# TITLE

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## Contribution of authors

AG, NH: initiated the study and managed the ethical review board application. SN and AG performed the statistical analyses. GG: Assisted in preparing the review board application. AG drafted the manuscript. AG, SN, NH and GG took part in designing the study and editing the manuscript.

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# Abstract

# Introduction

Elective total hip Arthroplasty (THA) is a successful choice of treatment for advanced hip osteoarthritis (OA). The number of THA performed has increased in the past decades. ([1-3](#_ENREF_1)) The comorbidity burden among individuals undergoing THA procedures has also increased during the same period([4](#_ENREF_4), [5](#_ENREF_5)) while the early postoperative mortality after THA is low and has decreased over the last years.([6-9](#_ENREF_6)) The higher prevalence of comorbidity in patients undergoing THA may be multifactorial, i.e. caused by an ageing population, improved pre- and post-operative care, improved treatment of comorbid conditions, or a result of more comorbidities being registered. Several studies have verified the connection between an increased comorbidity burden and a poorer outcome on a population level, i.e. an increased risk of early postoperative mortality, an increased risk of revision([4](#_ENREF_4), [10](#_ENREF_10)) and poorer patient outcomes([4](#_ENREF_4), [11](#_ENREF_11)) for patients with more comorbidities. On existing data sources, i.e. in- and outpatient data and prescription data, diagnosed based (or prescription based) coding algorithms are often used to obtain a comorbidity measure (i.e. Charlson Comorbidity Index (CCI), Elixhauser Score, and RxRisk-V). Inacio et al recently performed a study where the ability of Charlson Comorbidity Index (CCI), Elixhauser Score, and RxRisk-V to predict mortality after THA and TKA was evaluated([12](#_ENREF_12)). In our clinical departments comorbidity measures such as The American Society of Anesthesiologists physical status classification (ASA) and the Charnley Classification are preferred.

However, an existing connection on a large population scale does not easily extrapolate to the individual level in our clinical practise. Several universal and arthroplasty specific risk prediction tools have been introduced but none has been broadly accepted.([13](#_ENREF_13))

In this study we aimed to investigate how two clinically used comorbidity measures (ASA and Charnley Classification) influence the risk of early postoperative mortality compared to the diagnosed based CCI and ES and the prescription based RxRisk-V. We also investigated the prediction value of each comorbidity measure, for their included dimensions separately, and tried to find clinically usable “red flags” to predict high-risk patients.

# Methods

## Study design and study population

We performed a nationwide retrospective cohort study (Figure 1). All patients operated between 2008 and 2013 for THA due to primary osteoarthritis from the Swedish Hip Arthroplasty Register (SHAR) were included. Only elective primary hip arthroplasty procedures were included.

Follow-up started on the date of surgery and ended on the day of death, emigration, or December 31st 2013, whichever came first. Only the first surgery was accounted for in bilaterally operated patients to avoid dependency issues. Potential reoperations within 90 days were not accounted for. Ninety days and one year mortality was the primary outcome measure.

## Sources of data

***The Swedish Hip Arthroplasty Register*** registers all patients undergoing THA in Sweden since 1979. The SHAR has a stable completeness of registration around 96-98% and has been validated repeatedly.([14-16](#_ENREF_14))

***Statistics Sweden*** is a state-owned registry collecting information on the entire Swedish population i.e. level of education, personal and family income. Thanks to the ten-digit personal identity number all Swedish citizens are assigned at birth, linkage between different Swedish official and medical databases is made possible.

***The Swedish National Patient Register*** was started in 1964. It contains information on medical comorbidities and admissions to hospital care for all individuals in Sweden. The positive predictive value of the Swedish National Patient Register is estimated around 90±5% which indicates high validity of data.([17](#_ENREF_17))

## Comorbidity measures

***The Charlson Comorbidity Index*** (CCI) is a diagnose based coding algorithm used in research.([18](#_ENREF_18)) It was developed to quantify the influence of comorbidities on survival. In this study the original weighting and the weighting according to Quan were investigated. ([18](#_ENREF_18), [19](#_ENREF_19))

***The Elixhauser Score*** is also a diagnose based coding algorithm used in research. ([20](#_ENREF_20)) The Elixhauser Score is more detailed than the more commonly used CCI.

***The RxRisk-V Score*** is a pharmacy based coding algorithm used in research.([21](#_ENREF_21), [22](#_ENREF_22)) Prescription based comorbidity measures have been increasingly used over the last years. It has been argued that a prescription based measure would be more reliable than a diagnosed based measure, not having the same limitations such as incomplete or inaccurate coding.([23](#_ENREF_23), [24](#_ENREF_24))

***The American Society of Anesthesiologists physical status classification*** (ASA) is a six-category physical status evaluation system developed in 1941 and it has remained virtually unchanged([25](#_ENREF_25)). The ASA grade was included in the Swedish Hip Arthroplasty Register (SHAR) in 2008 which is why our study period begins that year. The ASA grade is easily assessed in a clinical setting.

