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Implantable device diagnostics on day of discharge identify heart failure patients at increased risk for early readmission for heart failure

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Aims We hypothesized that diagnostic data in implantable devices evaluated on the day of discharge from a heart failure hospitalization (HFH) can identify patients at risk for HF readmission (HFR) within 30 days.

Methods and results In this retrospective analysis of four studies enrolling patients with CRT devices, we identified patients with a HFH, device data on the day of discharge, and 30-day post-discharge clinical follow-up. Four diagnostic criteria were evaluated on the discharge day: (i) intrathoracic impedance >8 Ω below reference impedance; (ii) AF burden >6 h; (iii) CRT pacing <90%; and (iv) night heart rate >80 b.p.m. Patients were considered to have higher risk for HFR if ≥2 criteria were met, average risk if 1 criterion was met, and lower risk if no criteria were met. A Cox proportional hazards model was used to compare the groups. The data cohort consisted of a total of 265 HFHs in 175 patients, of which 36 (14%) were followed by HFR. On the discharge day, ≥2 criteria were met in 43 (16% of 265 HFHs), only 1 criterion was met in 92 (35%), and none of the four criteria were met in 130 HFHs (49%); HFR rates were 28, 16, and 7%, respectively. HFH with ≥2 criteria met was five times more likely to have HFR compared with HFH with no criteria met (adjusted hazard ratio 5.0; 95% confidence interval 1.9–13.5, $P = 0.001$).

Conclusion Device-derived diagnostic criteria evaluated on the day of discharge identified patients at significantly higher risk of HFR.

Keywords Heart failure • Implantable device diagnostics • Early readmission risk

Introduction

Acute heart failure (HF) is the primary cause of a significant proportion of cardiovascular hospitalizations worldwide.[1] In the USA, all-cause 30-day readmission after HF hospitalization has been reported to be ∼24%[2] to 27%,[3] with readmission rates being very similar year to year[2] and the most frequent cause for 30-day readmissions being HF.[3] In addition, readmissions occur consistently throughout the 30-day post-discharge time, with 31.7% taking place in the first 7 days.[4] Guidelines for HF care before and after discharge have been established worldwide to reduce early readmission.[5] Although randomized controlled studies have shown that intensive management at discharge and during the vulnerable period post-discharge may reduce re-hospitalization rates, these findings have not been consistently reproduced in larger clinical trials.[6–10] Improved ability to risk-stratify patients for 30-day readmission may increase the chances of a favourable outcome.

Implantable cardioverter defibrillator (ICD) and CRT defibrillator (CRT-D) devices provide daily measurements of several diagnostic parameters. Studies have shown that device diagnostics such as intrathoracic impedance,[11,12] atrial tachyarrhythmia burden and poor rate control,[13] heart rate variability, night heart rate (NHR),

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and patient activity,[14] or a combination of them,[15–17] can identify HF patients at increased risk for future events in an ambulatory setting. Recently, a combination of device diagnostics during the 7 days post-discharge from HF admission was shown to identify two groups of patients, one at increased risk and one at very low risk of 30-day readmission for HF.[18] The current study investigates whether implantable device diagnostics evaluated on the day of discharge has the ability to risk-stratify patients for 30-day readmission for HF.

Methods

Data set

This retrospective analysis included data from a cohort of 1562 patients with CRT-D devices from multiple studies with at least 90 days of follow-up data. The studies from which data were included were PARTNERS-HF[15] ($n = 699$ patients), OFISSER[20] ($n = 323$ patients), FAST[12] ($n = 147$ patients), CONNECT[18] ($n = 313$ patients), and case study files ($n = 80$ patients). Only the control arm patients with CRT-D devices, who were not being monitored based on AF diagnostic alerts, were included from the CONNECT study. Patients from this initial cohort were included in this analysis if they had a HF hospitalization, device diagnostic data available on the day of discharge, and 30 days of clinical follow-up after discharge. Each cardiovascular hospitalization was carefully adjudicated for signs and symptoms of HF, which included administration of i.v. or oral diuretic during the hospitalization.

Diagnostic parameters

The device diagnostics evaluated in this study are specific to Medtronic CRT-D devices. The four diagnostic parameters investigated in this work were intrathoracic impedance, AF diagnostics, NHR, and percentage CRT pacing. Patient activity was not investigated as that diagnostic does not provide relevant information during an admission. Heart rate variability was missing on the discharge day in multiple patients and hence was also not investigated.

