Patient-Reported Outcomes in Adults With Congenital Heart Disease Following Hospitalization (from APPROACH-IS)

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In this international study, we (1) compared patient-reported outcomes (PROs) in adults with congenital heart disease (CHD) who had versus had not been hospitalized during the previous 12 month, (2) contrasted PROs in patients who had been hospitalized for cardiac surgery versus nonsurgical reasons, (3) assessed the magnitude of differences between the groups (i.e., effect sizes), and (4) explored differential effect sizes between countries. APPROACH-IS was a cross-sectional, observational study that enrolled 4,028 patients from 15 countries (median age 32 years; 53% females). Self-report questionnaires were administered to measure PROs: health status; anxiety and depression; and quality of life. Overall, 668 patients (17%) had been hospitalized in the previous 12 months. These patients reported poorer outcomes on all PROs, with the exception of anxiety. Patients

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See page 140 for disclosure information.

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who underwent cardiac surgery demonstrated a better quality of life compared with those who were hospitalized for nonsurgical reasons. For significant differences, the effect sizes were small, whereas they were negligible in nonsignificant comparisons. Substantial inter-country differences were observed. For various PROs, moderate to large effect sizes were found comparing different countries. In conclusion, adults with CHD who had undergone hospitalization in the previous year had poorer PROs than those who were medically stable. Researchers ought to account for the timing of recruitment when conducting PRO research as hospitalization can impact results. **(Am J Cardiol 2021;145:135−142)**

Patient-reported outcomes (PROs) are "any reports of the status of a patient's health condition that come directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[1] PRO research has gained traction among patients with congenital heart disease (CHD).[2,3] A large proportion of these patients fare well, and typically present for routine evaluation at outpatient clinics every 1 to 5 years, depending on their clinical scenario and complexity of the heart defect.[4] However, patients sometimes require hospital admission, either because of deteriorating clinical status or for elective assessment or interventional procedure. When PROs are measured during or following hospitalization, it may be presumed that scores would generally be worse than when completed during outpatients visit or from patients' homes. Therefore, we aimed (1) to described PROs in individuals who had versus had not been hospitalized during the previous 12 months, (2) to contrast PROs in patients who had been hospitalized for cardiac surgery versus nonsurgical reasons, (3) to assess the magnitude of differences between the groups, and (4) to explore differential effect sizes between countries.

Methods

This analysis is a substudy of APPROACH-IS (Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease − International Study), a cross-sectional study conducted in 15 countries. The rationale and study protocol of APPROACH-IS were extensively described in a dedicated methods paper.[5] Briefly here, we included 4,028 adults (≥18 years) with CHD who were followed-up at a CHD center or included in a national/regional registry, and who had the physical, cognitive, and language capabilities required to complete self-report questionnaires.[5,6] The study was conducted in keeping with the Declaration of Helsinki and was approved by the Institutional Review Board of the University Hospitals Leuven/KU Leuven, Belgium (coordinating center) and by the local institutional review boards of the participating centers (when required). For 3,969 patients (98.5%), information about inpatient cardiac admissions was available. Therefore, the current study was performed on this subsample. Informed consent was obtained from each patient.

Three domains of PROs were assessed using self-report questionnaires: (1) perceived health status using the 12-item Short Form Health Survey (SF-12)[7] and the EuroQol-5D Visual Analog Scale[8]; (2) psychological functioning using the Hospital Anxiety and Depression Scale[9]; and (3) QoL using a Linear Analog Scale[10]; and the Satisfaction With Life Scale.[11] Demographic data were collected through self-report questionnaires. Medical data were obtained through chart review, including (1) whether patients had cardiac inpatient hospitalizations over the previous 12 months and (2) the date of the most recent cardiac surgery. Online Table 1 provides an expanded definition of the domains as applied in APPROACH-IS as well as the interpretation of scores for the individual PRO measures.

Data analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). PRO scores were expressed as means and standard deviations. Other descriptive statistics were reported as medians and interquartile ranges, given that the data were not normally distributed. Inferential statistics were performed using the Chi square test for nominal or ordinal level data, and the Whitney U test for continuous data. To avoid inflation of type 1 error, we applied the false discovery rate according to Benjamini-Hochberg.[12] A Benjamini-Hochberg adjusted p-level <0.05 was used as the cut-off for statistical significance. Statistical tests were two-sided. To express the magnitude of the difference between groups, we calculated standardized effect sizes (Cohen's d) for hospitalized patients compared with nonhospitalized patients. The following cut-off values for Cohen's d were used: 0.2 to 0.5 indicative of a small effect; >0.5 to 0.8 a moderate effect; and >0.8 a large effect.[13] For the differential effect sizes across the countries, only countries in which at least 10 patients had been hospitalized were included in the analysis. Thus, Argentina, Malta, and the Netherlands were excluded from these comparative analyses.

