percentages or independent *t*-test for continuous variables was used for comparing variables between groups. The univariate Cox regression analysis was performed for 1- and 2-year mortality where $p < 0.15$ was considered as statistically significant. Variables that differed significantly between groups and/or with $p < 0.15$ in the univariate analysis were selected and tested for colinearity and correlation prior to the backward multivariate Cox regression analysis. The Lambda and Pearson's correlation coefficients were used to determine significant correlation between nominal and continuous variables, respectively. The receiver operating characteristic (ROC) analysis was performed for continuous variables to determine a cutoff value for continuous variables. No imputation for missing data was performed and multivariable analysis was done on all the available patients for each analysis. $p < 0.05$ in multivariable analysis was considered as statistically significant. The power calculation package in the STATA version 12 was used for estimating the power of the study. A minimum detectable hazard ratio (HR) of 1.25 for mortality for a 1-unit change for each echocardiographic variable with a power of 80% with a 5% probability of a false-negative result was estimated. All the statistical analyses were done using the SPSS version 24 (SPSS Incorporation, Chicago, Illinois, USA).

To determine the inter- and intraobserver variability of longitudinal strain measurements, recordings from 30 patients were selected at random and another experienced observer repeated the analysis. The main observer reanalyzed the same data after several months. The intraclass correlation coefficient was used to test inter- and intraobserver variability (11).

RESULTS

Demographics, clinical characteristics, and periprocedural results with respect to 1- and 2-year mortality of the patient are given in **Table 1** and the echocardiographic parameters are shown in **Table 2**. A total of nine patients were excluded from the final analysis due to lack of available echocardiographic images in five cases, one case with AR and not AS, and three cases did not undergo TAVI. All-cause mortality at 1 and 2 years was 19.7% ($n = 43$) and 26.6% ($n = 58$), respectively, including 30-day mortality at 8.7% ($n = 19$). These 19 patients were excluded and the final analysis included 199 patients. There was no loss to follow-up with respect to primary endpoints.

Of all the 30-day survivors after TAVI, 1-year mortality was 12.1% ($n = 24$) and 2-year mortality was 19.5% ($n = 39$). As shown in **Table 1**, these patients had a higher burden of comorbidities with higher risk estimated by conventional surgical risk scores. Atrial fibrillation/flutter, COPD, and reduced estimated glomerular filtration rate (eGFR) were significantly more prevalent in both the mortality groups. The only echocardiographic measures significantly more frequent in both the mortality groups were moderate-to-severe MR and TR. The incidence of major bleeding perioperatively and vascular complications was also higher in the mortality groups, although few in number.

Those who died within 1 year had significantly lower body mass index (BMI), higher incidence of diabetes and previous myocardial infarction (MI), and fewer patients had undergone percutaneous coronary intervention (PCI). They also had a significantly higher incidence of SPAP ≥ 60 mm Hg and moderate-to-severe AR pre-TAVI in addition to higher RV end-diastolic area (RVEDA). There was significant positive correlation between higher SPAP and higher RVEDA ($p < 0.000$), but no difference in stroke volume index (SVI). Lower BMI, previous cerebrovascular events, and diabetes were borderline significant between the 2-year mortality group and survivors.

The results of the univariate and the multivariate Cox regression analysis are shown in **Table 3**. We identified lower BMI, previous MI, and SPAP ≥ 60 mm Hg as independent predictors of all-cause 1-year mortality beyond 30 days. Although not significant in multivariable analysis, there was a trend toward increased mortality in patients with SPAP 30–59 mm Hg. ROC analysis identified a cutoff value for BMI of 25

TABLE 1 | Demographic, clinical, and periprocedural characteristics stratified according to 1- and 2-year mortality.