Intrathoracic impedance is measured daily (as an average of 64 measurements from 12:00 h to 17:00 h) between the coil electrode on the right ventricular lead and the device can. The reference impedance, a measure of expected 'normal' impedance, is initialized on day 34 after implant as the average of the last 4 days of daily impedance measurement. It is then increased or decreased by a fixed amount depending on whether a 4-day weighted average of daily impedance is greater than or less than the reference impedance. AF is detected as a rapid atrial rate with a $\geq$2:1 atrioventricular conduction ratio. The AF burden (the total amount of AF in a day) includes AF, atrial tachycardia, and atrial flutter. Percentage CRT pacing denotes the amount of delivered ventricular pacing during the day. The NHR is the average ventricular rate from 24:00 h to 04:00 h.

Risk group definitions

For each diagnostic parameter, criteria were established to identify a higher than average risk category and a lower than average risk with respect to 30-day readmissions for HF. The investigated thresholds were limited to criteria that can be easily evaluated by a visual review of the diagnostic parameter. The intention was to identify thresholds such that when the criterion is met, the higher than average risk group include <20% of the index HF hospitalizations and they have a readmission rate >20%. If diagnostic data were missing, i.e. data are invalid or not applicable, it was considered that the diagnostic criterion was not met to indicate that no information is available from the diagnostic.

A summary score was computed as the total number of diagnostic parameters that met the higher risk criteria. The summary score was then categorized into three groups of HF readmission risk (lower than average, average, and higher than average). The lower than average risk group were those in whom none of the individual diagnostic parameter criteria thresholds is met (i.e. a summary score of 0). The higher than average risk group was designated the top 20% of the summary scores. The average risk category comprises all the remaining patients who were not classified into the higher than average or lower than average risk groups.

Statistical analysis

The baseline variables between the patients with and without a 30-day readmission for HF were compared using the Student *t*-test for continuous variables and the χ^2 test for categorical variables. The ability of each diagnostic parameter, evaluated on the day of discharge, to risk-stratify for 30-day HF readmission was analysed using a marginal Cox proportional hazards model, an extension of the Cox proportional hazards model that accounts for multiple index HF hospitalizations in patients. For patients with multiple HF hospitalizations, each hospitalization is considered as an index hospitalization for the purpose of the analysis if there was 30 days of follow-up information following discharge from that hospitalization. The summary score risk groups were also evaluated using the marginal Cox proportional hazards model to investigate whether a combined diagnostic criterion on the day of discharge can identify the patients who are at increased risk for 30-day readmission for HF. Additionally, a multivariate Cox proportional hazards model was used to adjust for baseline variables. Length of stay (LOS) during the index hospitalization, a known predictor for readmission, was also used as one of the variables in the model. Due to the small number of re-admission events, the number of variables included for adjustment in the multivariate model was limited to five. Multiple combinations of five variables from among baseline variables and LOS were evaluated for adjustment in the multivariate model. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for predicting 30-day HF readmissions were also evaluated for the two thresholds chosen for the summary risk score.

Results

For the 1562 patients identified from the four studies, the average device follow-up duration was 373 $\pm$ 146 days. *Figure 1* shows the patient inclusion process used for selecting the cohort of patients for the analysis. In the final cohort of 175 patients, 29 patients (17%) had 36 readmissions for HF within 30 days post-discharge, of which 12 happened within 7 days post-discharge. Thus, the average risk for readmission for HF within 30 days of discharge was 14% (36 out of 265) in this data cohort. There were a total of 29 deaths in the 213 patients with HF admissions. There were 11 deaths and 25 HF admissions in the 19 patients that had to be excluded due to unavailable device data on the day of discharge which is necessary for risk group definition. In the final selected cohort of 175 patients, there were a total of 18 deaths, 10 within

