

# Comparing Charlson and Elixhauser comorbidity indices with different weightings to predict in-hospital mortality: an analysis of national inpatient data

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## Research article

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# Abstract

**Background:** Understanding how comorbidity measures contribute to patient mortality are essential both to describe patient health status and to adjust for risks and potential confounding. The Charlson and Elixhauser comorbidity indices are well-established for risk adjustment and mortality prediction. Still, a different set of comorbidity weights might improve the prediction of in-hospital mortality. The present study, therefore, aimed to derive a set of new population-based Elixhauser comorbidity weightings, to validate and compare them against those of the Charlson and Elixhauser-based van Walraven weightings in an adult in-patient population-based cohort of general hospitals.

**Methods:** Retrospective analysis was conducted with routine data of 102 Swiss general hospitals (2012–2017) for 6.09 million inpatient cases. To derive the population-based weightings for the Elixhauser comorbidity index, we randomly halved the inpatient data and validated the results of part 1 alongside the established weighting systems in part 2, to predict in-hospital mortality. Charlson and van Walraven weightings were applied to Charlson and Elixhauser comorbidity indices. Derivation and validation of weightings were conducted with generalized additive models adjusted for age, gender and hospital types.

**Results:** Overall, the population-based weights' c-statistic (0.867, 95% CI: 0.865–0.868) was consistently, yet minimally higher than Elixhauser-van Walraven's (0.863, 95% CI: 0.862–0.864) and Charlson's (0.850, 95% CI: 0.849–0.851) in the derivation and validation groups. The net reclassification improvement of new weights improved the predictive performance by 1.6% on the Elixhauser-van Walraven and 4.9% on the Charlson weightings.

**Conclusions:** All weightings confirmed previous results with the national dataset. The new population-based weightings model improved slightly the prediction of in-hospital mortality in Swiss hospitals. The newly derive weights support patient population-based analysis of in-hospital mortality and seek country or specific cohort-based weightings.

## Background

Critical health outcomes such as mortality often require effective risk adjustment based on patient characteristics to predict in-hospital mortality. This is also true for comorbidities [1, 2], which function as major predictors of mortality [3]. Over one-third of hospitalized patients have at least one comorbidity; two-thirds of those over 65 [4, 2] and three-quarters of those over 85 have at least two [5]. In addition to mortality, comorbidities are associated with lower health-related quality of life, increased disability and higher utilization of both health care services and prescribed medications [6–8].

Data on comorbidities are valuable both for comparison between patient populations and for risk adjustment regarding associated outcomes, especially mortality [9]. Two of the best-known measures are the Charlson Comorbidity Index and the Elixhauser Comorbidity Index [10, 11]. When the Charlson Comorbidity Index was developed in 1987 it included 19 chronic conditions to predict one-year mortality,

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hauser Comorbidity Index, which was developed in 1998,

works on a similar system but includes 30 – or, for some variants, 31 – comorbidities. In addition to in-hospital mortality, it is also used to predict the length of stay, adverse events and hospital discharges [12, 13]. Despite this additional versatility (covering acute and chronic conditions) and strong evidence that the Elixhauser Comorbidity Index is statistically superior to the Charlson Comorbidity Index [14, 13], the Charlson Comorbidity Index continues to be used. Because of the fewer chronic conditions [15-17] and comparative ease of use in routine situations where time is limited.

Both indices work either via simple (unweighted) sum scores or as weighted scores assigning a risk weight to each comorbidity [6, 18, 19]. A weighted score provides an attractive advantage over plain dummy variables [20, 21], as it reduces the overfitting risk of more parameters, unjustifiable in small datasets [22] and limits computational requirements in large ones [21]. Additionally, evidence indicates that a weighted variable better reduces type I errors than dummy variables while addressing multicollinearity concerns in regression analysis and organizing multiple highly correlated variables into more meaningful information [23, 21]. The weight assigned to each comorbidity reflects a higher, lower or neutral risk of mortality [24]. For example, for hospitalized patients, metastatic cancer entails a considerably higher risk of death than obesity.

To add to the value of early versions of the Elixhauser comorbidities, van Walraven et al. [25] used roughly 13 years' inpatient admission data from one Canadian hospital (1996–2008) to develop a set of weights (VW weights, i.e., the regression coefficient divided by the coefficient in the model with the smallest absolute value) for the 30 Elixhauser comorbidities associated with in-hospital mortality. Using the backward selection and an alpha inclusion criterion of 0.05 to identify independently associated comorbidities, van Walraven identified 21 comorbidities significantly associated with mortality. A VW weight was assigned to each of the 21 Elixhauser comorbidities. Ultimately, VW weights ranged from -7 to 12, with a weight of 0 assigned to the 9 non-significant comorbidities.