Variable	Survivors 1-year ($n = 175$)	Non-survivors 1-year ($n = 24$)	*P*-value	Survivors 2-years ($n = 160$)	Non-survivors 2-years ($n = 39$)	*P*-value
Age, years	82 ± 7	81 ± 7	0.920	82 ± 7	82 ± 7	0.748
Female	79 (45)	10 (42)	0.748	76 (48)	13 (33)	0.111
BMI, kg/m^2	27 ± 5	24 ± 6	0.034	27 ± 5	25 ± 5	0.085
STS score	5.5 ± 3.3	9.2 ± 6	<0.0001	5.4 ± 3.3	7.9 ± 5.2	<0.0001
Euroscore 2	8.8 ± 6.4	13.8 ± 11	0.001	8.9 ± 6.5	11.5 ± 9.6	0.047
NYHA class			0.260			0.861
II	25 (14)	4 (17)		24 (15)	5 (13)	
III	109 (62)	11 (46)		97 (61)	23 (59)	
IV	41 (23)	9 (38)		39 (24)	11 (28)	
Heart failure	75 (43)	9 (38)	0.618	69 (43)	15 (38)	0.597
Hypertension	117 (67)	16 (67)	0.985	107 (67)	26 (67)	0.980
Atrial dysrhythmia	73 (42)	16 (67)	0.021	63 (39)	26 (67)	0.002
Coronary artery disease	118 (64)	17 (71)	0.738	109 (68)	26 (67)	0.861
Previous myocardial infarction	62 (35)	14 (58)	0.030	57 (36)	19 (49)	0.131
Previous PCI	73 (42)	5 (21)	0.049	67 (42)	11 (28)	0.117
Previous cardiac surgery	81 (46)	12 (50)	0.732	76 (48)	17 (44)	0.661
LBBB	16 (9)	2 (8)	0.897	14 (9)	4 (10)	0.769
Peripheral artery disease	58 (33)	8 (33)	0.985	51 (32)	15 (38)	0.433
Cerebrovascular disease	43 (25)	9 (38)	0.176	38 (24)	14 (36)	0.122
Previous cerebrovascular event	38 (22)	8 (33)	0.205	33 (21)	13 (33)	0.091
Immunocompromised	20 (11)	4 (17)	0.460	17 (11)	7 (18)	0.208
Diabetes	47 (27)	12 (50)	0.020	43 (27)	16 (41)	0.083
COPD	57 (33)	13 (54)	0.038	50 (31)	20 (51)	0.019
eGFR, ml/min/1.73 m^2	60 ± 19	50 ± 24	0.011	61 ± 18	51 ± 23	0.004
Poor mobility	19 (11)	4 (17)	0.404	18 (11)	5 (13)	0.783
Access			0.700			0.369
Transfemoral	102 (58)	15 (63)		96 (60)	21 (54)	
Transaortic	23 (13)	4 (16)		19 (12)	8 (21)	
Transapical	50 (29)	5 (21)		45 (28)	10 (25)	
Valve type			0.453			0.206
Edwards Sapien	136 (78)	17 (71)		126 (79)	27 (69)	
CoreValve	39 (22)	7 (29)		34 (21)	12 (31)	
Complications						
Stroke	4 (2.3)	0 (0)	0.454	3 (2)	1 (2)	0.783
New permanent pacemaker*	14 (9)	3 (15)	0.415	13 (9)	4 (12)	0.641
Moderate to severe PVL	17 (10)	1 (4)	0.374	15 (9)	3 (8)	0.743
Vascular complications**	10 (6)	5 (21)	0.009	9 (6)	6 (15)	0.038
Major or life threatening bleeding	3 (2)	2 (8)	0.052	2 (1)	3 (8)	0.021
Myocardial infarction	3 (2)	0 (0)	0.518	2 (1)	1 (3)	0.546
Acute kidney injury	4 (2)	0 (0)	0.454	4 (3)	0 (0)	0.319
Sepsis	5 (3)	0 (0)	0.402	5 (3)	0 (0)	0.264
Other TAVI complications	10 (6)	3 (13)	0.207	8 (5)	5 (13)	0.076

Values are mean ± SD or n (%).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVL, paravalvular leakage; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

**171 patients did not have a pacemaker prior to TAVI.*

***Includes minor and major vascular complications.*

kg/m^2 with a sensitivity of 0.8 and 1 specificity of 0.4. All the patients with SPAP $\geq$ 60 mm Hg in the mortality group died within the first year after TAVI. Thus, all the survivors with SPAP $\geq$ 60 mm Hg alive after 1 year were alive at 2 years. **Figure 1A** shows the survival curves for BMI and SPAP adjusted for previous MI. Of the patients with BMI $>$ 25 kg/m^2 and

TABLE 2 | Preoperative echocardiographic parameter stratified according to 1- and 2-year mortality.