***The Charnley Classification*** is also easily assessed in a clinical setting. It was introduced in 1972, it is wildly used, and it has been registered in the SHAR since the beginning. It is not strictly a comorbidity measure but stratifies patients into categories defined by walking ability. ([26](#_ENREF_26), [27](#_ENREF_27))

## Statistics

We adhered to the guidelines on statistical analyses of register data.([28](#_ENREF_28), [29](#_ENREF_29)) Means, medians and ranges were used to describe continuous data. 95% confidence intervals (CI) described estimation uncertainty. Categorical data were investigated by cross-tabulation and the Chi-square test. The Kaplan-Meier method was used to calculate unadjusted cumulative survival. In order to calculate crude and adjusted odds ratios (OR) with CI logistic regression models were fitted. Continuous variables were kept continuous when possible in order to strengthen the statistical analyses.([30](#_ENREF_30))

The performance of the logistic regression models was evaluated by its discrimination capacity using c-statistics. ….

We performed no imputation for missing data. The level of statistical significance was set at p<0.05.

## Ethical approval

All patients registered in the SHAR have received written information about the register. Registered patients have been given the choice not to participate in the registry or associated research but written informed consent for participation was not obtained. This is in consistency with the Swedish Patient Data Law from 2009. Our ethical approval was obtained from The Regional Ethical Review Board in Gothenburg (2013: 360-13).

# Results

Participants and comorbidities:

After the selection process (Figure 1) 44,214 individuals between 18 and 100 years old who hade undergone THA due to primary OA were analysed. The mean age was 86,3 years (SD 10.02) and there were somewhat more women (56.8%) than men (43.2%).

The highest proportion of patients with multiple comorbidities (i.e. three or more) was identified by the RxRisk-V measure (69.5%). For the Charlson Comorbidity Index the proportion of three or more comorbidities was 3.4% and for the Elixhauser Score it was 4.9%.

A vast majority of patients had an ASA score below three (85.2%). Individuals with an ASA score of 5 and 6 were excluded since those values describe moribund individuals.

When investigating the Charnley score we found that those with missing values had a considerably lower cumulative survival than those with a Charnley category registered. Since XX % of the study population did miss Charnley category registration further analyses regarding this parameter was not possible.

See Table 1 for more characteristics of the study population.

## Ninety day mortality after THA

Unadjusted cumulative 90-day survival was 0.9973 (95 % ci 0.9968; 0.9978) number of events 115. As expected we found that age (OR 1,1 [CI 1.06-1.12]) and gender (female gender adjusted OR 0.4 [CI 0.28-0.64] gave a statistically significant influence on the adjusted risk of death. Crude values indicated an increased risk of 90-day mortality for all three comorbidity index but only CCI remained statistically significant (adjusted OR 1.3[CI 1.09-1.45]) after adjustment was made as did the clinical ASA score. Within the social background variables only being a widow/-er (adjusted OR 1.7[CI 1.05-2.70]) fell out statistically significant after adjustment. Crude and adjusted odd ratios for 90-day mortality with 95% confidence intervals are presented in Table 2.

## One year mortality after THA

The unadjusted cumulative survival was 0.9908 (95 % ci 0.9899; 0.9917) for 1 year and the number of events 363. For the whole study period the number of events was 1412 and the unadjusted cumulative survival 0.9127 (95 % ci 0.9044; 0.9212). Age (OR 1,1 [CI 1.06-1.09]) and gender (female gender adjusted OR 0.6 [CI 0.44-0.69]) still gave a statistically significant influence on the adjusted risk of death. CCI remained statistically significant (adjusted OR 1.3[CI 1.2-1.45]) after adjustment was made as did the clinical ASA score. Within the social background variables marital status fell out statistically significant after adjustment (Data not shown).

## Prediction strength of investigated comorbidity measures

***The Charlson Comorbidity Index*** When examining the CCIs different dimensions we found that the total CCI performed better in predicting 90-day and one year mortality than the included dimensions separately. (See Table 3 A.) The original weighting (90-d c=0.65, 1-y c=0.65) was somewhat better in predicting both 90-day and one year mortality than the weighting according to Quan(90-d c=0.61, 1-y c=0.63). The original weighting of Charlson performed best of all investigated comorbidity measures better in predicting 90-day mortality. (See Table 3 A-C.)

***The Elixhauser Score*** The predictive strength of the Elixhauser score was better in prediciting 90-day and one year mortality than the included dimensions separately. (See Table 3B) with a 90 d c=0.63 and a 1 year c=0.65.

***The RxRisk-V Score***

Här saknas totalscorens värden i tabellen 3C.

***The American Society of Anesthesiologists physical status classification***

Har skulle det vara snyggt med en tabell motsvarande tabell 3. Tabell 3D. Vad tror du om det Szilard?

***Age, gender, ASA score, heart infarction and renal disease combined*** After trying combinations of dimensions included in the different comorbidity measures and clinically accessible data we found that the combination of age, gender, ASA score, presence of heart infarction and renal disease the last 12 months gave the best prediction strength for 90-day and one year mortality. (See Table 4) (AUC = 0.8134, 95 % ci 0.7746-0.8521).

# Discussion

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