

Performance of the SHARPEN Score and the Charlson Comorbidity Index for In-Hospital and Post-Discharge Mortality Prediction in Infective Endocarditis

Sofia Giusti Alves,¹ Fernando Pivatto Júnior,^{1,2} Filipe Barcellos Filippini,³ Gustavo Paglioli Dannenhauer,³ Gabriel Seroiska,⁴ Helena Marcon Bischoff,⁴ Luiz Felipe Schmidt Birk,⁴ Diego Henrique Terra,⁴ Daniel Sganzerla,⁵ Marcelo Haertel Miglioranza^{4,5,6,7}

Hospital de Clínicas de Porto Alegre (HCPA),¹ Porto Alegre, RS – Brazil

Hospital Nossa Senhora da Conceição (HNSC),² Porto Alegre, RS – Brazil

Instituto de Cardiologia de Santa Catarina,³ São José, SC – Brazil

Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSA),⁴ Porto Alegre, RS – Brazil

Unimed Porto Alegre Cooperativa Médica,⁵ Porto Alegre, RS – Brazil

Instituto de Cardiologia do Rio Grande do Sul (ICFUC-RS) – Laboratório de Pesquisa e Inovação em Imagem Cardiovascular,⁶ Porto Alegre, RS – Brazil

Hospital Mãe de Deus,⁷ Porto Alegre, RS – Brazil

Abstract

Background: SHARPEN was the first dedicated score for in-hospital mortality prediction in infective endocarditis (IE) regardless of cardiac surgery.

Objectives: To analyze the ability of the SHARPEN score to predict in-hospital and post-discharge mortality and compare it with that of the Charlson comorbidity index (CCI).

Methods: Retrospective cohort study including definite IE (Duke modified criteria) admissions from 2000 to 2016. The area under the ROC curve (AUC-ROC) was calculated to assess predictive ability. Kaplan-Meier curves and Cox regression was performed. P-value < 0.05 was considered statistically significant.

Results: We studied 179 hospital admissions. In-hospital mortality was 22.3%; 68 (38.0%) had cardiac surgery. Median (interquartile range, IQR) SHARPEN and CCI scores were 9(7-11) and 3(2-6), respectively. SHARPEN had better in-hospital mortality prediction than CCI in non-operated patients (AUC-ROC 0.77 vs. 0.62, $p = 0.003$); there was no difference in overall ($p = 0.26$) and in operated patients ($p = 0.41$). SHARPEN > 10 at admission was associated with decreased in-hospital survival in the overall (HR 3.87; $p < 0.001$), in non-operated (HR 3.46; $p = 0.006$) and operated (HR 6.86; $p < 0.001$) patients. CCI > 3 at admission was associated with worse in-hospital survival in the overall (HR 3.0; $p = 0.002$), and in operated patients (HR 5.57; $p = 0.005$), but not in non-operated patients (HR 2.13; $p = 0.119$). Post-discharge survival was worse in patients with SHARPEN > 10 (HR 3.11; $p < 0.001$) and CCI > 3 (HR 2.63; $p < 0.001$) at admission; however, there was no difference in predictive ability between these groups.

Conclusion: SHARPEN was superior to CCI in predicting in-hospital mortality in non-operated patients. There was no difference between the scores regarding post-discharge mortality.

Keywords: Endocarditis; Comorbidity; Survival Analysis.

Introduction

Infective endocarditis (IE) has a high incidence, with 1.5-11.6 cases per 100,000 population,¹ and in-hospital mortality rates ranging from 17.5 to 30%.¹⁻³ Patients who survive the first episode of IE continue to present with excess

mortality and morbidity, especially within the first year after discharge.⁴ Recent changes in IE epidemiological profile may have contributed to the maintenance of elevated morbidity and mortality. IE incidence has increased in patients with risk factors for adverse outcomes, such as advanced age, multiple comorbidities, prosthetic valves, and intracardiac devices; also, an increase in nosocomial cases has been reported.^{2,5,6}

Considering IE a significant health burden, optimizing evaluation and treatment is essential. There is evidence of improvement in clinical outcomes with the use of a multidisciplinary alert strategy and standardized IE protocols based on disease severity.⁷⁻¹⁰ In this context, score-based risk stratification can refer high-risk patients to specialized or intensive care.¹¹ Considering that early surgery has been shown to reduce IE mortality, risk scores may be particularly

Mailing Address: Sofia Giusti Alves •
Hospital de Clínicas de Porto Alegre – Rua Ramiro Barcelos, 2350. Postal
Code 90410-000, Porto Alegre, RS – Brazil
E-mail: sofiagiustia@gmail.com
Manuscript received July 04, 2023, revised manuscript October 03, 2023,
accepted October 18, 2023
Editor responsible for the review: Gláucia Maria Moraes de Oliveira

DOI: <https://doi.org/10.36660/abc.20230441>

Central Illustration: Performance of the SHARPEN Score and the Charlson Comorbidity Index for In-Hospital and Post-Discharge Mortality Prediction in Infective Endocarditis



SHARPEN and Charlson risk scores for Infective Endocarditis mortality prediction

- 179 hospital admissions (2000-2016)
- Surgery for IE during the admission: 38%
- In-hospital mortality: 22.6%
- Post-discharge mortality: 54.1%

Accuracy

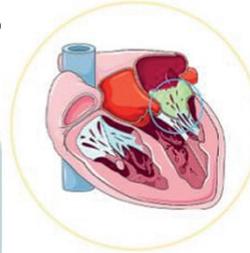
In-hospital mortality

Non-operated: SHARPEN was superior to the CCI (AUC 0.77 vs. 0.62; $P=0.03$)

Operated: SHARPEN and CCI were equivalent (AUC 0.72 vs. 0.80; $P=0.72$)

Post-discharge mortality

SHARPEN and CCI were equivalent (AUC 0.71 vs. 0.67; $P=0.515$)



SHARPEN score:

The first dedicated risk model for mortality prediction in infective endocarditis patients regardless of surgery

Survival analysis

In-hospital mortality

– SHARPEN > 10

Decreased survival in both operated (HR 6.86; $p<0.001$) and non-operated (HR 3.46; $p=0.006$) subgroups

– CCI>3

Decreased survival in the operated (HR 5.57; $p<0.005$), but not in non-operated subgroup (HR 2.13; $p=0.119$)

Post-discharge mortality

Decreased survival in admissions with SHARPEN > 10 (HR 3.11; $p<0.001$) and CCI >3 (HR 2.63; $p<0.001$)

Arq Bras Cardiol. 2023; 120(12):e20230441

useful to guide patient selection.¹² Furthermore, its application for mortality prediction after a hospitalization due to IE could help identify patients who would benefit from a closer post-discharge follow-up.

Several surgical risk scores have been developed specifically for IE¹³⁻²⁰ and compared with traditional surgical risk scores, such as EuroSCORE and the STS score.²¹⁻²³ However, these scores have not been validated in non-operated patients who represent almost 50% of all hospitalizations for IE⁶ or for long-term prognostic evaluation. The ICE-Pro prospective Cohort Study is an exception regarding evaluation of mortality for IE after discharge, which was determined at six months.²⁴ Therefore, it is necessary to improve the prognostic evaluation of patients undergoing medical therapy alone.