Variable*	Survivors 1-year ($n = 175$)	Non-survivors 1-year ($n = 24$)	*P*-value	Survivors 2-year ($n = 160$)	Non-survivors 2-years ($n = 39$)	*P*-value
LVEF, % ($n = 194$)			0.375			0.230
≥50	90 (53)	10 (42)		83 (54)	17 (43)	
31–49	60 (35)	12 (50)		53 (34)	19 (49)	
≤30	20 (12)	2 (8)		19 (12)	3 (8)	
LVGLS ($n = 180$)	−11.1 ± 3.8	−11.1 ± 4.1	0.991	−11.1 ± 3.8	−11.4 ± 4.0	0.645
MAPSE septal, cm ($n = 193$)	0.7 ± 0.3	0.6 ± 0.2	0.168	0.7 ± 0.3	0.6 ± 0.2	0.106
MAPSE lateral, cm ($n = 193$)	1.0 ± 0.3	0.9 ± 0.2	0.253	1.0 ± 0.3	0.9 ± 0.3	0.173
MAPSE average, cm ($n = 193$)	0.9 ± 0.3	0.8 ± 0.2	0.165	0.9 ± 0.3	0.8 ± 0.2	0.101
IVSDd, cm ($n = 185$)	1.2 ± 0.3	1.1 ± 0.3	0.403	1.2 ± 0.3	1.2 ± 0.3	0.592
AVA, cm^2 ($n = 196$)	0.6 ± 0.2	0.6 ± 0.2	0.603	0.6 ± 0.2	0.6 ± 0.2	0.830
AVA index, cm^2/m^2 ($n = 196$)	0.3 ± 0.1	0.3 ± 0.1	0.857	0.3 ± 0.1	0.3 ± 0.1	0.534
AV gradient max, mmHg ($n = 196$)	84 ± 24	85 ± 31	0.798	85 ± 24	81 ± 27	0.410
AV gradient mean, mmHg ($n = 197$)	52 ± 15	51 ± 17	0.635	53 ± 16	49 ± 15	0.194
AV max velocity, m/s ($n = 197$)	4.5 ± 0.7	4.5 ± 0.8	0.710	4.6 ± 0.7	4.4 ± 0.7	0.237
LVOT diameter, cm	2.1 ± 0.3	2.1 ± 0.3	0.998	2.1 ± 0.2	2.1 ± 0.3	0.296
LVOT VTI, cm ($n = 197$)	19.8 ± 5.9	18.1 ± 5.9	0.181	19.8 ± 6.0	18.6 ± 4.9	0.230
SV index, ml/m^2 ($n = 197$)	37 ± 11	36 ± 10	0.641	37 ± 11	37 ± 11	0.877
E/é ($n = 135$)	19.2 ± 8.3	18.9 ± 6.3	0.916	19 ± 8	19 ± 7	0.897
E/A ($n = 137$)	1.1 ± 0.6	1.2 ± 0.8	0.768	1.1 ± 0.6	1.3 ± 0.8	0.313
E deceleration time, ms ($n = 197$)	229 ± 92	214 ± 90	0.461	231 ± 94	212 ± 81	0.242
E velocity, cm/s ($n = 197$)	96 ± 34	95 ± 36	0.891	97 ± 34	91 ± 35	0.366
LA volume index, ml/m^2 ($n = 186$)	53 ± 20	59 ± 20	0.192	52 ± 21	57 ± 19	0.213
MR moderate to severe ($n = 194$)	29 (17)	9 (38)	0.018	23 (15)	15 (38)	0.001
AR moderate to severe ($n = 190$)	27 (16)	8 (35)	0.031	25 (16)	10 (26)	0.160
Mitral stenosis	8 (5)	1 (4)	0.751	8 (5)	1 (2)	0.480
SPAP, mmHg			0.008			0.258
≥60	12 (7)	6 (25)		12 (7)	6 (15)	
30–59	104 (60)	14 (58)		95 (60)	23 (60)	
<30	59 (33)	4 (17)		53 (33)	10 (25)	
TAPSE, cm ($n = 186$)	1.6 ± 0.5	1.5 ± 0.5	0.235	1.6 ± 0.5	1.5 ± 0.6	0.309
TASV, cm/s ($n = 120$)	9.6 ± 3.2	8.8 ± 2.8	0.455	9.7 ± 3.3	8.5 ± 2.6	0.169
RV FAC, % ($n = 179$)	36 ± 13	35 ± 12	0.820	36 ± 13	35 ± 12	0.734
RVEDA, cm^2 ($n = 179$)	19 ± 5	22 ± 5	0.029	20 ± 5	21 ± 5	0.155
RVESA, cm^2 ($n = 179$)	13 ± 5	14 ± 4	0.107	13 ± 5	14 ± 4	0.267
TR moderate to severe ($n = 194$)	29 (17)	11 (46)	0.001	26 (17)	14 (36)	0.008
RVLS, % ($n = 154$)	−16.4 ± 6.5	−17.1 ± 7.2	0.667	−17 ± 7	−16 ± 7	0.875