Results

Overall, 16.8% of patients had been hospitalized for cardiac reasons during the previous 12 months. Of these patients, 22.8% were hospitalized for cardiac surgery. Demographic and clinical characteristics of patients who had inpatient cardiac admissions over the past year versus those who did not are shown in Table 1. Hospitalization for cardiac reasons was significantly associated with older age, not working, poorer functional class, complex CHD, cardiac surgery and catheter interventions in the past, heart failure, history of arrhythmias, having pacemakers or implantable cardioverter defibrillator, and history of depression, anxiety and other psychiatric disorders (Table 1). There were no significant differences in demographic

Table 1
Demographic and medical background of adults with congenital heart disease who had vs. had not been hospitalized in the previous 12 months

Variable	No inpatient cardiac admissions over the past year 3301 (83.2%)	Inpatient cardiac admissions over the past year 668 (16.8%)	p Value‡	Inpatient cardiac admissions for cardiac operation 152 (22.8%)	Inpatient cardiac admissions not for cardiac operation 516 (77.2%)	p Value‡
Women	1,741 (53.0%)	344 (51.5%)	0.479†	69 (45.4%)	275 (53.3%)	0.313†
Median age years	31 (IQR 24-41)	33.0 (IQR 26-46)	**<0.001***	33 (IQR 26-44)	33 (IQR 26-47)	0.974*
Educational level			0.071†			0.432†
Less than high school	176 (5.4%)	42 (6.4%)		8 (5.3%)	34 (6.7%)	
High school	1,387 (42.4%)	297 (44.9%)		57 (38.0%)	240 (47.0%)	
College degree	683 (20.9%)	150 (22.7%)		45 (30.0%)	105 (20.5%)	
University degree	1,023 (31.3%)	172 (26.0%)		40 (26.7%)	132 (25.8%)	
Employment status			**<0.001**†			1.000†
Part-time or full-time work	2,145 (65.3%)	370 (55.8%)		88 (58.3%)	282 (55.1%)	
Job seeking, unemployed, or disability	386 (11.8%)	123 (18.6%)		27 (17.9%)	96 (18.8%)	
Homemaker or retired	251 (7.6%)	74 (11.2%)		13 (8.6%)	61 (11.9%)	
Full-time student	273 (8.3%)	50 (7.5%)		15 (9.9%)	35 (6.8%)	
Other	228 (6.9%)	46 (6.9%)		8 (5.3%)	38 (7.4%)	
Marital status			0.133†			0.930†
Married or living with partner	1,684 (51.3%)	330 (49.5%)		78 (52.0%)	252 (48.8%)	
Never married	1,434 (43.7%)	295 (44.3%)		61 (40.7%)	234 (45.3%)	
Divorced or widowed	162 (4.9%)	38 (5.7%)		10 (6.7%)	28 (5.4%)	
Other	3 (0.1%)	3 (0.5%)		1 (0.7%)	2 (0.4%)	
Patient-reported New York Heart Association class			**<0.001**†			0.903†
I	1,832 (56.8%)	248 (38.3%)		61 (41.5%)	187 (37.4%)	
II	1,090 (33.8%)	261 (40.3%)		57 (38.8%)	204 (40.8%)	
III	201 (6.2%)	86 (13.3%)		19 (12.9%)	67 (13.4%)	
IV	102 (3.2%)	52 (8.0%)		10 (6.8%)	42 (8.4%)	
Complexity of heart defect			**<0.001**†			0.378†
Simple	849 (25.7%)	162 (24.3%)		29 (19.1%)	133 (25.8%)	
Moderate	1,648 (49.9%)	289 (43.3%)		77 (50.7%)	212 (41.1%)	
Complex	804 (24.4%)	217 (32.5%)		46 (30.3%)	171 (33.1%)	
Number of cardiac operations	1 (IQR 1-2)	2 (IQR 1-3)	**<0.001***	2 (IQR 1-3)	1 (IQR 1-2)	**<0.001***
Number of catheter interventions	0 (IQR 0-1)	0 (IQR 0-1)	**<0.001***	0 (IQR 0-1)	0 (IQR 0-1)	1.000*
History of heart failure			**<0.001**†			0.934†
Never	2,954 (90.8%)	518 (79.4%)		115 (78.2%)	403 (79.8%)	
Past, not current	220 (6.8%)	78 (12.0%)		20 (13.6%)	58 (11.5%)	
Current	81 (2.5%)	56 (8.6%)		12 (8.2%)	44 (8.7%)	
History of arrhythmia	791 (24.1%)	303 (45.4%)	**<0.001**†	73 (48.0%)	230 (44.6%)	1.000†
Other medical condition	1,412 (43.0%)	312 (47.0%)	0.072†	71 (47.0%)	241 (47.0%)	0.993†
Pacemaker	209 (6.3%)	87 (13.0%)	**<0.001**†	20 (13.2%)	67 (13.0%)	1.000†
Implantable Cardioverter Defibrillator	87 (2.6%)	39 (5.8%)	**<0.001**†	14 (9.2%)	25 (4.8%)	0.396†
Known cognitive impairment	44 (1.3%)	4 (0.6%)	0.127†	0 (0.0%)	4 (0.8%)	0.831†
History of mood disorder	190 (5.8%)	61 (9.1%)	**0.002**†	12 (7.9%)	49 (9.5%)	0.985†
History of anxiety disorder	147 (4.5%)	44 (6.6%)	**0.028**†	11 (7.2%)	33 (6.4%)	0.987†
History of other psychiatric diagnosis	52 (1.6%)	19 (2.8%)	**0.035**†	3 (2.0%)	16 (3.1%)	0.926†