Since then, primarily in North America, studies have used VW weights to predict in-hospital mortality, especially in clearly defined patient groups such as surgical, orthopaedic, or cancer patients and those in single hospitals or intensive care unit (ICU) [25, 26, 21, 13, 12]. Moreover, the comorbidity weighting system might differ between all hospitalization and a restricted cohort; mortality and other outcomes; and between the countries [27]. Few studies have applied comorbidity adjustments to national or regional inpatient datasets [21, 28]. Therefore, an analysis of a large heterogeneous patient population from a national dataset (Switzerland) is justified both to provide an overview of Elixhauser comorbidities in a European sample and potentially to optimize the comorbidity weights. In addition to increasing the generalizability of these comorbidity weights, the use of such a dataset, representing all hospital inpatient cases (i.e., hospitalisation episodes) from a large, heterogeneous patient population, would allow a very accurate comparison of weighting systems. Therefore, the aims of our study were 1) to derive a new population-based comorbidity weighting on a Swiss adult national inpatient dataset to predict in-hospital mortality; 2) to validate Charlson, Elixhauser-van Walraven and new weightings on a Swiss adult national inpatient dataset; and 3) to compare the predictive performance of in-hospital mortality of the three

# Methods

## Study design and population

This is a retrospective population-based analysis of six years' data (2012–2017) from the Swiss national inpatient dataset. Upon our application, subject to a data protection contract (as stipulated by article 22 of the Swiss Federal Act on Data Protection), the Swiss Federal Statistics Office (FSO) provided anonymized data from all Swiss hospital inpatient cases hospitalized between 2012 and 2017. This included not only general hospitals but also special care (e.g., paediatric, gynaecological) facilities [29]. The FSO classifies general hospitals (University hospitals, Tertiary hospitals, and three Basic hospitals) into five different levels, based on the number of cases treated per year and/or a special hospital score assigned by Swiss Medical Association (“FMH-Kategorien”). For this study, special care hospitals and children were excluded because of the low levels of comorbidities and the relatively low risk of dying in the hospital [25]. For data protection reasons, age was grouped in five-year groups, and all inpatient cases below 20 years of age were excluded. The flowchart for the final adult population included 102 general hospitals (6,094,672 inpatient cases) for the analysis is reported in supplementary figure F1 (Additional file 1).

## Dataset and classification of comorbidities indices

The dataset included patient characteristics including sex, age, hospital types, primary and secondary diagnoses based on International Classification of Diseases-10 (ICD-10) codes and hospital discharge information including in-hospital mortality. As condition coding in Switzerland is based on the ICD-10 German Modification (ICD-10 GM), reported in supplementary table S1 (Additional file 1), we used this to identify both Charlson and Elixhauser comorbidities. Specifically, we used Quan et al.'s ICD-10 codes [19] to determine each of the 17 Charlson and 31 Elixhauser comorbidities via the “Comorbidity” package in R [18]. This transforms ICD-10 codes into binary data the relevant comorbidities, their (unweighted) sum scores, and their Charlson and VW-weighted scores.

## Descriptive analysis

The study population's general characteristics (hospital types, patient's sex, and age groups) were reported in the alive and mortality cohorts with percentages. The distributions of Charlson and Elixhauser comorbidities, unweighted and weighted scores were computed as percentages of index values of 0, 1–2, and  $\geq 3$  and  $< 0$ , 0, 1–4, and  $\geq 5$ ; and as the Charlson weight do not use negative weightings, its weights were calculated for index values of 0, 1–4, and  $\geq 5$ . For each characteristic and comorbidities, standardized mean differences (SMD) between the alive and mortality cohort were provided. SMDs greater than 0.1 indicate potentially relevant differences [30], i.e., showing unbalanced covariates and might have an effect on outcomes.

## Derivation of population-based comorbidity weights

The study population was randomly split into a derivation (50%) and a validation (50%) group. The derivation group was used to determine the adjusted association of all 31 Elixhauser comorbidities with death, treating the anonymous hospital identifier as a random effect [31]. Because of the large sample size, we fitted generalized additive regression models (GAM) to compute the odds ratios (OR) using the package “mgcv” [32] and R programming language, version 3.5.2 [33]. Thus, we utilized GAM with random effect components on the hospital level. To identify Elixhauser comorbidities associated with in-hospital mortality, we retained variables based on an alpha inclusion criterion of 0.01.

To derive the population-based weightings from the regression model’s parameter estimates, we used the method described by Sullivan et al. [34]. Comorbidities not significantly associated with mortality were assigned a weight of zero. The number of (weighted) points assigned to each comorbidity equalled its regression coefficient divided by the coefficient in the model with the smallest absolute value [25, 21, 14, 34] rounded to the nearest whole number. Each person’s new Elixhauser comorbidity weighting score was then calculated by summing up all points of all their coded comorbidities.