Values are mean ± SD or n (%).

AR, aortic regurgitation; AV, aortic valve; AVA, AV area; FAC, fractional area change; IVSDd, intraventricular septum diameter in diastole; LA, left atrium; LVGLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAPSE, mitral annular plane systolic excursion; MR, mitral regurgitation; MV, mitral valve; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVLS, right ventricular longitudinal strain; SPAP, systolic pulmonary artery pressure; SV, stroke volume; TAPSE, tricuspid annular peak systolic excursion; TASV, tricuspid annular systolic velocity; TR, tricuspid regurgitation.

**Numbers in brackets indicate the number of cases where the measurement was available.*

SPAP < or ≥ 60 mm Hg, 98 and 89% patients were alive after 1 year, respectively. In patients with BMI ≤ 25 kg/m^2 and SPAP < 30 mm Hg, SPAP 30–59 mm Hg, or SPAP ≥ 60 mm Hg, 1-year survival was 93, 77, and 44%, respectively. In patients with BMI ≤ 25 kg/m^2 and SPAP ≥ 30 mm Hg, the survival at 1 year for patients without previous MI was 88% compared to 55% in patients with previous MI ($p = 0.030$). Predictors of all-cause 2-year mortality were moderate-to-severe MR, COPD, and reduced eGFR. Previous cerebrovascular event was borderline significant ($p = 0.078$). **Figure 1B** shows COPD and moderate-to-severe MR grouped adjusted for eGFR. The main impact on survival is the presence of both the COPD and moderate-to-severe MR. In patients without COPD and moderate-to-severe MR, 87% patients were alive after 2

TABLE 3 | Results of the univariate and multivariate regression analysis of mortality at 1 and 2 years beyond 30 days after TAVI.