SHARPEN is a risk score for IE developed by Chee et al.¹¹ to predict in-hospital mortality in operated and non-operated patients.²⁵ Our study aims to prognostic value of SHARPEN score during hospitalization and after discharge in both operated and non-operated patients admitted for IE and to compare its performance with that of the Charlson comorbidity index (CCI).²⁶

Patients and methods

We performed a unicentric retrospective cohort study enrolling all active IE cases (on antibiotic treatment)²⁷ from 2000 to 2016 in patients aged ≥ 18 years. Only patients with a definite diagnosis of IE according to the modified Duke criteria were included.²⁸ Our institution is a public tertiary teaching hospital located in southern Brazil. It has 784 beds and access to care is provided exclusively through the Brazilian

Unified Health System, mostly to low-income patients. An average of 30-60 valve replacements are performed per year at the institution. The study was approved by the institution Research Ethics Committee.

Hospitalizations for IE were identified by the International Classification of Diseases, 10th revision (ICD-10) code²⁹ recorded in the discharge summary or at any point during hospitalization. The following codes were searched: B37.6 (Candidal endocarditis), I33.0 (acute and subacute IE), I33.9 (acute and subacute endocarditis, unspecified), I38 (endocarditis, valve unspecified), and I39.8 (endocarditis and heart valve disorders in diseases classified elsewhere). After this initial screening, the patients' medical records were reviewed to ensure that inclusion criteria were met. Figure 1 shows the study flowchart. Data regarding the hospitalization period were collected from electronic and physical medical records. Post-discharge follow-up assessment involved evaluation of medical charts to verify whether the surviving patients had appointments and/or hospitalizations after hospital discharge, telephone number of the remaining patients and, finally, review of death certificates. All patients that were not registered as deceased in neither of these data sources by October 1st, 2022 (which marked the conclusion of the follow-up assessment) were considered alive.

SHARPEN score¹¹ (2-20 points, Supplementary File S1) was calculated retrospectively for each hospitalization which was classified as low or high risk for in-hospital mortality according to the best cut-off point observed. Three points were assigned to systolic blood pressure < 90 mm Hg at presentation or non-intravenous (IV) drug abuser; two points to manifestations of heart failure (HF) during hospitalization,

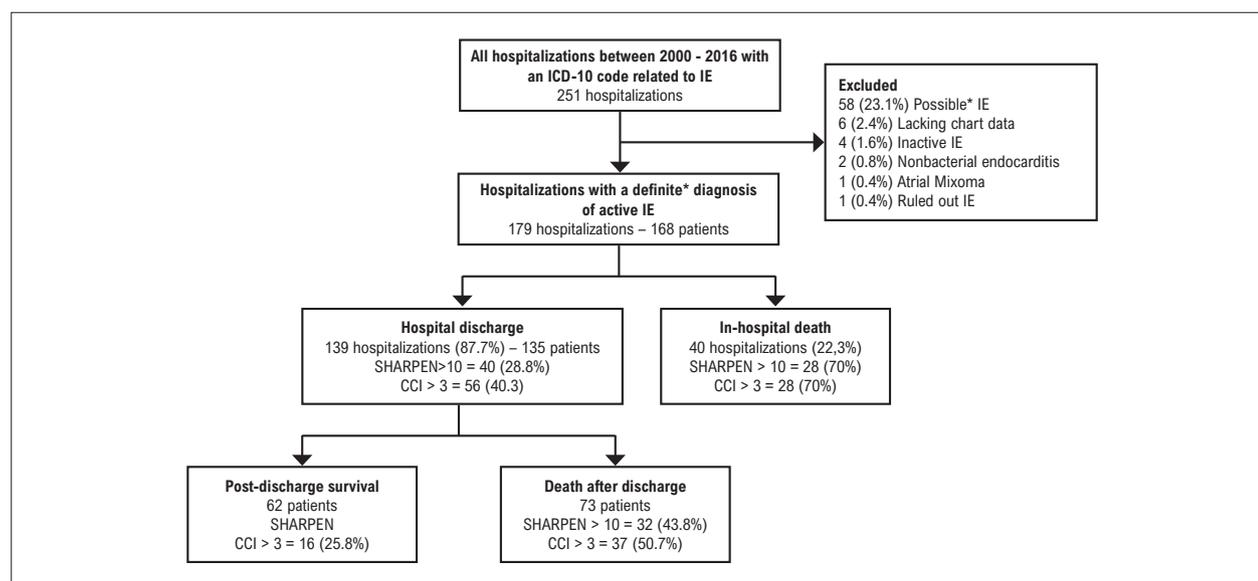


Figure 1 – Flowchart. IE: infective endocarditis; ICD-10: International Classification of Diseases, 10th revision; CCI: Charlson comorbidity index. *Modified Duke criteria. Data presented as n (%).

creatinine at admission > 2.26 mg/dL, diagnosis of nosocomial pneumonia, or peak C-reactive protein (CRP) > 200 mg/dL during hospitalization; and 2, 4, and 6 points to age groups < 50, 50-65, and > 65 years, respectively. The diagnosis of HF was defined based on the Framingham criteria.³⁰ Nosocomial pneumonia was defined as pneumonia occurring \geq 48 hours after hospital admission. The CCI was calculated for each patient (Supplementary File S2), and the comorbidity definitions of the original study were used.²⁶ The urgency of operation was defined according to the EuroSCORE II criteria.²⁷

Statistical analysis

Data were analyzed using SPSS, version 21.0, and MedCalc, version 12.5. For descriptive analysis, categorical variables were expressed as absolute and relative frequencies, continuous variables with normal distribution as mean (\pm standard deviation [SD]), and continuous variables with non-normal distribution as median (interquartile range [IQR]). The Shapiro-Wilk test was used to test the normality of distribution. For between-group comparisons, categorical variables were compared by the chi-square test and quantitative variables were compared by Student's t test if normally distributed or by the Mann-Whitney U test if not normally distributed. Fisher exact test was used in case of low data frequency. The predictive ability of SHARPEN score and CCI was assessed by calculating the area under the ROC curve (AUC-ROC). AUC-ROCs were compared using the DeLong test, and the best cut-off point in each scoring system was determined by the Youden index. Survival analysis was performed using Kaplan-Meier curves. Cox regression models were used to calculate the hazard ratio (HR) of in-hospital and post-discharge mortality. P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the sample

Of 251 hospitalizations initially identified, 179 hospital admissions of 168 patients met the inclusion criteria; 10 patients had more than one admission for active IE during the study period (Supplementary File S3). The median (IQR) length of hospital stay was 45 (33-64) days, with 93 (52.0%) admission to the intensive care unit (excluding admissions for postoperative monitoring only). The baseline characteristics of the sample are shown in Table 1. Antibiotic therapy was initiated at a median of 1 (0-6) day after hospital admission. There were no cases of IE in cardiac devices.

Transesophageal echocardiography was performed in most patients (n = 145; 81.0%). In 162 (90.5%) patients, vegetations were detected, which were larger than 10 mm in 69 (38.5%) of them. Aortic (n = 68; 38.0%) and mitral valve (n = 60; 33.5%) IE were the most common presentations, and 36 (20.1%) patients had more than one valve involved. Positive blood cultures were found in 154 (86.0%) patients; *Staphylococcus aureus* (22.0%) and viridans group streptococci (15.1%) were the most common agents. Intravenous catheter-associated infection occurred in 12 (6.7%) of the sample. There were no cases of intracardiac devices infection.