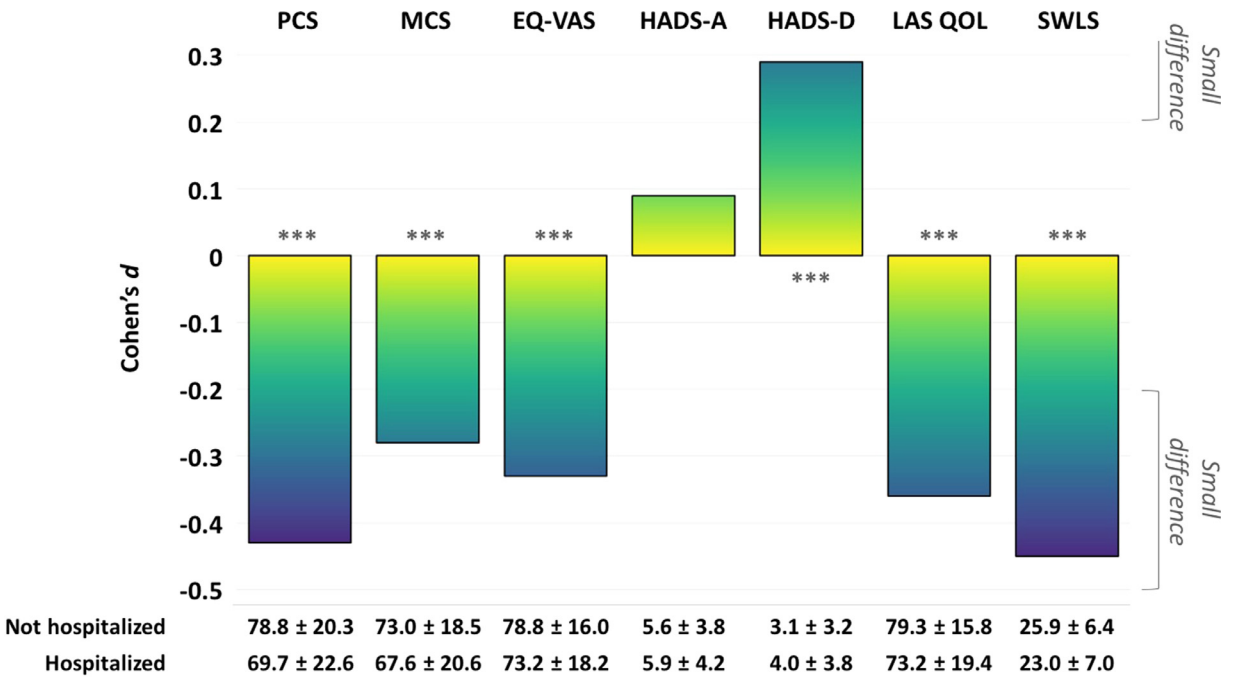
* Mann-Whitney U test;
† Chi square test;
‡ Benjamini-Hochberg adjusted p-value.

variables or medical history according to reason for hospitalization, namely cardiac surgery versus other reason, except for the number of surgeries.