Variable	1-year mortality						2-year mortality					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Atrial dysrhythmia	2.60	1.11–6.07	0.027	–	–	NS	2.70	1.39–2.52	0.003	–	–	NS
BMI, kg/m^2	0.90	0.81–0.99	0.028	0.88	0.80–0.98	0.018	0.94	0.87–1.00	0.07	–	–	NS
COPD	2.39	1.03–5.11	0.043	–	–	NS	2.09	1.12–3.92	0.021	1.9	1.01–3.58	0.046
Diabetes	2.61	1.17–5.81	0.019	–	–	NS	1.83	0.97–3.46	0.064	–	–	NS
eGFR, ml/min/1.73 m^2	0.97	0.95–0.99	0.009	–	–	NS	0.98	0.96–0.99	0.002	0.98	0.96–0.99	0.002
Previous MI	2.41	1.07–5.43	0.034	2.69	1.14–6.32	0.023	1.70	0.89–3.13	0.11	–	–	NS
Previous PCI	0.39	0.15–1.04	0.061	–	–	NS	0.57	0.28–1.14	0.113	–	–	NS
Previous CVE	–	–	NS	–	–	NS	1.78	0.91–3.46	0.09	–	–	NS
AR moderate to severe	2.58	1.09–6.09	0.03	–	–	NS	1.78	0.86–3.66	0.12	–	–	NS
MR moderate to severe	2.55	1.12–5.84	0.26	–	–	NS	2.87	1.51–5.48	0.001	2.93	1.53–5.63	0.001
SPAP, mmHg												
<30	–	–	–	–	–	–	–	–	–	–	–	–
30–59	1.91	0.63–5.80	0.254	2.10	0.66–6.45	0.21	1.26	0.60–2.65	0.54	–	–	NS
≥60	6.32	1.79–22.5	0.004	5.93	1.67–21.1	0.006	2.62	0.95–7.23	0.062	–	–	NS

Data are displayed as hazard ratio (HR), 95% CI, with corresponding p-value.

NS, not significant; TAVI, transcatheter aortic valve implantation; AR, aortic regurgitation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVE, cerebrovascular event; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; SPAP, systolic pulmonary artery pressure.

years compared to only 44% patients in the presence of both the conditions.

Strain analysis did not provide additional predictive value and remained statistically insignificant when evaluated in EF subgroups. As previously reported, the intraclass correlation coefficient for longitudinal strain measurement was 0.799 (95% CI: 0.695–0.868) and 0.924 (95% CI: 0.885–0.950) for inter- and intraobserver variability, respectively (11).

In the more recent validation cohort, 30-day mortality was 1.6% ($n = 4$). There was no significant difference in mortality beyond 30 days after TAVI between the original study cohort and the validation cohort after 1 and 2 years (12.1 vs. 9.1%, $p = 0.30$ and 19.5 vs. 16.1%, $p = 0.34$, respectively). The validation cohort had significantly lower incidence of previous MI (23 vs. 38%, $p > 0.001$) and moderate-to-severe MR (19.1 vs. 9.4%, $p = 0.002$), in addition to better eGFR (64 vs. 59 ml/min/1.73 m^2, $p = 0.006$). There was no significant difference in the incidence of COPD ($p = 0.273$), SPAP $\geq$ 60 mm Hg ($p = 0.489$), or BMI ($p = 0.291$) between the two cohorts. Based on the factors identified and the Cox proportional hazards model from the original cohort, reduced eGFR remained the only significant predictor of mortality at 2 years after multivariable adjustment (HR: 0.98, 95% CI: 0.96–0.99, $p < 0.001$) in the more recent and less comorbid cohort.

DISCUSSION

Based on our original study cohort of high-risk patients, we found 1-year mortality 30 days beyond TAVI to be predicted by low BMI, increased SPAP, and a history of previous MI. COPD, moderate-to-severe MR, and reduced eGFR were predictors of mortality at 2 years. In this study, all-cause mortality at 1- and 2 years is similar to international registry data from the same period (12, 13). We did not include 30-day mortality in an attempt to better identify risk factors not influenced by perioperative factors. Predictors of mortality identified in this study, both the clinical parameters and echocardiographic measures, have previously been described in registry studies (9, 12–15). This study evaluated more parameters than those included in registry studies indicating the possible importance of the factors identified in this patient population. Longitudinal strain analysis of the left and right ventricle, in addition to a thorough preoperative echocardiographic evaluation, did not yield any additional predictive value. Besides reduced eGFR, the factors identified were not significant when evaluated in a more recent and less comorbid cohort with similar 1- and 2-year mortality rates 30 days beyond TAVI. However, our results are likely still relevant for a subgroup of high-risk patients in the current TAVI population.