While 87 (48.6%) hospitalizations had surgical indication, the procedure was performed during the same admission in only 68 (78.2%) of them - urgently in 64 (94.1%) and on an emergency basis in 4 (5.9%) patients. The most common surgical indications were acute HF (n = 54; 79.4%) and uncontrolled infection (n = 28; 41.2%). The main reasons for not operating at the same hospitalization despite indication were the following: planning to undergo elective surgery in a subsequent hospitalization (n = 7; 6.8%) and

Table 1 – Baseline characteristics and in-hospital complications

Variable	Overall (n = 179)	Hospital discharge (n = 139)	In-hospital death (n = 40)	p
Baseline characteristics				
Age (years)*	57.4 (42.3-68.5)	54.7 (40.6-66.0)	64.7 (54.5-72.1)	.004
Male	126 (70.4)	101 (72.7)	25 (62.5)	.30
LVEF (%)	63 (58-68)	63 (58-68)	62 (56-69)	.97
Left-sided IE	164 (91.6)	124 (89.2)	40 (100)	.020
Hypertension	92 (51.4)	68 (48.9)	24 (60.0)	.29
Diabetes†	37 (20.7)	27 (19.4)	10 (25.0)	.58
Previous cardiac surgery	31 (17.3)	24 (17.3)	7 (17.5)	1.0
Systolic BP < 90mmHg at presentation*	26 (14.5)	15 (10.9)	11 (27.5)	.018
Peak CRP during hospitalization > 200mg/L*	26 (14.5)	16 (11.5)	10 (25.0)	.060
Prosthetic valve IE	23 (12.8)	18 (12.9)	5 (12.5)	1.0
Creatinine > 2.26mg/dL at presentation*	20 (11.2)	12 (8.6)	8 (20.0)	.082
CKD requiring dialysis‡	14 (7.8)	8 (5.8)	6 (15.0)	.088
Intravenous drug abuse*	13 (7.3)	11 (7.9)	2 (5.0)	.74
HIV	9 (5.0)	6 (4.3)	3 (7.5)	.42
Cardiac dysfunction (LVEF ≤ 40%)	8 (4.5)	6 (4.3)	2 (5.0)	.85
In-hospital complications				
Moderate/severe regurgitation	107 (59.8)	79 (56.8)	28 (70.0)	.19
Heart failure*†	97 (54.2)	69 (49.6)	28 (70.0)	.036
Cardiac surgery	68 (38.0)	54 (38.8)	14 (35.0)	.80
Pneumonia (≥ 48h after admission)*	38 (21.2)	22 (15.8)	16 (40.0)	.002
Embolic events (excluding cerebrovascular events)	35 (19.6)	25 (18.0)	10 (25.0)	.45
Hemodialysis‡	33 (18.4)	12 (9.2)	21 (61.8)	< .001
Intracranial complications (hemorrhage/ischemic stroke)	31 (17.3)	21 (15.1)	10 (25.0)	.22
Ruptured chordae tendineae	23 (12.8)	19 (13.7)	4 (10.0)	.73
Perivalvular abscess	18 (10.1)	14 (10.1)	4 (10.0)	1.0
Fistula	14 (7.8)	10 (7.2)	4 (10.0)	.52
Pseudoaneurysm	3 (1.7)	3 (2.2)	0 (0)	1.0

Data presented as median (interquartile range) or number (%). CKD: Chronic kidney disease; HIV: human immunodeficiency virus; IE: infective endocarditis; LVEF: left ventricular ejection fraction; NS: non-significant; BP: blood pressure.*Component of the SHARPEN score. †Component of the Charlson comorbidity index. ‡Excluding patients with pre-admission chronic kidney disease requiring dialysis (n = 14).

having hemodynamic instability (n = 5; 26.3%). Mechanical aortic valve replacement (n = 19, 10.6%) and biological mitral valve replacement (n = 12, 6.7%) were the most frequently performed procedures. The mean (± SD) times of cardiopulmonary bypass and ischemia were 136 (± 46) and 104 (± 42) minutes, respectively.

In-hospital mortality was 22.3% (95% confidence interval [CI]: 16.2-28.4%), and septic shock was the main cause of death (n = 20; 11.2%). Mortality was similar in operated and non-operated patients (20.6 vs. 23.4%, p = 0.797).

Prognostic evaluation using the SHARPEN score and the CCI for in-hospital mortality prediction

Patients had a median (IQR) SHARPEN score of 9 (7-11) points. Median (IQR) SHARPEN scores of patients discharged from the hospital and those who died during hospitalization were 9 (7-11) and 11 (9-13) points, respectively (p < 0.001). The best cut-off point observed for mortality prediction in the SHARPEN score was > 10 points. Overall, 111 (62.0%) hospitalizations were classified as low (2-10 points) and 68 (38.0%) as high risk (11-20 points) with in-hospital mortality rates of 10.8 and 41.2%, respectively (p < 0.001).

Patients had a median (IQR) CCI of 3 (2-6) points. Median (IQR) CCI of patients discharged from the hospital and those who died during hospitalization were 3 (1-5) and 5 (3-7), respectively (p < 0.001). The optimal cut-off point for mortality prediction in CCI was > 3 points. Overall, 95 (56.1%) hospitalizations were classified as low (≤ 3 points) and 84 (46.9%) as high risk (> 3 points) with in-hospital mortality rates of 12.5 and 33.3%, respectively (p < 0.001). Table 2 shows the characteristics of the SHARPEN score and the CCI in overall, non-operated and operated patients.

Figure 2 shows the ROC curves for in-hospital mortality prediction according to the SHARPEN and the CCI. There was no difference in the AUC of the SHARPEN score between operated and non-operated patients (p = 0.058). On the other hand, we found a statistically significant difference in the AUC of the CCI between operated and non-operated patients (p = 0.039). When comparing the SHARPEN and CCI abilities to predict in-hospital mortality, we found no difference in the overall sample (p = 0.26) and in operated patients (p = 0.41). However, in the non-operated subgroup, the SHARPEN score was superior to the CCI (p = 0.003).

In-hospital survival analysis

There is a statistically significant association between SHARPEN score > 10 and decreased in-hospital survival, which persisted when analyzing the non-operated and operated patients separately. In-hospital survival curves according to the SHARPEN score are shown in Figure 2.

We also found an association between CCI > 3 points and decreased in-hospital survival in overall and in operated patients; in the non-operated subgroup, however, there was no statistically significant association between an elevated CCI and decreased in-hospital mortality. In-hospital survival curves according to the CCI are shown in Figure 4.

Post-discharge survival analysis

Out of the 135 patients that received hospital discharge after the first hospitalization due to IE, 73 (54.1%) died during the follow-up; 25 (34.2%) of the deaths were registered in the first year of follow-up. The median (IQR) post-discharge follow-up was 8.95 (3.23-14.1) years, which corresponded to 1,223 patient-years and an incident rate of six events per 100 patient-years. The mean (\pm SD) post-discharge survival was 12.3 (\pm 3.30) years. There was no statistically significant difference in post-discharge mortality rates between non-

operated and operated patients (58.5 vs. 47.2% respectively, $p = 0.264$).

Post-discharge death rates were significantly higher in patients with a SHARPEN score of 11-20 points (80.0 vs. 43.2% 2-10 points; $p < 0.001$) and in those with a CCI > 3 points (69.8 vs. 43.9% CCI ≤ 3 points; $p = 0.006$). Survival was lower in patients with a SHARPEN score 11-20 points and CCI > 3 points. Figure 5 shows the Kaplan-Meier curves for post-discharge survival according to both scores evaluated in our study.