### **Validation and comparison of weighted comorbidity models**

To validate and compare the performance of the three comorbidity weighting systems, we first created four multivariate in-hospital mortality prediction GAMs for the derivation group. The first model, ‘base’, contained no comorbidity data – only age group, sex, and hospital types. The other three models used the same variables as the base model, with the first, ‘Charlson’, using Charlson weightings, the second, ‘van Walraven’, using the Elixhauser index with van Walraven weightings, and the third, ‘population-based weights’, using our newly-developed weightings. We then validated all weightings in validation groups by splitting the validation group into six groups by year of discharge. Altogether, 24 c statistics (including base models) were computed to validate the Charlson, van Walraven, and population-based weights models in the validation sample. An additional four models were created using all cases (combining derivation and validation groups) to evaluate the performance of each model in the total patient population.

We assessed the various comorbidity weightings according to the model performance criteria. Discrimination, i.e., each model’s ability to distinguish patients discharged alive from those who died in hospital, was compared using the concordance (c) statistic. The c-statistic quantified each model’s ability to assign high probabilities of mortality to patients who died [35]. It’s possible values range from 0.50 to 1.0, with 0.50 indicating no ability to discriminate, values less than 0.70 are considered poor, those between 0.70 and 0.80 acceptable, and those of 0.80 or above excellent [36]. Using bootstrap methods, we computed 95% confidence intervals for each c-statistic. We also graphed receiver-operating characteristic curves (ROC) for the visual presentation of the derivation group’s c statistics. We compared the base model and existing comorbidity models with population-based weight model using net reclassification improvement (NRI) for binary models [37-39] from the “nricens” package in R [40] using the population-based derivation sample. NRI measures the degree of improvement in predicted inpatient

mortality probabilities when comorbidity weights are added to the base model [21, 41]. Higher NRI values indicate more accurate reclassification.

### Code validation and sensitivity analyses

We also evaluated the R comorbidity package's code handling accuracy in the Swiss setting. To do so we sampled 100 cases and manually reviewed the Swiss ICD-10 codes of the raw data, checking whether the "comorbidity" package had assigned each to the appropriate Charlson or Elixhauser comorbidity. We also performed sensitivity analyses to explore Switzerland's Major Diagnostic Categories' (MDCs) associations, which are based on ICD-10 GM (one way of expressing the reason for admission), if any, regarding the change in the predictability of in-hospital mortality in combination with the above models and to test whether the combined models' patterns differed from those of uncombined ones. MDCs are 24 mutually exclusive categories into which all primary diagnoses are assigned based on the Swiss diagnostic-related group (DRG) system for hospital reimbursement [42].

## Results

### Population characteristics

Overall, the adult inpatient population between 2012 and 2017 in all Swiss general hospitals (102) consisted of 6,094,672 cases. Among all hospitalized cases in our study population mortality was 2.3%. The characteristics of the adult inpatient cases are presented in Table 1. Inpatient cases had between 0 and 9 Charlson comorbidities (median 0, interquartile range (IQR): 0-1) and between 0 and 16 Elixhauser comorbidities (median 1, IQR: 0-2). The different categories of three comorbidity weightings are presented in supplementary table S2 (Additional file 1).

**Table 1** General characteristics of the total study population

Parameters	Alive cohort (%)	Mortality cohort (%)	SMD
Total population: N = 6,094,672	5,952,005 (97.7)	142,667 (2.3)	
Female	3,280,823 (55.1)	63,912 (44.8)	0.208
Age group			1.006
20-24 years	215,672 (3.6)	292 (0.2)	
25-29 years	327,562 (5.5)	375 (0.3)	
30-34 years	415,022 (7.0)	526 (0.4)	
35-39 years	348,591 (5.9)	718 (0.5)	
40-44 years	299,985 (5.0)	1,368 (1.0)	
45-49 years	350,899 (5.9)	2,503 (1.8)	
50-54 years	408,028 (6.9)	4,312 (3.0)	
55-59 years	430,721 (7.2)	6,503 (4.6)	
60-64 years	466,543 (7.8)	9,068 (6.4)	
65-69 years	528,374 (8.9)	13,322 (9.3)	
70-74 years	554,612 (9.3)	16,899 (11.8)	
75-79 years	535,543 (9.0)	19,888 (13.9)	
80-84 years	509,225 (8.6)	24,853 (17.4)	
85-89 years	365,924 (6.1)	24,042 (16.9)	
90-94 years	161,236 (2.7)	14,156 (9.9)	
95+ years	34,068 (0.6)	3,842 (2.7)	
Hospital types			0.157
University (level 1)	1,078,612 (18.1)	29,379 (20.6)	
Tertiary care (level 2)	3,274,382 (55.0)	83,686 (58.7)	
Basic care (level 3)	736,465 (12.4)	14,863 (10.4)	
Basic care (level 4)	671,182 (11.3)	10,695 (7.5)	
Basic care (level 5)	191,364 (3.2)	4,044 (2.8)	
Number of Charlson comorbidities			1.234
0	3,642,650 (61.2)	17,465 (12.2)	
1-2	1,907,761 (32.1)	80,876 (56.7)	
>= 3	401,594 (6.7)	44,326 (31.1)	
Number of Elixhauser comorbidities			1.039
0	2,509,169 (42.2)	11,036 (7.7)	
1-2	2,106,780 (35.4)	43,494 (30.5)	
>= 3	1,336,056 (22.4)	88,137 (61.8)	