In this study, the only independent echocardiographic predictors of mortality beyond 30 days were SPAP $\geq$ 60 mm Hg and moderate-to-severe MR for 1- and 2-year mortality, respectively. Neither EF nor longitudinal function, including longitudinal strain, differed between groups. PHT has been shown to predict poor outcome after TAVI (15, 16). O'Sullivan et al. found that precapillary PHT and combined pre- and postcapillary PHT were predictive of 1-year mortality; however, isolated postcapillary (LV induced) PHT was not predictive of 1-year mortality (17). Postcapillary PHT is a possible reversible condition improving after treatment of AS and concomitant heart failure. Thus, in patients with severe PHT, a thorough evaluation of its underlying cause and possible reversibility pre-TAVI are necessary for individualized risk assessment. Both the mortality groups had more than twice the prevalence of

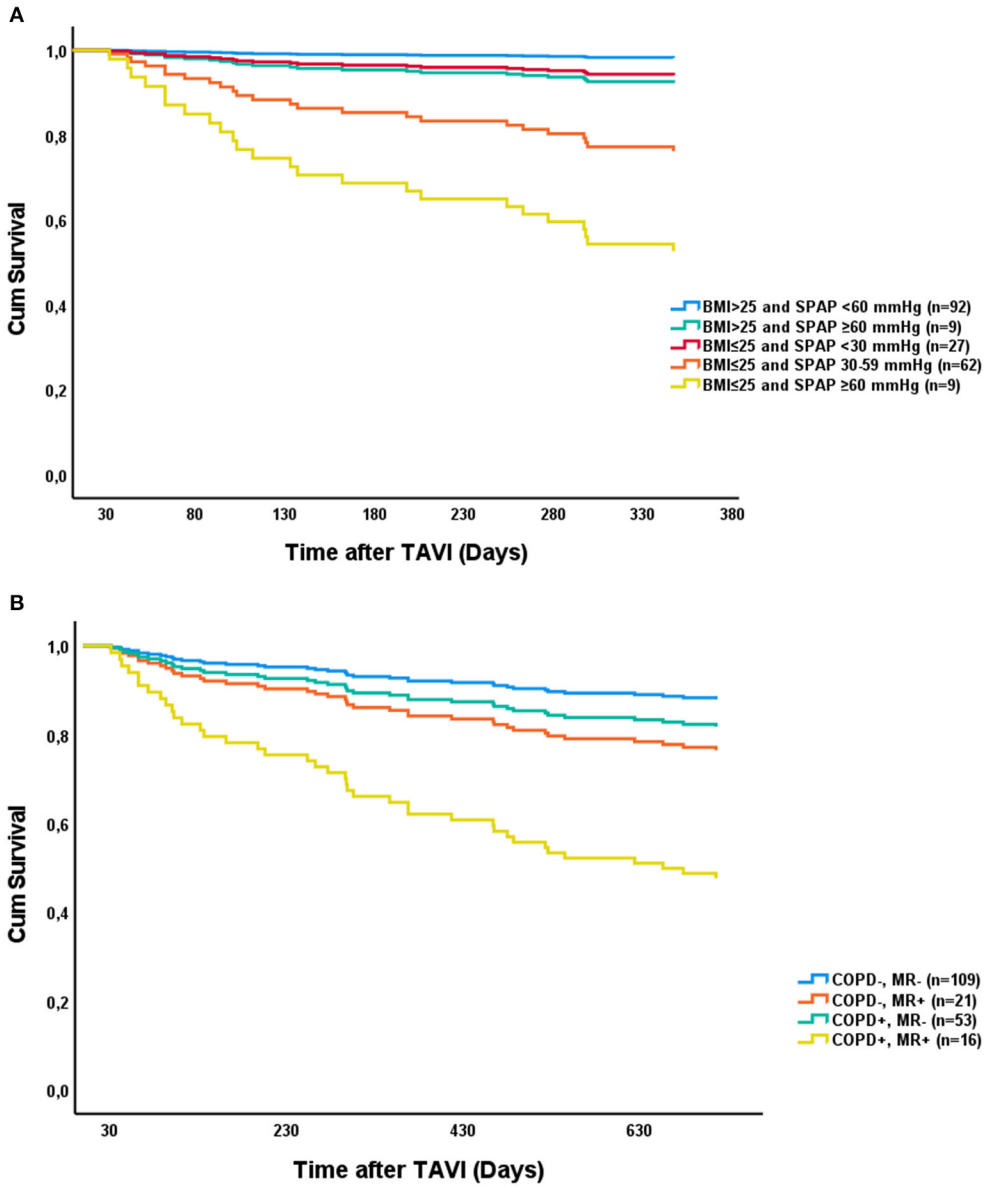

FIGURE 1 | Survival curves representing the Cox proportional hazards analysis for: BMI (kg/m^2) and SPAP grouped and adjusted for previous MI **(A)** with respect to 1-year mortality and moderate-to-severe MR and COPD grouped adjusted for eGFR (ml/min/1.73 m^2) with respect to 2-year mortality **(B)**. BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure.

moderate-to-severe MR and moderate-to-severe MR was an independent predictor of 2-year mortality. In a meta-analysis by Nombela-Franco et al., moderate-to-severe MR was associated with increased 1-year mortality despite an improvement in the severity of regurgitation in approximately 50% of patients post-TAVI (18). MR might be organic or functional, the latter being the most common and most likely to improve post-TAVI. Whether or not MR should be treated concomitant with AS that remains a topic for further study, it is not known if the treatment of MR before or after TAVI will reduce risk of long-term mortality (19). A thorough evaluation of its cause could be beneficial prior to TAVI and medical therapy should be optimized regardless of etiology.

Previous MI and the presence and complexity of coronary artery disease (CAD) have been associated with 1-year mortality (13, 20, 21). We found previous MI to be an independent predictor of 1-year mortality, but no difference in incidence of CAD between the survivors and the mortality group. Previous MI could result in ischemic heart failure and cause substrates for arrhythmias in patients with AS, which might explain the

current finding. CAD is prevalent among patients with AS evaluated for TAVI, especially in the high-risk groups (1, 22). CAD is a heterogeneous condition frequently associated with other comorbidities and the extent of myocardium at risk differs. In elderly high-risk patients undergoing TAVI, complete revascularization is not necessarily a prerequisite for favorable outcome (23). Patients with CAD, with or without previous MI, evaluated for TAVI that could benefit from an individualized revascularization strategy based on the complexity and severity of CAD taking into consideration the extent of myocardium at risk.