Table 2 – Characteristics of the SHARPEN score and Charlson comorbidity index

Statistics % (95%CI)	SHARPEN > 10			CCI > 3		
	Overall	Non-operated	Operated	Overall	Non-operated	Operated
Sensitivity	70.0 (53.5-83.4)	71.4 (41.9-91.1)	69.2 (48.2-85.7)	70.0 (53.5-83.4)	69.2 (48.2-85.7)	71.4 (41.9-91.6)
Specificity	71.2 (62.9-78.6)	72.2 (58.3-83.5)	70.6 (59.7-79.9)	59.7 (51.1-67.9)	50.6 (39.5-61.6)	74.1 (60.4-85)
Positive likelihood ratio	2.43 (1.75-3.39)	2.57 (1.49-4.43)	2.35 (1.55-3.57)	1.74 (1.30-2.31)	1.40 (1.0-1.96)	2.76 (1.57-4.82)
Negative likelihood ratio	0.42 (0.26-0.68)	0.40 (0.17-0.92)	0.44 (0.24-0.79)	0.50 (0.31-0.82)	0.61 (0.33-1.12)	0.39 (0.17-0.90)
Mortality	22.3	20.6	23.4	22.3	23.4	20.6
Positive predictive value	41.1 (33.4-49.3)	40.0 (27.9-53.4)	41.8 (32.1-52.2)	33.3 (27.2-39.9)	30 (23.5-37.5)	41.67 (28.9-55.5)
Negative predictive value	89.2 (83.6-93.1)	90.7 (80.7-95.8)	88.2 (80.6-93.1)	87.4 (80.9-91.9)	84.3 (74.4-90.9)	90.9 (81.1-95.9)
Accuracy	70.9 (63.7-77.5)	72.1 (59.8-82.3)	70.3 (60.8-78.6)	62.0 (54.5-69.1)	54.95 (45.2-64.4)	73.5 (61.4-83.5)

CCI: Charlson comorbidity index; CI: confidence interval.

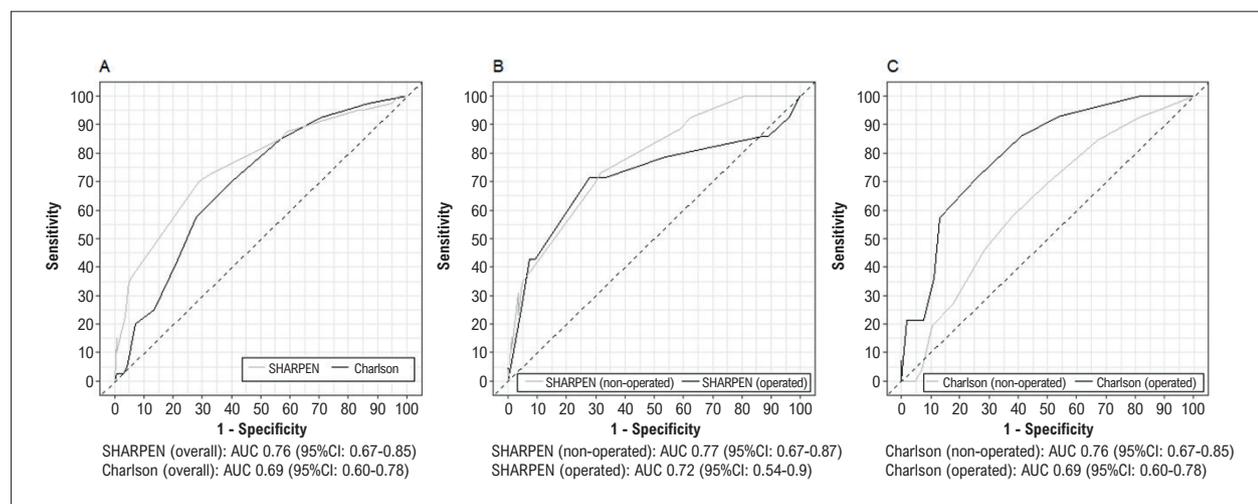


Figure 2 – SHARPEN score and Charlson Comorbidity Index's ROC curves for in-hospital mortality prediction. 2A: ROC curves for SHARPEN score and Charlson Comorbidity Index in the whole sample. 2B: ROC curves for SHARPEN score in operated and non-operated patients. 2C: ROC curves for Charlson Comorbidity Index in operated and non-operated patients. CCI: Charlson comorbidity index; AUC: area under the curve; CI: confidence interval.