*Abbreviations:* SMD standardized mean difference between alive and mortality cohort

## Prevalence of Charlson and Elixhauser comorbidity indices

The most common Charlson comorbidity was any malignancy (including lymphoma and leukaemia, except malignant neoplasm of the skin) in both cohorts, alive (10.2 %) and mortality (37.6%). The prevalence for each Charlson comorbidity in the total population and the derivation, group is presented in [supplementary table S2 \(Additional file 1\)](#)

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The most common Elixhauser comorbidities were uncomplicated hypertension (22.7 %) in the alive cohort, whereas in the mortality cohort, it was solid tumour without metastasis (33.7%). The prevalence for each Elixhauser comorbidity from the total population and derivation group is presented in the supplementary table S4 (Additional file 1).

### Derivation of population-based weights

In the derivation group, two of the 31 Elixhauser comorbidities showed no association with hospital mortality and were removed, leaving 29 in the final model. Sixteen were associated with increased mortality risk, with the strongest associations coming from metastatic cancer (OR: 4.09, 95% CI: 3.98–4.21) and liver disease (OR: 3.83, 95% CI: 3.70–3.97). At the other end of the spectrum, thirteen comorbidities were associated with a decreased risk of hospital mortality. The strongest of these were deficiency anaemia (OR: 0.54, 95% CI: 0.51–0.56) and obesity (OR: 0.59, 95% CI: 0.56–0.63). The adjusted coefficients were used to derive population-based weights with a new maximum weight of 17, for metastatic cancer, and a new minimum of -7, for deficiency anaemia (Table 2).

**Table 2** Prevalence, adjusted odds ratio and weights from the (new) population-based derivation sample and the van Walraven (VW) derivation sample [25]

Elixhauser comorbidities	Alive cohort (%) Population-based sample	Mortality cohort (%) derivation	SMD	Adjusted odds ratio (95% CI)		Weights	
				VW <sup>a</sup>	New <sup>b</sup>	VW <sup>a</sup>	New <sup>b</sup>
Derivation group	2,975,887 (97.7)	71,449 (2.3)					
Congestive heart failure	163,685 (5.5)	16,333 (22.9)	0.514	1.96 (1.85–2.07)	3.07 (3.00–3.14)	7	13
Cardiac arrhythmias	341,280 (11.5)	20,754 (29.0)	0.448	1.71 (1.62–1.80)	1.69 (1.66–1.73)	5	6
Valvular disease	117,450 (3.9)	6,568 (9.2)	0.213	0.91 (0.82–0.99)	0.92 (0.89–0.95)	-1	-1
Pulmonary circulation disorders	53,292 (1.8)	4,813 (6.7)	0.247	1.48 (1.34–1.62)	1.62 (1.57–1.68)	4	6
Peripheral vascular disorders	141,051 (4.7)	6,912 (9.7)	0.192	1.26 (1.17–1.36)	1.27 (1.24–1.31)	2	3
Hypertension (uncomplicated)	676,609 (22.7)	15,692 (22.0)	0.019	-	0.69 (0.68–0.70)	0	-4
Hypertension (complicated)	218,656 (7.3)	11,003 (15.4)	0.256	-	0.79 (0.77–0.81)	0	-3
Paralysis	61,546 (2.1)	5,153 (7.2)	0.246	1.93 (1.75–2.12)	2.60 (2.52–2.69)	7	11
Other neurological disorders	120,045 (4.0)	8,011 (11.2)	0.273	1.83 (1.70–1.96)	2.45 (2.39–2.52)	6	10
Chronic pulmonary disease	170,770 (5.7)	8,269 (11.6)	0.209	1.36 (1.29–1.44)	1.31 (1.27–1.34)	3	3
Diabetes, uncomplicated	245,817 (8.3)	9,059 (12.7)	0.145	-	1.09 (1.06–1.11)	0	1
Diabetes, complicated	66,161 (2.2)	2,763 (3.9)	0.096	-	0.89 (0.86–0.93)	0	-1
Hypothyroidism	126,062 (4.2)	3,454 (4.8)	0.029	-	0.76 (0.74–0.79)	0	-3
Renal failure	289,047 (9.7)	20,526 (28.7)	0.497	1.63 (1.54–1.73)	2.06 (2.02–2.11)	5	8
Liver disease	49,916 (1.7)	5,822 (8.1)	0.303	2.97 (2.73–3.22)	3.83 (3.7–3.97)	11	16
Peptic ulcer disease, excluding bleeding	5,808 (0.2)	258 (0.4)	0.032	-	-	0	0
AIDS/HIV	2,300 (0.1)	85 (0.1)	0.013	-	-	0	0
Lymphoma	25,049 (0.8)	1,759 (2.5)	0.127	2.55 (2.31–2.81)	2.19 (2.07–2.31)	9	9
Metastatic cancer	119,667 (4.0)	18,907 (26.5)	0.657	3.30 (3.10–3.52)	4.09 (3.98–4.21)	12	17
Solid tumour without metastasis	268,298 (9.0)	24,046 (33.7)	0.631	1.47 (1.39–1.56)	2.36 (2.3–2.42)	4	10
Rheumatoid arthritis/collagen vascular diseases	47,305 (1.6)	1,254 (1.8)	0.013	-	0.91 (0.86–0.97)	0	-1
Coagulopathy	90,551	9,528 (13.3)	0.382	1.30 (1.22–1.40)	2.12 (2.07–2.18)	3	9