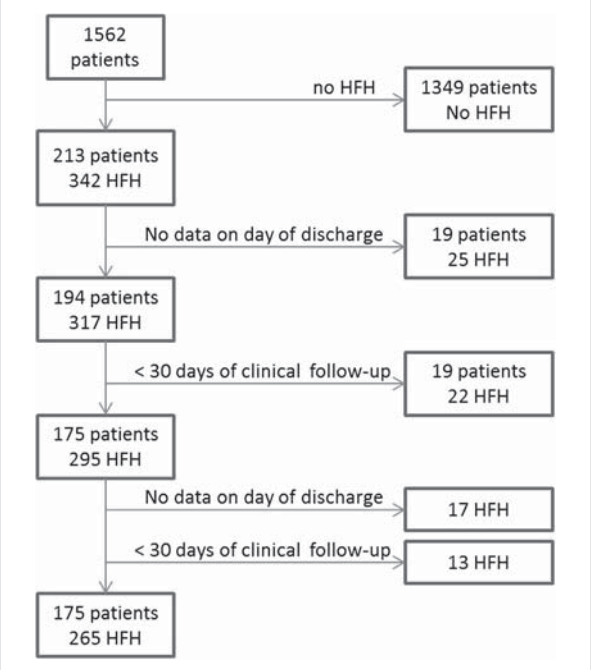

Figure 1 Inclusion and exclusion process to select the final cohort of 175 patients with 265 heart failure hospitalizations (HFH). Thirty-eight patients out of 213 patients with HFH were excluded due to either unavailable device data on the day of discharge or unavailable clinical follow-up data for 30 days post-discharge.

90 days and 8 after 90 days post-discharge from the HF event. The baseline characteristics at the time of enrolment in each of the individual studies of patients with or without a 30-day readmission for HF in the final patient cohort are compared in *Table 1*. None of the baseline parameter differences, except history of hypertension, reached statistical significance in this small group of patients.

The thresholds identified for each individual diagnostic parameter are shown in *Table 2*. *Table 2* also details the total number of index hospitalizations (i.e. sample size) when the diagnostic criterion for an individual diagnostic parameter was met and when it was not met, and what percentage of those were followed by 30-day readmission for HF (i.e. event rate). Intrathoracic impedance 8 Ω below reference, an indication of residual fluid, and CRT pacing below 90%, an indicator of loss of CRT, had the ability to identify risk for 30-day readmission as a univariate. The thresholds were chosen with the goal of having <20% of the index hospitalizations with a >20% readmission rate; however, that goal could not be achieved for all the individual parameters. Also, whole number threshold values were preferred so that the risk stratification method could be easily implemented in clinical practice using a simple and straight forward evaluation of the device diagnostics reports available today. The summary score was computed as the total numbers of individual diagnostic criteria that were satisfied, a method which provides equal weighting to each diagnostic parameter. A weighted sum of scores was not evaluated to preserve simplicity of implementation in clinical practice.

The summary score was divided into three risk groups as shown in *Table 2*. A summary score of 0 identified HF patients ($n = 130$, 49% of initial HF hospitalizations) at lower than average risk for 30-day HF readmission, whereas a summary score of ≥2 identified HF patients ($n = 43$, 16% of initial HF hospitalizations) at higher than average risk for 30-day HF readmission. An example case with a summary score of 0 is shown in *Figure 2A*, and an example case with summary score ≥2 is shown in *Figure 2B*. The group with higher than average risk was four times more likely to be readmitted within 30 days for HF compared with the group with lower than average risk [hazard ratio (HR) 4.4, 95% confidence interval (CI) 1.6–12.0, $P = 0.004$]. HF patients with a summary score in the average risk category were twice more likely to experience a readmission for HF than those patients with a lower than average risk group (HR 2.4, 95% CI 1.1–5.3, $P = 0.028$). The Kaplan–Meier curve for incidence of readmission for HF for the 60 days post-discharge from index hospitalization for the three groups is shown in *Figure 3*. Of the high risk group, 7, 28, and 44% were readmitted for HF within 7, 30, and 60 days, respectively, of the index hospitalization. On the other hand, only 4, 7, and 12% of the low risk group were readmitted for HF within 7, 30, and 60 days, respectively.

Index HF hospitalization with 30-day readmission for HF had a median LOS of 3 days compared with 4 days for index HF hospitalizations with no readmission for HF. When adjusting for age, gender, NYHA class, and LOS during the index hospitalization in a multivariate model, the combined score had independent ability to identify patients at risk for 30-day readmission for HF (adjusted HR between higher risk and lower risk 5.0, 95% CI 1.9–13.5, $P = 0.001$; adjusted HR between average risk and lower risk 2.5, 95% CI 1.1–5.5, $P = 0.027$). A shorter LOS during the index HF hospitalization (1–2 days) also independently predicted 30-day HF readmission in this model compared with a longer LOS of ≥7 days (HR 3.9, $P = 0.009$). Mean and median LOS was similar for different diagnostic risk groups. Multiple combinations of baseline variables in *Table 1* were evaluated, all yielding similar results to those described above.