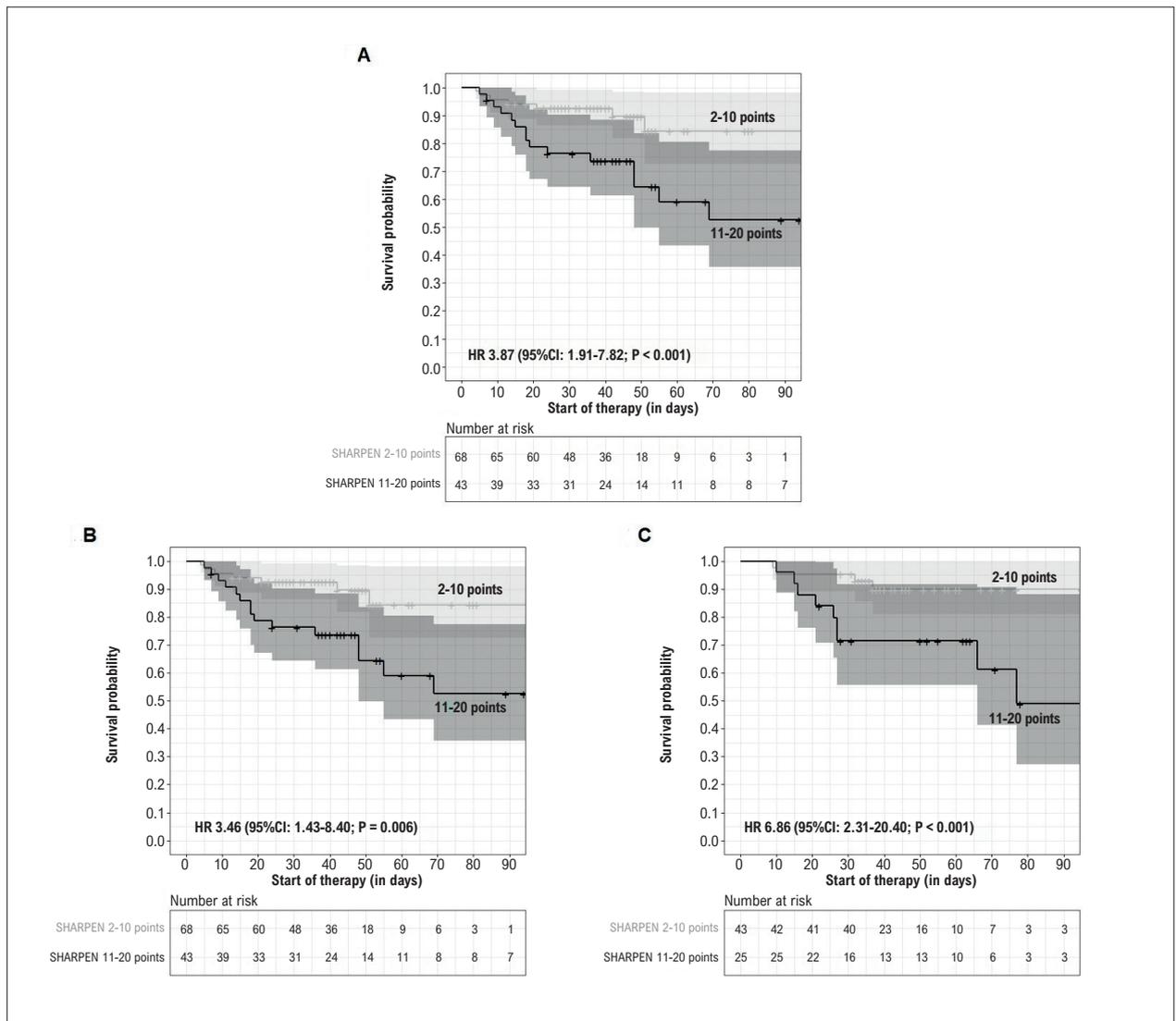


Figure 3 – In-hospital survival according to SHARPEN score in (3A) overall, (3B) non-operated and (3C) operated patients. CI: confidence interval; HR: hazard ratio. The line shadow represents the 95% confidence interval of the estimate.

Prognostic evaluation using the SHARPEN score and the CCI for post-discharge mortality prediction

Figure 6 shows the ROC curves for post-discharge mortality prediction according to the SHARPEN and the CCI. There was no statistically significant difference in the AUCs of the SHARPEN score between operated and non-operated patients ($p = 0.086$). Also, there was no difference in the AUCs of the CCI between operated and non-operated patients ($p = 0.683$). No differences were found between the SHARPEN score and the CCI to predict post-discharge mortality, in the overall ($p = 0.515$), operated ($p = 0.547$) and non-operated groups ($p = 0.468$).

Discussion

Results of our study revealed three important findings: 1) SHARPEN score is accurate in predicting in-hospital

mortality in both operated and non-operated patients; 2) the accuracy of the SHARPEN score is similar to that of the CCI and significantly better in non-operated patients; 3) Higher SHARPEN and CCI scores are associated with elevated mortality after discharge from a hospitalization due to IE.

Hospital mortality rates in our sample were similar to those described in the study by Chee et al.¹¹ (22.3 vs. 23.2%, respectively). A Brazilian cohort study published by Lemos et al., including 359 patients from 2006 to 2019, 285 (79.4%) operated, showed an in-hospital mortality of 24.5%, which is also comparable to ours.³¹ However, even though both the original study¹¹ and the multicentric EURO-ENDO registry⁶ have shown reduced mortality in IE patients who did not have an indication for surgery, we found no difference in mortality when comparing operated and non-operated patients. A possible explanation for

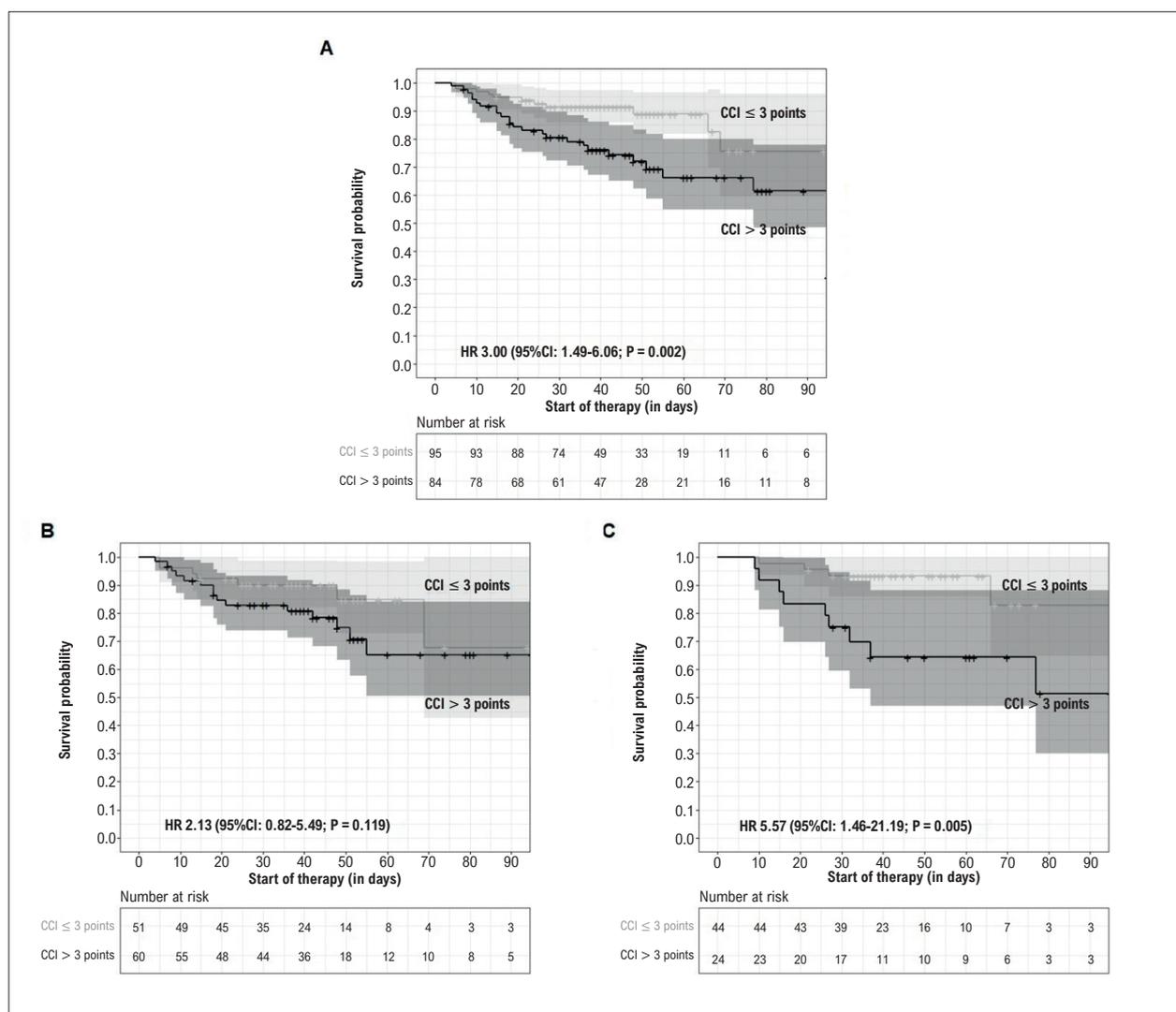


Figure 4 – In-hospital survival according Charlson comorbidity index (CCI) in (4A) overall, (4B) non-operated and (4C) operated patients. CCI: Charlson comorbidity index; CI: confidence interval; HR: hazard ratio. The line shadow represents the 95% confidence interval of the estimate.

these divergences is the existence of a “survivor bias”, in which patients who are fit for surgery are more likely to survive, while those unable to undergo surgery despite indications have an inherently worse prognosis.^{11,32,33} The lower surgical rate in the original study,¹¹ when compared to ours (26.9 vs. 38.0%), suggests that surgery may have been contraindicated in high-risk patients.³⁴

The SHARPEN score was compared with the CCI due to its ability to predict in-hospital mortality in previous studies.^{6,35,36} Even though the CCI had a relatively poor accuracy for in-hospital mortality prediction, a score > 3 was associated with elevated mortality during the hospitalization, except in the non-operated group. This effect may be related to the association between an elevated CCI and lower surgery rates,⁶ which was also found to be an independent predictor of mortality.³⁶

Similarly to the study by Lu et al.,³⁷ the CCI was also able to predict long-term mortality in our sample.