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Obesity	68,155 (2.3)	1,011 (1.4)	0.065	0.64 (0.53– 0.77)	0.59 (0.56– 0.63)	-4	-6
Weight loss	98,545 (3.3)	9,527 (13.3)	0.369	1.85 (1.67– 2.04)	1.67 (1.63– 1.71)	6	6
Fluid and electrolyte disorders	257,618 (8.7)	17,440 (24.4)	0.434	1.61 (1.53– 1.69)	1.58 (1.55– 1.61)	5	5
Blood loss anaemia	19,759 (0.7)	685 (1.0)	0.033	0.81 (0.70– 0.93)	0.66 (0.60– 0.71)	-2	-5
Deficiency anaemia	72,290 (2.4)	1,886 (2.6)	0.013	0.80 (0.71– 0.90)	0.54 (0.51– 0.56)	-2	-7
Alcohol abuse	96,708 (3.2)	3,086 (4.3)	0.056	-	0.75 (0.72– 0.78)	0	-3
Drug abuse	38,044 (1.3)	583 (0.8)	0.045	0.50 (0.42– 0.60)	0.67 (0.61– 0.73)	-7	-5
Psychoses	29,598 (1.0)	404 (0.6)	0.049	-	0.72 (0.65– 0.79)	0	-4
Depression	173,898 (5.8)	3,715 (5.2)	0.028	0.73 (0.67– 0.80)	0.73 (0.70– 0.75)	-3	-3

*Abbreviations:* SMD standardized mean difference between alive and mortality cohort, *New*<sup>b</sup> population-based, *VW*<sup>a</sup> van Walraven, - excluded in the final model

Note: Total cohort % exceed 100% for each cohort, as comorbidities are mutually inclusive, *New* weights are calculated dividing the coefficient of each comorbidity by the coefficient in the model with the smallest absolute value

### Validation and comparison of weighted comorbidity models

All three comorbidity weighting systems (Charlson, Elixhauser van Walraven and population-based) indicated higher in-hospital mortality risk than the base model. They also showed equivalent discrimination in the derivation and validation groups (Table 3). Overall, the Charlson weighting model's c-statistic was 0.850 (95% CI: 0.849–0.851), the van Walraven model was 0.863 (95% CI: 0.862–0.864) and population-based weights model was 0.867 (95% CI: 0.865–0.868) in the total sample. There were similar results for both, the derivation and validation groups except the slight change on c statistic and CI on six validation samples as shown in Table 3. Additionally, c statistics for the validation sample is shown in supplementary table S5 (Additional file 1). In comparison, the model with population-based weights discrimination was slightly better with some c-statistic variability across the six years' data.

**Table 3** Performance measures of the base, Charlson, van Walraven and population-based weights models for in-hospital mortality in derivation, validation and all cases groups

	C Statistic (95% CI)							All cases N= 6,094,672 All years (2012- 2017)
	Derivation group n = 3,047,336 All years (2012- 2017)	Validation groups						
	n <sub>1</sub> = 491,962 Year 1	n <sub>2</sub> = 496,684 Year 2	n <sub>3</sub> = 504,741 Year 3	n <sub>4</sub> = 514,267 Year 4	n <sub>5</sub> = 520,277 Year 5	n <sub>6</sub> = 519,405 Year 6		
Population-based weights model	0.757 (0.755-0.759)	0.758 (0.752-0.759)	0.758 (0.754-0.762)	0.756 (0.753-0.760)	0.752 (0.748-0.756)	0.756 (0.752-0.759)	0.750 (0.746-0.754)	0.757 (0.755-0.759)
Charlson weights model	0.850 (0.847-0.851)	0.849 (0.846-0.852)	0.852 (0.849-0.855)	0.854 (0.851-0.857)	0.849 (0.846-0.852)	0.854 (0.851-0.857)	0.844 (0.841-0.847)	0.850 (0.849-0.851)
Base model	0.863 (0.862-0.864)	0.862 (0.859-0.865)	0.866 (0.863-0.869)	0.867 (0.864-0.869)	0.863 (0.860-0.866)	0.869 (0.866-0.872)	0.862 (0.859-0.864)	0.863 (0.862-0.864)
Population-based weights model	0.867 (0.865-0.868)	0.865 (0.862-0.868)	0.869 (0.866-0.871)	0.871 (0.873)	0.866 (0.863-0.869)	0.872 (0.874)	0.865 (0.862-0.867)	0.867 (0.865-0.868)