Among patients who had been hospitalized during the previous year, scores on all PROs except for anxiety were significantly worse than scores of patients without hospitalizations (Figure 1). The Cohen's d for all significant PROs were between 0.2 and 0.5, indicating a small difference between the groups. For anxiety, the Cohen's d was smaller than 0.2, thus indicating a negligible difference.

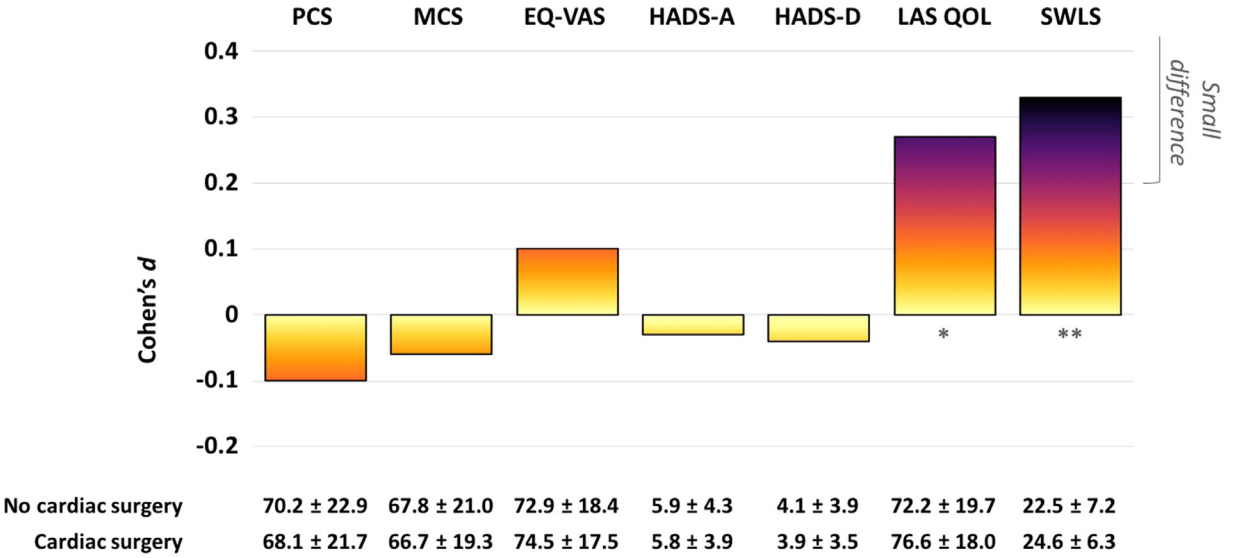
Comparisons of PROs in patients who had been hospitalized for cardiac surgery with those who had been hospitalized for nonsurgical reasons showed that surgical patients reported significantly better quality of life, both on the linear analog scale and the satisfaction with life scale (Figure 2). The effect sizes for these differences were greater than 0.2. For the other PROs, the differences between surgical and nonsurgical patients with hospitalization were negligible.

When examining effect sizes of any hospitalization (vs no hospitalization) in different countries, substantial intercountry differences were detected (Figure 3). For the Physical Component Summary of the SF-12, large effect sizes were observed in Australia, Sweden and Switzerland. In Belgium, France, Norway, Taiwan, and the USA, effect sizes were moderate. For the Mental Component Summary



Legend: *PCS=Physical Component Summary; MCS=Mental Component Summary; EQ-VAS=EuroQol 5 Dimensions-Visual Analog Scale; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; LAS QOL=Linear Analog Scale Quality of Life; SWLS=Satisfaction with Life Scale*
** p<0.05; ** p<0.01; *** p<0.001*

Figure 1. Standardized effect size (Cohen's *d*) for adults with congenital heart disease who had versus had not been hospitalized during the previous 12 months.



Legend: *PCS=Physical Component Summary; MCS=Mental Component Summary; EQ-VAS=EuroQol 5 Dimensions-Visual Analog Scale; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; LAS QOL=Linear Analog Scale Quality of Life; SWLS=Satisfaction with Life Scale*
** p<0.05; ** p<0.01; *** p<0.001*

Figure 2. Standardized effect size (Cohen's *d*) for adults with congenital heart disease who had been hospitalized for cardiac surgery versus had been hospitalized for other reasons during the previous 12 months.