The application of risk scores specifically designed for IE patients is preferable due to the particularities of this disease, which are not always contemplated by general-use risk scores. This belief is reinforced by the fact that the EuroSCORE, one of the main surgical risk scores used in clinical practice, was shown to underestimate mortality in valvular surgery for active IE.³⁸ Although it is very interesting to have specific scores for assessment of mortality in IE, it is worth highlighting that the SHARPEN score also includes general aspects (e.g. use of vasoactive drugs for HF, presence of renal failure, blood pressure), that are in fact included in other scores like the SOFA³⁹ and qSOFA⁴⁰ scores.

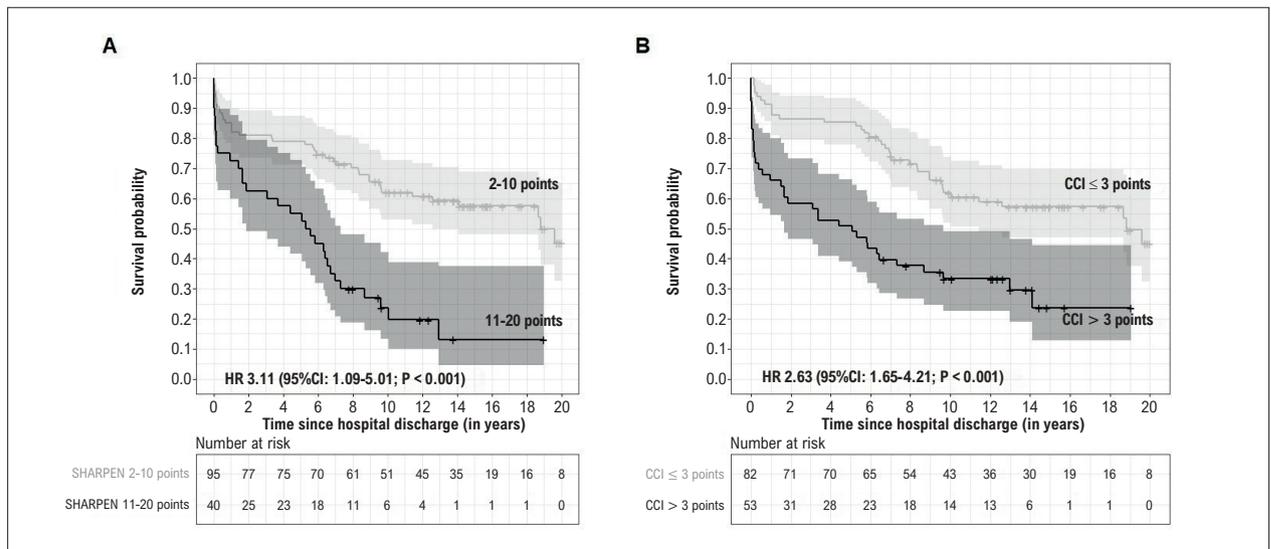


Figure 5 – Post-discharge survival according to (5A) SHARPEN score and (5B) Charlson comorbidity index. CCI: Charlson comorbidity index; CI: confidence interval; HR: hazard ratio. The line shadow represents the 95% confidence interval of the estimate.

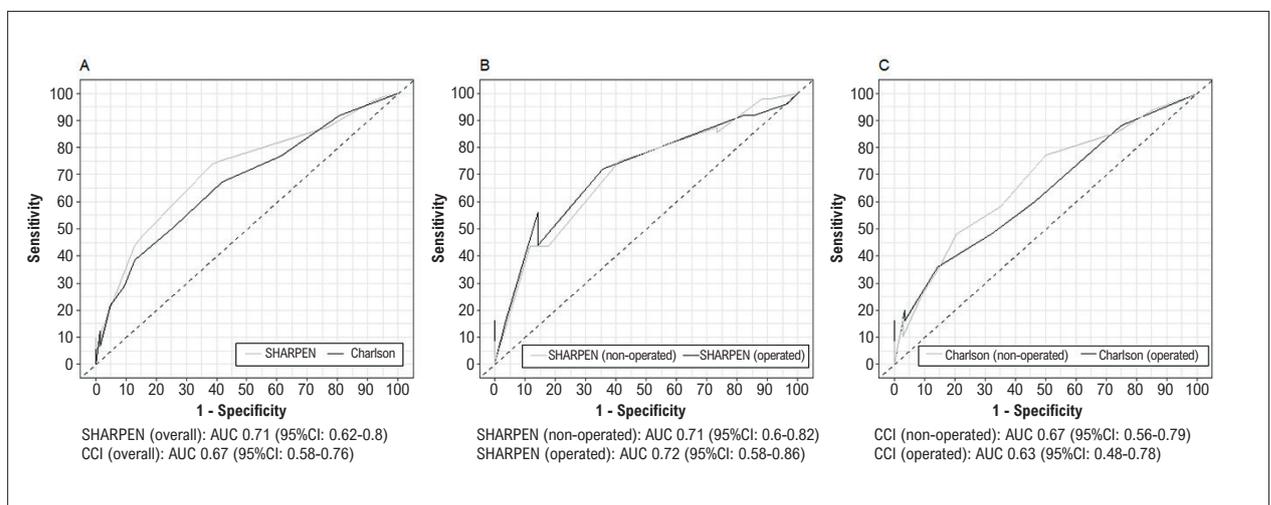


Figure 6 – SHARPEN score and Charlson Comorbidity Index's ROC curves for post-discharge mortality prediction; 6A: ROC curves for SHARPEN score and Charlson Comorbidity Index in the overall sample; 6B: ROC curves for SHARPEN score in operated and non-operated patients; 6C: ROC curves for Charlson Comorbidity Index in operated and non-operated patients. CCI: Charlson comorbidity index; AUC: area under the curve; CI: confidence interval.

Few studies have addressed the application of surgical risk scores in non-operated patients with IE. Gatti et al.⁴¹ reported that three scores specific for IE (STS-IE, ICE score, and EndoSCORE) and two scores specific for cardiac surgery (logistic EuroSCORE and EuroSCORE II) had a satisfactory performance. However, the prognostic assessment may be biased by several factors: surgical scores contain variables related to perioperative risk, which are of little relevance to non-operated patients; besides, the omission of non-operated patients from the validation process increases the risk of survivor bias.^{32,33} Considering that the SHARPEN score was designed and

validated specifically for IE patients, regardless of the need for surgery, and showed improved discriminatory power in non-operated patients, its application would be more advantageous.

This is the first study to analyze the SHARPEN score performance in long-term mortality prediction. Even though its accuracy was considered poor, patients with an elevated score have lower survival rates after discharge despite having completed treatment for IE. HF and age, both of them components of the SHARPEN score, were also found to be independent predictors of mortality after hospital discharge in a study by Tahon et al.⁴² Due to the

reduced size of our sample, we were not able to evaluate the SHARPEN performance separately in operated and non-operated groups.

The present study has limitations. The sample was relatively small and restricted to a single tertiary care center. The low mean of 10.5 IE patient/year can also be considered a limitation. In this long period of analysis, both clinical and surgical management of these patients may have changed over time. Retrospective data collection can compromise the quality of the data obtained. Finally, the number of patients at risk greatly reduces with increasing time after hospital discharge, which reduces the validity of the data (as can be seen from the 95% CIs in the survival curves).