Abbreviations: VW van Walraven, CI confidence interval

Base model: age groups, sex, hospital types

Charlson weights model: base and Charlson weights

VW weights model: base and Elixhauser/ van Walraven weights

Population-based weights model: base and Elixhauser/ Population-based weights

As shown in Fig. 1, the population-based weights model's discrimination was clearly better than the Charlson's or base model's, and only slightly better than the van Walraven's. The NRI confirm this picture (Table 4). Comparing the population-based weights with VW weights showed an NRI of 1.6% (95%-CI: 1.3–2.0) with differences in predicted probabilities of mortality (among those who died) of 1.4% and differences in predicted probabilities of alive (among those who lived) by 0.02%.

**Table 4** Comparison of population-based weights model with Base, Charlson and VW models based on the Net Reclassification Improvement (NRI)

Comparison models	NRI (95% CI)	Derivation group			
		Mortality increased Pr(Up Case)	Alive increased Pr(Up Ctrl)	Mortality decreased Pr(Down Case)	Alive decreased Pr(Down Ctrl)
Population-based weights vs. Base model	0.355 (0.352-0.357)	0.448 (0.445-0.450)	0.074 (0.074-0.074)	0.134 (0.133-0.136)	0.115 (0.115-0.116)
Population-based weights vs. Charlson weights model	0.049 (0.044-0.052)	0.297 (0.294-0.299)	0.058 (0.058-0.059)	0.251 (0.250-0.253)	0.062 (0.061-0.062)
Population-based weights vs. VW weights model	0.016 (0.013-0.020)	0.157 (0.155-0.159)	0.021 (0.021-0.022)	0.143 (0.140-0.145)	0.024 (0.023-0.024)

*Abbreviations: NRI* Net Reclassification Improvement, *CI* confidence interval

$Pr(Up, Down) | (Case, Ctrl)$  represents the proportion of patients whose predicted probabilities increased or decreased for in-hospital mortality and alive cohorts respectively

$NRI = (Pr(Up|Case) - Pr(Down|Case)) + (Pr(Down|Ctrl) - Pr(Up|Ctrl))$

Base model: age group, sex, hospital types

Charlson weights model: base and Charlson weights

VW weights model: base and Elixhauser/ van Walraven weights

Population-based weights model: base and Elixhauser/ Population-based weights

Finally, the sensitivity analysis using MDCs did not offer any improvements in the models' performance.

## Discussion

This study used a six-year dataset of a multi-million-patient population to explore Charlson and Elixhauser comorbidities with different weightings to predict in-hospital mortality. We first derived a set of population-based weightings for the 31 Elixhauser comorbidities using the national inpatient dataset. The analysis confirmed Charlson and Elixhauser comorbidities with van Walraven's weightings performance for mortality prediction, while the newly derived population-based weightings slightly improved the mortality prediction for the 31 Elixhauser comorbidities.

Although, the optimized population-based weightings performed only slightly better than the Charlson and Elixhauser-van Walraven sets they also supplied weights for eight Elixhauser comorbidities (e.g. diabetes, hypertension, and psychosis) eliminated by van Walraven et al. (2009) [25]. Of the risk-associated comorbidities retained in both the van Walraven and the population-based weights, several comorbidities showed similar results, e.g., the highest odds ratios to metastatic cancer and liver disease.

And regarding the comorbidities with negative associations, only small differences were observed between the van Walraven and population-based weights (e.g., hypothyroidism or obesity were likely to be healthier).

From an epidemiological perspective, overall hospitalization mortality was only 2.3%, but in-hospital mortality is higher in patients with chronic diseases. Chronic diseases such as cancer, heart and liver diseases increase the risk of dying in hospitals, while certain other less severe diseases, (e.g., hypertension, anaemia and hypothyroidism) have negative weights. This is due to the relatively high frequency of those less critical comorbidities and inpatients having less worse outcomes. These results are in line with those of Zellweger et al.'s [43] study using the Swiss national death registry of hospital inpatient data from 2010–2012. Furthermore, van Walraven et al.'s [25] study based on a single Canadian hospital's records and Thompson et al., [21] using Maryland State inpatient data, showed similar results. These relations could insight the global burden of in-hospital mortality is due to rising chronic diseases.