Chronic obstructive pulmonary disease is known to have a negative impact on survival after TAVI (9, 24). In our cohort, there was a significant difference in the incidence of COPD between survivors and 1- and 2-year mortality, with COPD being an independent predictor of 2-year mortality. A study by Mok et al. showed that patients with COPD had a >1.5 risk of death at midterm follow-up after TAVI and most of these patients died of respiratory failure secondary to COPD (25). Despite being an irreversible condition with a poor prognosis, patients with COPD may benefit from more intensive follow-up during treatment for concomitant disease both prior to and beyond initial perioperative period. Various degrees of renal failure are common in patients treated with TAVI and its impact on poor outcome is well-documented (26). The cause is likely multifactorial including advanced age, association between renal failure and other comorbidities, and increased risk of periprocedural complications. Although depending on stage, renal failure needs to be taken into consideration in the preoperative evaluation.

Frailty measures have been associated with worse outcome following TAVI (27). A study by Martin et al. from the UK TAVI registry showed that frailty measures, including poor mobility, were predictive of 1-year mortality (28). In this study, the incidence of poor mobility did not differ between the groups, albeit further frailty measures were not performed. Frailty can be described as an age-related syndrome characterized by physiological decline and vulnerability to adverse health events. Although we did not use a specific score to evaluate degree of frailty in this study, patients considered too frail by the multidisciplinary team were not offered treatment. This included severe immobility and dementia. Compared to current clinical practice, the criteria for treatment in this study were strict. There is still a debate on how to best assess it due to instrument variability, but the most cited includes weight loss as one of its components (29, 30). A meta-analysis and systematic review by Lv et al. showed that a high BMI was associated with reduced short- and long-term mortality corresponding to our results (31). The reason for this apparent "obesity paradox" is not yet clear. Several mechanisms have been suggested including younger age, earlier diagnosis, higher metabolic reserve, and cardiac cachexia. Patients with low BMI and/or malnourishment might benefit from prehabilitation prior to treatment to counteract the apparent negative effects of lower BMI and other frailty measures.