For the group with a summary score ≥2, the sensitivity, specificity, PPV, and NPV for predicting a 30-day readmission for HF were 33, 86, 28, and 89%, respectively. Thus, 33% of HF readmissions will have a summary score ≥2, and 86% of the cases with no HF readmission within 30 days will have a summary score <2. Also, 30-day HF readmission occurs in 28% of the cases when the summary score is ≥2, and no 30-day HF readmission occurs in 89% of the cases with a summary score <2. For the risk group with a summary score ≥1, the sensitivity, specificity, PPV, and NPV were 75, 53, 20, and 93%, respectively. Notably, no 30-day HF readmissions occurred in 93% of cases with a summary score of 0. The area under the receiver operating characteristic curve (c-statistic) was 0.67 (95% CI 0.58–0.76).

Discussion

The current analysis showed that a combined diagnostic score on the day of discharge based on diagnostics available in CRT-D devices can identify patients at increased risk for 30-day

Table 1 Comparison of baseline demographics in patients with and without a 30-day readmission for heart failure

	Total ($n = 175$)	HFH patients with 30-day readmission ($n = 29$)	HFH patients without 30-day readmission ($n = 146$)	*P*-value
Mean age (SD)	70 (10)	68 (10)	70 (10)	0.23
% Male	72%	72%	72%	0.98
Mean EF (SD)	23 (9)	23 (8)	23 (9)	0.98
EF ≤35%	99%	100%	98%	0.53
NYHA				0.73
I	2%	3%	1%	
II	8%	7%	9%	
III	79%	83%	78%	
IV	11%	7%	12%	
CAD	77%	79%	77%	0.79
HTN	79%	63%	82%	0.03
Diabetes	50%	67%	46%	0.07
MI	48%	59%	46%	0.21
AF	40%	42%	39%	0.83
Baseline medications				
ACEI/ARB	69%	66%	70%	0.62
Beta-blockers	86%	79%	88%	0.24
Diuretics	92%	93%	92%	0.80
Digoxin	35%	38%	35%	0.74
Aldosterone receptor blocker	34%	28%	35%	0.46
Anti-arrhythmic drugs	32%	24%	33%	0.33
Anti-thrombotic	82%	83%	81%	0.85
Warfarin	40%	34%	41%	0.52

ACEI, ACE inhibitor; HFH, heart failure hospitalization; HTN, hypertension; MI, myocardial infarction; SD, standard deviation.

readmission for HF. The combined score was an independent risk factor when adjusted for baseline variables (age, gender, and NYHA class) and LOS in the hospital. As individual diagnostic parameters, low intrathoracic impedance compared with the reference and reduced CRT pacing on the day of discharge were significantly different in patients readmitted for HF within 30 days of discharge.

Recent studies have shown the utility of assessment of clinical diagnostics such as BNP,[21] renal dysfunction,[22] body weight,[23] and arrhythmias[24] in predicting readmissions. A recent report showed that device diagnostics evaluated during the 7-day post-discharge period can also predict HF readmission within 30 days.[18] The post-discharge summary score[18] is marginally different from that of the present study with respect to the diagnostic parameters and the thresholds used. The primary difference is that the present study investigates diagnostics on a single day, the day of discharge, while the post-discharge summary score[18] evaluates the diagnostic trends over a 7-day period following discharge to assess the risk of readmission. Comparing the risk states on the day of discharge in this study and 7-days post-discharge described in the earlier report,[18] the risk state stayed the same in 51.2% of the cases. The risk state became higher (low to medium or high, and medium to high risk) in 39.4% of the cases and the risk state became lower in 9.4% of the cases. Thus, one may use the risk state evaluated on the day of discharge to plan the immediate post-discharge care which may include a clinic visit within 3 days. Subsequently, risk states evaluated based on device data for the 7 days following discharge may be used to decide the course of subsequent care. Combinations of the device diagnostics as well as the clinical diagnostic parameters assessed during the hospital stay should improve the ability to risk-stratify patients for 30-day readmission and to adjust the follow-up regimens accordingly.