Despite the need for larger multicenter studies, the acceptable accuracy and high negative predictive value of the SHARPEN score in our sample suggest that it may be useful in clinical practice to select high-risk patients that require optimized care during hospitalization and close follow-up after discharge in order to prevent adverse outcomes. Although the SHARPEN score is composed of easily obtainable variables, this risk score was designed for calculation right after the diagnosis of IE, which may occur in varying stages of the hospitalization. As a future perspective, we propose the analysis of the prognostic value of patient reclassification during hospitalization.

Conclusion

The SHARPEN score was reproducible as a predictor of in-hospital mortality in both operated and non-operated IE patients with an acceptable accuracy. Furthermore, we found that patients classified as high-risk persisted with a significantly higher mortality after hospital discharge as compared with low-risk patients. Although the SHARPEN score accuracy to predict in-hospital mortality was similar to that of the CCI in the overall EI patients, there was a significantly better accuracy in non-operated patients. Therefore, our findings highlight the potential benefits of applying the SHARPEN score in clinical practice.

References

1. Leone S, Ravasio V, Durante-Mangoni E, Crapis M, Carosi G, Scotton PG, et al. Epidemiology, Characteristics, and Outcome of Infective Endocarditis in Italy: The Italian Study on Endocarditis. *Infection*. 2012;40(5):527-35. doi: 10.1007/s15010-012-0285-y.
2. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century: The International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169(5):463-73. doi: 10.1001/archinternmed.2008.603.
3. García-Cabrera E, Fernández-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological Complications of Infective Endocarditis: Risk Factors, Outcome, and Impact of Cardiac Surgery: A Multicenter Observational Study. *Circulation*. 2013;127(23):2272-84. doi: 10.1161/CIRCULATIONAHA.112.000813.
4. Thuny F, Giorgi R, Habachi R, Ansaldo S, Le Dolley Y, Casalta JP, et al. Excess Mortality and Morbidity in Patients Surviving Infective

Acknowledgements

The authors would like to thank the research participants as well as the Conceição Hospital Group

Author Contributions

Conception and design of the research: Alves SG, Pivatto Júnior F, Filippini FB, Dannenhauer GP, Miglioranza MH; Acquisition of data: Alves SG, Pivatto Júnior F, Filippini FB, Dannenhauer GP, Seroiska G, Bischoff HM, Birk LFS, Terra DH, Miglioranza MH; Analysis and interpretation of the data: Alves SG, Pivatto Júnior F, Filippini FB, Dannenhauer GP, Seroiska G, Bischoff HM, Birk LFS, Terra DH, Sganzerla D, Miglioranza MH; Statistical analysis: Alves SG, Pivatto Júnior F, Sganzerla D, Miglioranza MH; Obtaining financing: Miglioranza MH; Writing of the manuscript: Alves SG, Pivatto Júnior F, Filippini FB, Dannenhauer GP, Miglioranza MH; Critical revision of the manuscript for important intellectual content: Alves SG, Pivatto Júnior F, Filippini FB, Dannenhauer GP, Seroiska G, Bischoff HM, Birk LFS, Terra DH, Sganzerla D, Miglioranza MH.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

This study was partially funded by CNPq and FAPERGS.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Grupo Hospitalar Conceição under the protocol number 3.282.189. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

- Endocarditis. *Am Heart J*. 2012;164(1):94-101. doi: 10.1016/j.ahj.2012.04.003.
5. Ambrosioni J, Hernandez-Meneses M, Téllez A, Pericàs J, Falces C, Tolosana JM, et al. The Changing Epidemiology of Infective Endocarditis in the Twenty-First Century. *Curr Infect Dis Rep*. 2017;19(5):21. doi: 10.1007/s11908-017-0574-9.
6. Habib G, Erba PA, Lung B, Donal E, Cosyns B, Laroche C, et al. Clinical Presentation, Aetiology and Outcome of Infective Endocarditis. Results of the ESC-EORP EURO-ENDO (European Infective Endocarditis) Registry: A Prospective Cohort Study. *Eur Heart J*. 2019;40(39):3222-32. doi: 10.1093/eurheartj/ehz620.
7. Davierwala PM, Marin-Cuartas M, Misfeld M, Borger MA. The Value of an "Endocarditis Team". *Ann Cardiothorac Surg*. 2019;8(6):621-9. doi: 10.21037/acs.2019.09.03.
8. Botelho-Nevers E, Thuny F, Casalta JP, Richet H, Gouriet F, Collart F, et al. Dramatic Reduction in Infective Endocarditis-Related Mortality with a