The existing weighting systems [11, 25, 21, 13] represent data from a specific geographical region, patient group, or even limited numbers of hospitals or settings, matching the generalizability of these weighting systems remained difficult. As this study addresses such issues, with a large dataset representing the Swiss inpatient population, it provides population-based comorbidity adjustments for the prediction of

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Statistic reported in our study is 10% higher than those reported

in van Walraven's study [25]. Several reasons might explain this increase: e.g. the GAM modelling approach including random effects, the study cohort and hospital types included. With the new eight derivations, the additional eight significant variables might have played a role too. However, a slightly improved performance of the population-based weights system suggests that it might be worthwhile to derive country- or region-specific comorbidity weights from representative patient populations.

C-statistics and ROCs are widely used to assess predictive performance. Nonetheless, one downside of comparing c-statistic and ROCs is that differences between c-statistics are often small, [44] as it was the case when we compared our new weights and van Walraven's. Over the past decade, it has become common to use NRIs to compare different models' performance, even though it might differ with the cut-offs taken for analysis [45, 38]. In our study, taking the same cut-offs, NRI calculations confirmed the three weighting systems' rankings i.e., population-based, van Walraven and Charlson weightings.

The primary strength of this study was the large sample size and the heterogeneity of the Swiss inpatient population across all general hospitals over six years, which made it representative of the entire country. To our knowledge, this study is the first to derive and validate Elixhauser weightings in Swiss hospital inpatient data. We used standard regression methodology for large datasets, including random effects at the hospital level, and internally validated our models. We also used accepted methods to modify our adjusted model into a population-based weightings system that re-includes the association of several comorbidities (e.g., diabetes, hypertension, Psychoses) formerly excluded from the Elixhauser index in the VW study [34]. Despite differences in individual comorbidities' prevalence and weightings, Charlson, Elixhauser/VW, and the population-based weights performed well across the derivation, validation, and all-cases groups. We also used NRIs, allowing a robust comparison of model performance. Finally, the methods we applied were explicit and can be replicated by other researchers, who can adjust or control for patient comorbidity via their own and national databases.

Our study also has certain notable limitations. We derived our weights using statistical criteria, while clinical knowledge might be needed to determine each comorbidity's value. Since we used codes assigned in routine data, the capture of the comorbidities could be influenced by other factors, such as physician and nurse documentation, code assignment accuracy, and the possibility that capture of comorbidities is biased towards those for which the Swiss DRG / MDC pays more [46, 42]. Moreover, current comorbidity indices are not suitable predictors of patient-centred outcomes like rehabilitation, readmission, fee-for-services while weightings might differ in restricted cohorts, other outcomes and countries [27]. Additionally, Swiss data protection regulations prevented us from obtaining the inpatients' exact age, we could not differentiate children exactly under 18 years and could not specify each year. This also might have influenced the predictive accuracy of the tested models.

## Conclusions

We found that Elixhauser/van Walraven and the population-based weights indicated similar risks of in-hospital mortality. With the national inpatient dataset, we confirmed the validity of the Elixhauser/van

Walraven weightings. The population-based weightings performed well across derivation and validation groups and with slightly better discrimination than the Elixhauser/van Walraven weightings. Although the population-based weightings showed slightly improved mortality predictions, Elixhauser/van Walraven weightings worked well in this population dataset. Researchers wishing to use the Elixhauser comorbidities could, therefore, utilize the population-based weights derived in this study or the Elixhauser/van Walraven weightings. Most importantly, given access to similar data, researchers can use the methods described here to validate existing weightings such as van Walraven or derive their own country- or region-specific comorbidity weights.

## Abbreviations

ECI	Elixhauser Comorbidity Index
CCI	Charlson Comorbidity Index
ICD-10 GM	International Classification of Diseases version-10 German Modification
DRGs	Diagnosis-Related Groups
SMD	Standardized Mean Differences
NRI	Net Reclassification Improvement
MDCs	Major Diagnostic Categories
ROC	Receiver-Operating Characteristic
FSO	Federal Statistical Office
SBK	Swiss Nurses' Association
GAM	Generalized Additive Model
FMH	Swiss Medical Association
CI	Confidence Interval

## Declarations

### Ethics approval and consent to participate

Further ethical approval was deemed unnecessary, as the study was subjected to data protection contract (as stipulated by article 22 of the Swiss Federal Act on Data Protection) with Swiss Federal Statistics Office. Consent to participate was not applicable.

## Consent for publication

Not applicable.

## Availability of data and material

Upon application, the data that support the findings of this study are available from Federal Statistical Office (FSO), Switzerland.

## Competing interests

The authors declare that they have no competing interests.