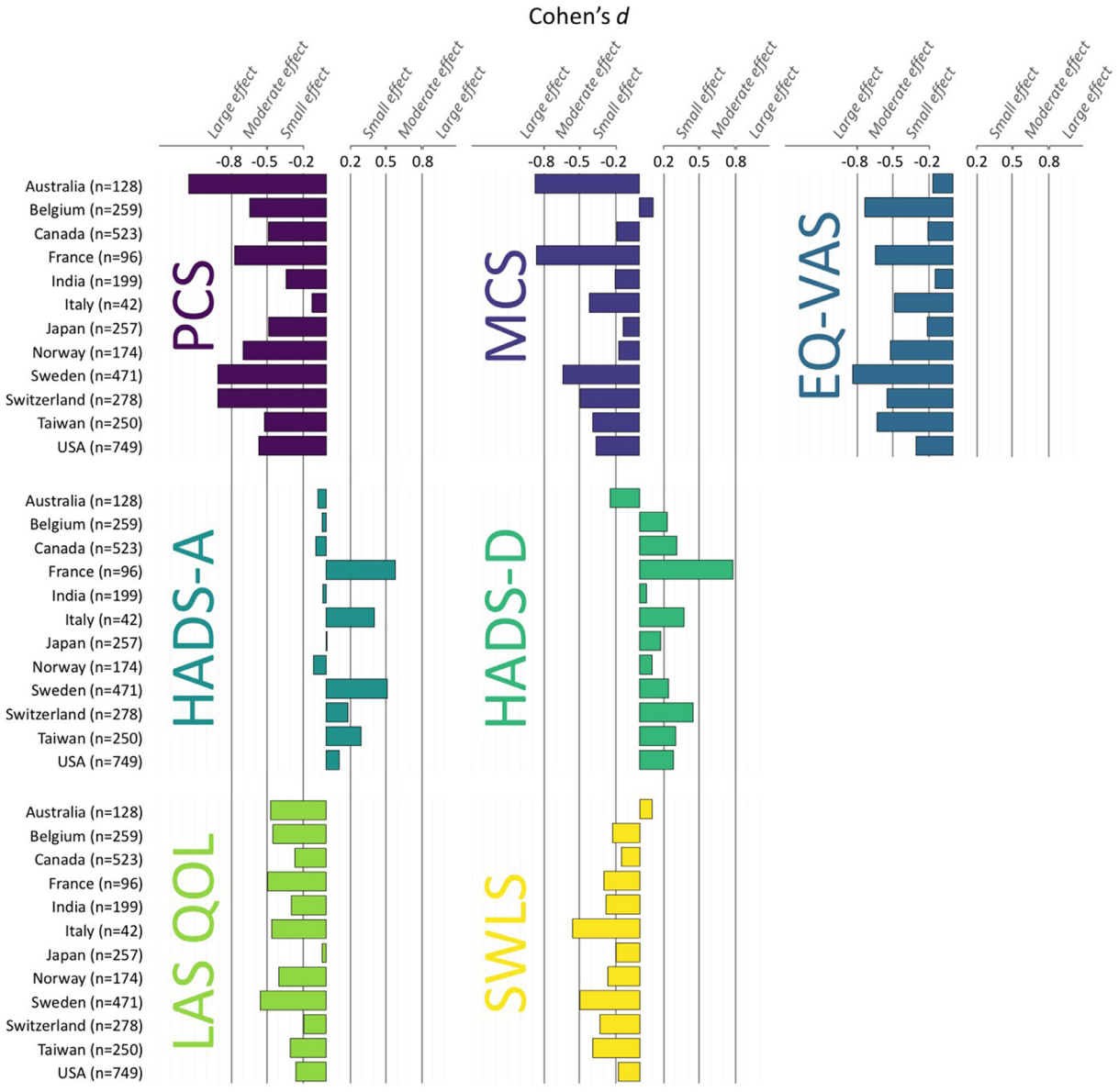


Figure 3. Standardized effect size (Cohen's *d*) for adults with congenital heart disease who had versus had not been hospitalized during the previous 12 months in different countries.

of the SF-12, large effect sizes were found in Australia and France, and a moderate effect size in Sweden. For self-rated health measured using the EuroQol-5D Visual Analog Scale, a large effect size was noted in Sweden, and moderate effect sizes in Belgium, France, Norway, Switzerland, and Taiwan. The difference in symptoms of anxiety and depression between hospitalized versus nonhospitalized patients was negligible or small in most countries, except for France and Sweden. For quality of life, Sweden showed a moderate difference on the linear analog scale, and Italy on the Satisfaction with Life Scale.