- Management-Based Approach. *Arch Intern Med.* 2009;169(14):1290-8. doi: 10.1001/archinternmed.2009.192.
9. Chirillo F, Scotton P, Rocco F, Rigoli R, Borsatto F, Pedrocco A, et al. Impact of a Multidisciplinary Management Strategy on the Outcome of Patients with Native Valve Infective Endocarditis. *Am J Cardiol.* 2013;112(8):1171-6. doi: 10.1016/j.amjcard.2013.05.060.
 10. Kaura A, Byrne J, Fife A, Deshpande R, Baghai M, Gunning M, et al. Inception of the 'Endocarditis Team' is Associated with Improved Survival in Patients with Infective Endocarditis who are Managed Medically: Findings from a Before-and-After Study. *Open Heart.* 2017;4(2):e000699. doi: 10.1136/openhrt-2017-000699.
 11. Chee QZ, Tan YQ, Ngiam JN, Win MT, Shen X, Choo JN, et al. The SHARPEN Clinical Risk Score Predicts Mortality in Patients with Infective Endocarditis: An 11-year study. *Int J Cardiol.* 2015;191:273-6. doi: 10.1016/j.ijcard.2015.04.236.
 12. Chatterjee S, Sardar P. Early Surgery Reduces Mortality in Patients with Infective Endocarditis: Insight from a Meta-Analysis. *Int J Cardiol.* 2013;168(3):3094-7. doi: 10.1016/j.ijcard.2013.04.078.
 13. Gaca JG, Sheng S, Daneshmand MA, O'Brien S, Rankin JS, Brennan JM, et al. Outcomes for Endocarditis Surgery in North America: A Simplified Risk Scoring System. *J Thorac Cardiovasc Surg.* 2011;141(1):98-106. e1-2. doi: 10.1016/j.jtcvs.2010.09.016.
 14. De Feo M, Cotrufo M, Carozza A, De Santo LS, Amendolara F, Giordano S, et al. The Need for a Specific Risk Prediction System in Native Valve Infective Endocarditis Surgery. *ScientificWorldJournal.* 2012;2012:307571. doi: 10.1100/2012/307571.
 15. Martínez-Sellés M, Muñoz P, Arnáiz A, Moreno M, Gálvez J, Rodríguez-Roda J, et al. Valve Surgery in Active Infective Endocarditis: A Simple Score to Predict In-Hospital Prognosis. *Int J Cardiol.* 2014;175(1):133-7. doi: 10.1016/j.ijcard.2014.04.266.
 16. Gatti G, Perrotti A, Obadia JF, Duval X, lung B, Alla F, et al. Simple Scoring System to Predict In-Hospital Mortality After Surgery for Infective Endocarditis. *J Am Heart Assoc.* 2017;6(7):e004806. doi: 10.1161/JAHA.116.004806.
 17. Gatti G, Benussi B, Gripshi F, Della Mattia A, Proclemer A, Cannata A, et al. A Risk Factor Analysis for In-Hospital Mortality After Surgery for Infective Endocarditis and a Proposal of a New Predictive Scoring System. *Infection.* 2017;45(4):413-23. doi: 10.1007/s15010-016-0977-9.
 18. Olmos C, Vilacosta I, Habib G, Maroto L, Fernández C, López J, et al. Risk Score for Cardiac Surgery in Active Left-Sided Infective Endocarditis. *Heart.* 2017;103(18):1435-42. doi: 10.1136/heartjnl-2016-311093.
 19. Di Mauro M, Dato GMA, Barili F, Gelsomino S, Santè P, Corte AD, et al. A Predictive Model for Early Mortality After Surgical Treatment of Heart Valve or Prosthesis Infective Endocarditis. The EndoSCORE. *Int J Cardiol.* 2017;241:97-102. doi: 10.1016/j.ijcard.2017.03.148.
 20. Varela L, López-Menéndez J, Redondo A, Fajardo ER, Miguelena J, Centella T, et al. Mortality Risk Prediction in Infective Endocarditis Surgery: Reliability Analysis of Specific Scores. *Eur J Cardiothorac Surg.* 2018;53(5):1049-54. doi: 10.1093/ejcts/ezx428.
 21. Gatti G, Sponga S, Peghin M, Givone F, Ferrara V, Benussi B, et al. Risk Scores and Surgery for Infective Endocarditis: In Search of a Good Predictive Score. *Scand Cardiovasc J.* 2019;53(3):117-24. doi: 10.1080/14017431.2019.1610188.
 22. Pivatto F Jr, Bellagamba CCA, Pianca EG, Fernandes FS, Butzke M, Busato SB, et al. Analysis of Risk Scores to Predict Mortality in Patients Undergoing Cardiac Surgery for Endocarditis. *Arq Bras Cardiol.* 2020;114(3):518-24. doi: 10.36660/abc.20190050.
 23. Wang TK, Oh T, Voss J, Gamble G, Kang N, Pemberton J. Comparison of Contemporary Risk Scores for Predicting Outcomes After Surgery for Active Infective Endocarditis. *Heart Vessels.* 2015;30(2):227-34. doi: 10.1007/s00380-014-0472-0.
 24. Park LP, Chu VH, Peterson G, Skoutelis A, Lejko-Zupa T, Bouza E, et al. Validated Risk Score for Predicting 6-Month Mortality in Infective Endocarditis. *J Am Heart Assoc.* 2016;5(4):e003016. doi: 10.1161/JAHA.115.003016.
 25. Alves SG, Pivatto F Jr, Filippini FB, Dannenhauer GP, Miglioranza MH. SHARPEN Score Accurately Predicts In-Hospital Mortality in Infective Endocarditis. *Eur J Intern Med.* 2021;92:124-7. doi: 10.1016/j.ejim.2021.05.036.
 26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *J Chronic Dis.* 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8.
 27. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg.* 2012;41(4):734-44; discussion 744-5. doi: 10.1093/ejcts/ezs043.
 28. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis. *Clin Infect Dis.* 2000;30(4):633-8. doi: 10.1086/313753.
 29. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Geneva: WHO; 1993 [cited 2023 Nov 8]. Available from: <http://apps.who.int/classifications/apps/icd/icd10online/>; 2007.
 30. Ho KK, Pinsky JL, Kannel WB, Levy D. The Epidemiology of Heart Failure: The Framingham Study. *J Am Coll Cardiol.* 1993;22(4 Suppl A):6A-13A. doi: 10.1016/0735-1097(93)90455-a.
 31. Lemos LHB, Silva LRD, Correa MG, Golebiovski W, Weksler C, Garrido RQ, et al. Infective Endocarditis in the Elderly: Distinct Characteristics. *Arq Bras Cardiol.* 2021;117(4):775-781. doi: 10.36660/abc.20201134.
 32. Sy RW, Bannon PG, Bayfield MS, Brown C, Kritharides L. Survivor Treatment Selection Bias and Outcomes Research: A Case Study of Surgery in Infective Endocarditis. *Circ Cardiovasc Qual Outcomes.* 2009;2(5):469-74. doi: 10.1161/CIRCOUTCOMES.109.857938.
 33. Chu VH, Park LP, Athan E, Delahaye F, Freiburger T, Lamas C, et al. Association between Surgical Indications, Operative Risk, and Clinical Outcome in Infective Endocarditis: A Prospective Study from the International Collaboration on Endocarditis. *Circulation.* 2015;131(2):131-40. doi: 10.1161/CIRCULATIONAHA.114.012461.
 34. Vilacosta I, Blanco CO, Cepeda CS, Díaz JL, Durán CF, Balcones DV, et al. Prognosis in Infective Endocarditis. In: Habib G, editor. *Infective Endocarditis.* New York: Springer; 2016. p. 89-103.
 35. Gálvez-Acebal J, Rodríguez-Baño J, Martínez-Marcos FJ, Reguera JM, Plata A, Ruiz J, et al. Prognostic Factors in Left-Sided Endocarditis: Results from the Andalusian Multicenter Cohort. *BMC Infect Dis.* 2010;10:17. doi: 10.1186/1471-2334-10-17.
 36. Armiñanzas C, Fariñas-Alvarez C, Zarauza J, Muñoz P, González Ramallo V, Martínez Sellés M, et al. Role of Age and Comorbidities in Mortality of Patients with Infective Endocarditis. *Eur J Intern Med.* 2019;64:63-71. doi: 10.1016/j.ejim.2019.03.006.
 37. Lu KJ, Kearney LG, Ord M, Jones E, Burrell LM, Srivastava PM. Age Adjusted Charlson Co-Morbidity Index is an Independent Predictor of Mortality Over Long-Term follow-Up in Infective Endocarditis. *Int J Cardiol.* 2013;168(6):5243-8. doi: 10.1016/j.ijcard.2013.08.023.
 38. Oliveira JLR, Santos MAD, Arnoni RT, Ramos A, Togna DD, Ghorayeb SK, et al. Mortality Predictors in the Surgical Treatment of Active Infective Endocarditis. *Braz J Cardiovasc Surg.* 2018;33(1):32-9. doi: 10.21470/1678-9741-2017-0132.
 39. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-Related Organ Failure Assessment) Score to Describe Organ Dysfunction/Failure. On Behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22(7):707-10. doi: 10.1007/BF01709751.

-
40. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-74. doi: 10.1001/jama.2016.0288.
41. Gatti G, Chocron S, Obadia JF, Duval X, Lung B, Alla F, et al. Using Surgical Risk Scores in Nonsurgically Treated Infective Endocarditis Patients. *Hellenic J Cardiol*. 2020;61(4):246-52. doi: 10.1016/j.hjc.2019.01.008.
42. Tahon J, Geselle PJ, Vandenberk B, Hill EE, Peetermans WE, Herijgers P, et al. Long-Term Follow-Up of Patients with Infective Endocarditis in a Tertiary Referral Center. *Int J Cardiol*. 2021;331:176-82. doi: 10.1016/j.ijcard.2021.01.048.

*Supplemental Materials

For additional information, please click here.



This is an open-access article distributed under the terms of the Creative Commons Attribution License