## Funding

This study was supported by Swiss Nurses' Association (SBK). The funders had no role in the design, conduct, analysis or reporting of this study.

## Authors' contributions

This paper is derived from the PhD dissertation research in the field of health service and patient safety of the first author. NS and MS had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. NS, RS, OE, DA, and MS contributed to the conception and design of the study. NS drafted the manuscript and all the authors contributed substantially to the interpretation, visualization of the data, critically revised, edited the manuscript for important intellectual content and agreed to be accountable for all aspects. All of the authors listed above approved this version of the manuscript to be published.

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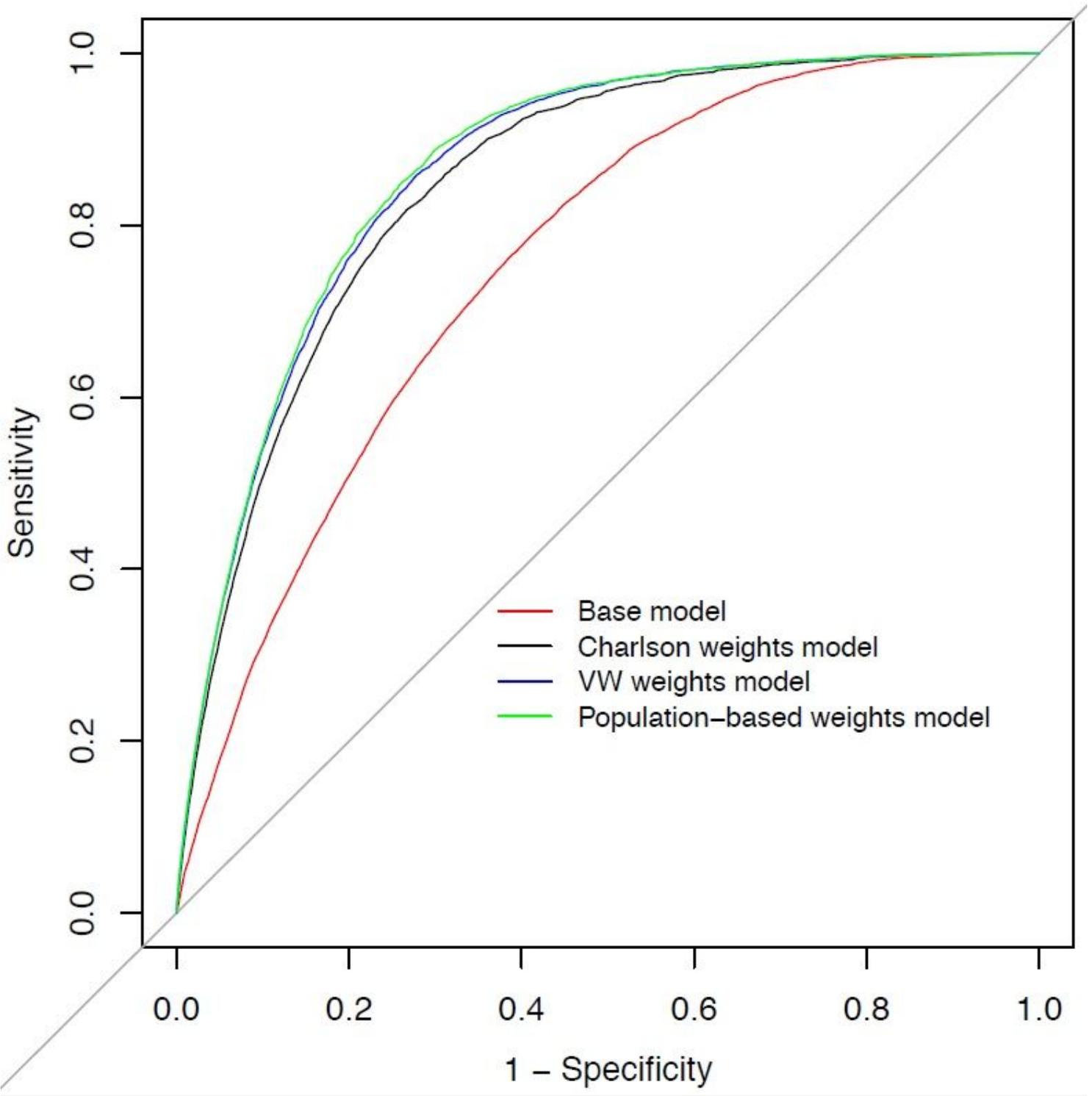
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## Figures



**Figure 1**

Receiver-operating characteristic (ROC) curves for generalized additive models predicting in-hospital mortality. Base model: age group, sex, hospital types; Charlson weights model: base and Charlson weights; VW weights model: base and Elixhauser/ van Walraven weights; Population-based weights model: base and Elixhauser/ population-based weights

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