Discussion

In the present study, we found that PROs were worse in patients who had been hospitalized in the previous year compared with those who had not been hospitalized, and that most differences were not negligible. While the overall effect sizes were modest, in some countries the effect sizes were in the moderate to large range, suggesting that hospitalizations have a differential impact on PROs in CHD. Effect sizes were the largest for PROs that reflect patients' physical status, namely the SF-12 Physical Component Summary and the EuroQol-5D Visual Analog Scale. Patients who underwent cardiac surgery demonstrated a better quality of life in the wake of hospitalization than those hospitalized for other reasons.

The question in this study was less about "if" there would be a difference between hospitalized versus nonhospitalized patients and more about "how large" the difference would be. This is of importance for researchers studying and interpreting PRO measures. For example, some researchers have administered PROs at hospital discharge,[14] which is ideal to study patient outcomes at this

point in time and to explore whether they are predictive of clinical outcomes or readmissions.[15,16] However, this timing of data collection would not enhance our understanding of the "typical" status' of a patient population. The present study confirms that the timing of PRO assessment matters, because PROs are about 0.3 to 0.4 standard deviations worse among patients within 1 year of hospitalization. Further, the reason for hospitalization appears relevant, as patients who were hospitalized for cardiac surgeries reported quality of life that was 0.3 standard deviations better than those who were admitted for other reasons. The impact of surgery on physical functioning and mental health after hospitalization was negligible in the present study.

The better quality of life in patients who were hospitalized for cardiac surgery is fascinating. We did not have data on the reason for hospital admissions, but we can assume that surgery resulted in an improvement of the clinical status of the patients, whereas nonsurgical patients may not have experienced such an improvement. This is in line with a previous study showing that patients who underwent a reoperation reported a better status over time than those who did not had a reoperation.[17] Clinical characteristics, such as heart failure, arrhythmias, cardiac implantable devices, or complexity of the heart defect, did not differ between surgical and nonsurgical patients.

The present study is important for researchers when setting up new PRO research. However, from a clinical perspective, it also shows that a close health status monitoring upon discharge is important. Indeed, the fact that PROs are worse in patients following hospitalization suggests that there is a need for comprehensive follow-up care, including cardiac rehabilitation and psychological support. Proactive rehabilitation and supportive psychological care may prevent hospitalization-associated deterioration of PROs.[18,19]

The APPROACH-IS project had several methodological strengths: over 4,000 patients from 15 countries were included; a high degree of complete data were obtained; and valid and reliable PRO instruments were used.[6,20] This large international sample yields data that are more generalizable than single-center or single-country studies and allows us to investigate intercountry variations and the impact of healthcare system factors on PROs.[6,20–25] Nonetheless, there were some methodological limitations to be considered when interpreting our results. First, APPROACH-IS is a cross-sectional study, and thus causality cannot be determined.[5] Second, in most participating countries, only one center partook in the project, which might hamper the representativeness of the sample. Third, a possible selection bias could not be excluded, as patients without the physical or mental capacities to complete the self-report questionnaires were ineligible for the study.[5] However, a comparison of participants and nonparticipants in the Swedish branch of APPROACH-IS revealed only small differences in demographic and clinical data.[26] Fourth, we did not have information on the interval between the last hospitalization and the date of data collection, nor on the number of hospitalizations in the preceding 12 months, the length of stay, or the precise reason for hospital admission. Based on the year of the last cardiac surgery, we were able to determine whether the hospitalization was for surgery. Fifth, we did not undertake multivariable analyses, because hospitalizations should not be considered an independent predictor of PROs. Indeed, hospitalization is a proxy for underlying medical conditions. Sixth, although the overall sample of APPROACH-IS was large, some subanalyses, such as the comparison of surgical versus nonsurgical hospitalizations, could be underpowered. However, it is unlikely that our analyses were subject to type 2 errors, because all modest differences in effect sizes were statistically significant.

In conclusion, adults with CHD within 1 year of hospitalization had poorer PROs than those who have not had a recent hospitalization. Differential effect sizes were observed across participating countries. Patients who underwent cardiac surgery demonstrated a better quality of life compared with those hospitalized for nonsurgical reasons. Researchers ought to account for the timing of patient recruitment when conducting PRO research as hospitalization can impact results.

Disclosure

None of the authors have a conflict of interest.

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Credit Statement

Philip Moons, Conceptualization, Methodology, Formal analysis, Resources, Writing - Original Draft, Visualization, Supervision, Project administration, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.088.

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