Methods for combining the device diagnostic information to manage HF patients in an ambulatory setting have been suggested previously.[15–17] In an ambulatory setting, the goal is to provide a warning sign for worsening HF, by detecting changes in diagnostics different from normal, to prevent an index HF hospitalization. In contrast to the ambulatory setting, in the inpatient setting the patient is already in acute decompensated HF when the diagnostics are being evaluated. The goal in this case is to evaluate if the therapy provided to patients during the HF admission was effective and whether patients were being discharged after adequate recovery during the admission. The hypothesis is that inadequate treatment or incomplete recovery during the admission is a risk for a second HF event. For example, intrathoracic impedance decreases are monitored in the ambulatory setting as an indication of developing fluid overload. However, in the in-hospital setting, intrathoracic impedance is very likely to be already reduced due to fluid overload, and the amount of recovery of intrathoracic impedance towards the reference impedance is a measure of the effectiveness of therapy during admission. Investigation of the trends in the diagnostics in the 7 days post-discharge[18] determines whether there are any setbacks in the recovery from the HF event.

Table 2 Performance results for each device diagnostic criterion and the summary score with regards to the ability to identify patients at risk for 30-day readmissions for heart failure following an index heart failure hospitalization

Diagnostic criteria	No. of index HF hospitalizations (%)	No. of 30-day HF readmissions (%)	Hazard ratio (95% CI)	*P*-value
Reference: daily impedance >8 Ω			2.6 (1.2–5.6)	0.018
Yes	25 (10%)	7 (28.0%)		
No	222 (90%)	26 (11.7%)		
AF burden >6 h			1.7 (0.6–5.1)	0.325
Yes	44 (17%)	9 (20.5%)		
No	221 (83%)	27 (12.2%)		
CRT pacing <90%			3.1 (1.4–6.8)	0.005
Yes	49 (18%)	14 (28.6%)		
No	216 (82%)	22 (10.2%)		
Night heart rate > 80 b.p.m.			1.4 (0.7–2.7)	0.340
Yes	70 (30%)	12 (17.1%)		
No	167 (70%)	21 (12.6%)		
Summary score groups				
0	130 (49%)	9 (6.9%)	Reference	
1	92 (35%)	15 (16.3%)	2.4 (1.1–5.3)	0.028
≥2	43 (16%)	12 (27.9%)	4.4 (1.6–12.0)	0.004

CI, confidence interval; HF, heart failure.

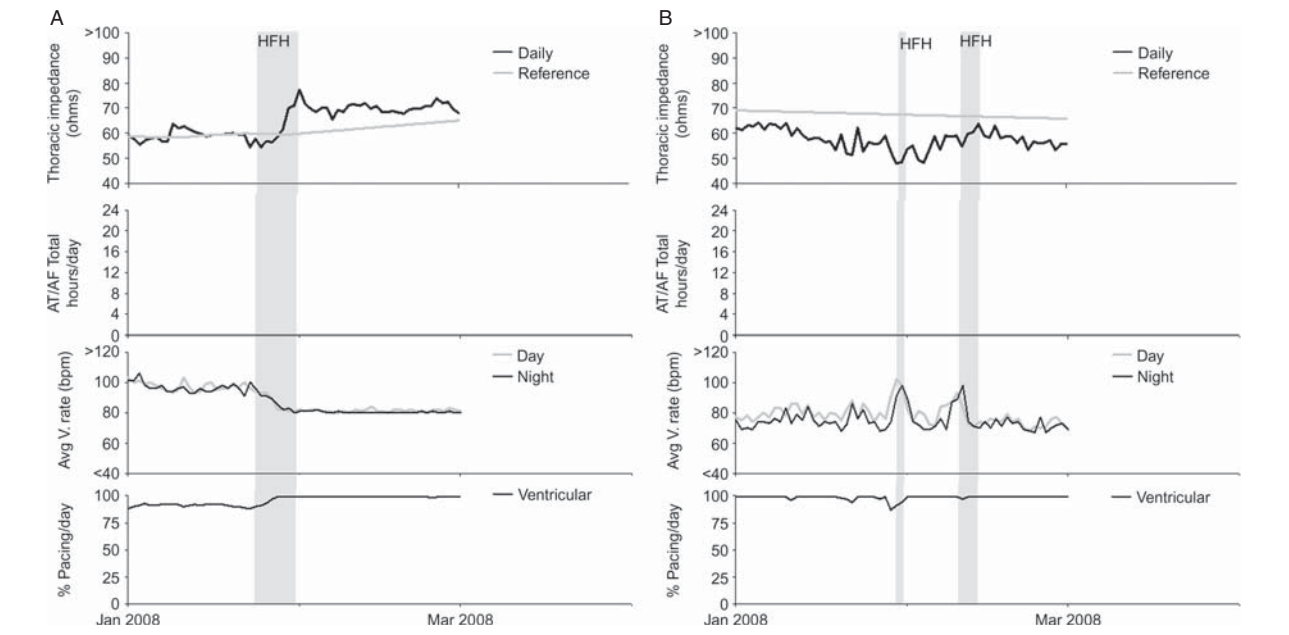

Figure 2 Example cases where (*A*) no diagnostic criteria were met on the day of discharge and (*B*) ≥2 diagnostic criteria were met. Diagnostic data are plotted for 30 days prior to discharge and 30 days post-discharge. Occurrence of heart failure hospitalization (HFH) is shaded in grey, with the index event having the discharge day around day 30 on the plots. AT/AV, atrial tachycardia/atrial fibrillation; Avg V. rate, average ventricular rate.