Guidelines from both the European Society of Cardiology and the American Heart Association emphasize the importance of a multidisciplinary evaluation by a heart team prior to TAVI considering technical aspects, comorbid status, expected benefits, and the preferences of the patients (32, 33). In addition to technical feasibility, criteria for when TAVI is futile are now included in guidelines, but the decision to not offer interventional treatment is still often challenging. The heterogeneity of the current TAVI population with respect to comorbid profile and improved patient selection, in addition to continuously evolving valve and sheath technology, warrants further study of TAVI subgroups and their individual risk profiles.

Study Limitations

This study has several limitations. First, this study included relatively few patients from only two centers and was performed during an early stage after the implementation of TAVI as a treatment option. Second, all the procedures were performed in general anesthesia. At present, the majority of patients are treated using TF access performed in local anesthesia. The negative impact of general anesthesia on outcome would likely be evident early post-TAVI. Since we only included patients who survived beyond 30 days, the use of general anesthesia does not probably affect our results nor make it less representable for the current subgroup of patients with high-risk TAVI. Third, we used only first- and second-generation valves, whereas third- and fourth-generation valves are currently in use. Complications related to valve deployment and vascular injury were associated with unfavorable perioperative outcome and were more frequent with early valve generations. Beyond the perioperative period evaluated in this study, paravalvular leak (PVL) is the isolated valve-related factor most strongly associated with mortality. Although less frequent, it is still an issue with new-generation valves. Despite relatively low incidence of PVL in this study with no difference in incidence between groups, valve generation must be taken into consideration when interpreting our results in light of continuous improvements in valve technology. Fourth, this study population was older with more comorbidities than the current TAVI population in general. All these factors might make our results less generalizable today. Lastly, this study had relatively low power and event rate and our results might, therefore, be over fitted. However, the factors identified were highly significant and are strengthened by similar findings in previous research. Despite the TAVI population now being generally less comorbid than in this study, our results are still relevant when evaluating high-risk patients in the current TAVI population.

CONCLUSION

Despite expanding indications for TAVI, there is still an unmet need for better identification of patients where TAVI is futile. Prediction of futility of treatment in terms of mortality after TAVI in elderly high-risk patients is challenging and requires a multidisciplinary, multimodal, and individual approach to diagnosis, treatment, and follow-up. Factors identified as predictors of mid- and long-term outcome after TAVI vary between studies indicative of the heterogeneity of this patient population. Certain preexisting conditions have inherent poor prognosis, where some are irreversible and others are amendable to optimization both before and after treatment. Active treatment

and close follow-up of patients with high comorbid burden before, during, and after TAVI might ameliorate the inherent risks of preexisting conditions.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data used in our study can unfortunately not be shared, even upon request. The reason being that it contains sensitive information that could compromise patient anonymity and contain sensitive medical information. The access and distribution of such data are strictly regulated by law. Requests to access the datasets should be directed to didrikkj@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Committee for Medical Research Ethics North Norway and Regional Ethical Committee for Medical Research Ethics South East Norway. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DK: methodology, validation, formal analysis, investigation, data curation, writing-original draft, and visualization. HS: conceptualization, methodology, formal analysis, and writing-original draft. SA: conceptualization, resources, data curation, and writing-review and editing. JE: investigation, resources, data curation, and writing-review and editing. SM and LA: investigation, resources, and writing-review and editing. RB: investigation, resources, data curation, and writing-original draft. AR: conceptualization, methodology, validation, investigation, resources, data curation, writing-original draft, visualization, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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