The enhanced ability to risk-stratify HF patients when diagnostics are combined and integrated[15–17] instead of considering each single parameter as separate information may be one reason why studies evaluating the use of diagnostic information[25–29] in the ambulatory setting have provided inconsistent results. This study and the earlier report on post-discharge diagnostics[18] are applications of this integrated diagnostics approach in an in-hospital setting to identify the patients who are at risk for a readmission for HF within 30 days post-discharge. The increase in HRs for higher risk thresholds when using a summary score vs. any of the HRs for

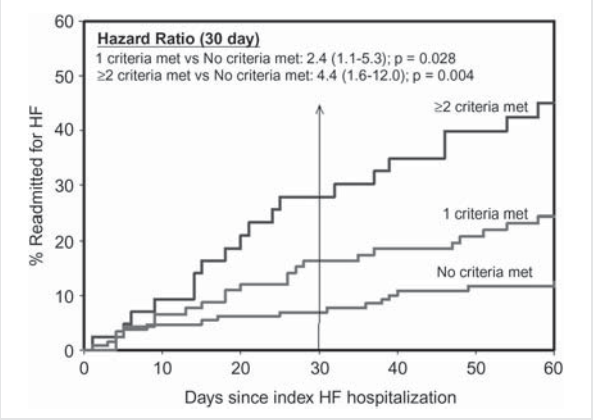

Figure 3 Kaplan–Meier curves showing the readmissions for heart failure (HF) following discharge after an index HF hospitalization for the three groups categorized based on the combination of diagnostic parameters.

individual parameters highlights the benefit of combining diagnostics. Further, intensive management of patients at discharge and post-discharge has already been shown to improve outcomes in randomized studies.[7,8,10]

None of the large randomized disease management studies[25–29] has investigated the use of device diagnostics for discharge and post-discharge management in acute decompensated HF in addition to ambulatory monitoring for chronic HF. In the intervention arm of these studies, device diagnostics might be integrated into a risk stratification algorithm for discharge planning and post-discharge care. Patients identified to have lower than average risk for readmission for HF might be considered for earlier and routine office visits post-discharge, whereas patients with higher than average risk might be considered for a delayed discharge or more immediate and intensive post-discharge follow-up. The high risk group make up <20% of the discharges, thus providing a good triaging tool for effective resource allocation. The larger event rates following discharge compared with the ambulatory setting may allow more significant improvements in outcome.

Limitations

The retrospective analysis was done by pooling data collected in multiple studies in order to increase the sample size for the data cohort. Despite pooling of data, the small number of readmissions in this pooled data cohort limits the number of covariates that can be adjusted for in the statistical model. The original studies were not designed with the intention of evaluating the risk for 30-day readmission and hence well-known risk factors for poor outcomes post-discharge[30] such as BNP, body weight, blood pressure, troponin, serum sodium, or measures of renal function were not collected on a systematic basis during the hospitalization. It was thus not possible to answer the question of whether device diagnostics had incremental value over and above all the known discharge day predictors of 30-day readmission. Due to limited sample size, no validation cohort is presented in this study. There is a possibility of selection bias in the data analysis cohort as a high risk group of 19 patients with 25 HF events and 11 deaths, with 4 HF readmissions and 6 deaths within 30 days post-discharge, had to be excluded due to unavailability of device data on the day of discharge. A larger prospective study, designed to measure other potential clinical factors in addition to device diagnostics, is needed to validate the current analysis and compare the performance of device diagnostics and conventional clinical predictors in identifying patients at risk for readmission for HF.

Conclusion

The current study creates a risk stratification scheme on the day of discharge from a HF admission that can identify the risk for early readmission for HF using a simple scoring system combining device diagnostics information. Future studies are required first to validate the scoring system in a large independent data cohort, and to compare presently available clinical methods for risk stratification.

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