The LENT index predicts 30 day outcomes following hospitalization for heart failure

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Abstract

Aims The LE index (Length of hospitalization plus number of Emergent visits ≤ 6 months) predicts 30 day all-cause readmission or death following hospitalization for heart failure (HF). We combined N-terminal pro-B type natriuretic peptide (NT-proBNP) levels with the LE index to derive and validate the LENT index for risk prediction at the point of care on the day of hospital discharge.

Methods and results In this prospective cohort sub-study of the Patient-centred Care Transitions in HF clinical trial, we used log-binomial regression models with LE index and either admission or discharge NT-proBNP as the predictors and 30 day composite all-cause readmission or death as the primary outcome. No other variables were added to the model. We used regression coefficients to derive the LENT index and bootstrapping analysis for internal validation. There were 772 patients (mean [SD] age 77.0 [12.4] years, 49.9% female). Each increment in the LE index was associated with a 25% increased risk of the primary outcome (RR 1.25, 95% CI 1.16–1.35; C-statistic 0.63). Adjusted for the LE index, every 10-fold increase in admission and discharge NT-proBNP was associated with a 48% (RR 1.48; 95% CI 1.10, 1.99; C-statistic 0.64; net reclassification index [NRI] 0.19) and 56% (RR 1.56; 95% CI 1.08, 2.25; C-statistic 0.64; NRI 0.21) increased risk of the primary outcome, respectively. The predicted probability of the primary outcome increased to a similar extent with incremental LENT, regardless of whether admission or discharge NT-proBNP level was used.

Conclusions The point-of-care LENT index predicts 30 day composite all-cause readmission or death among patients hospitalized with HF, with improved risk reclassification compared with the LE index. The performance of this simple, 3-variable index - without adjustment for comorbidities - is comparable to complex risk prediction models in HF.

Keywords Heart failure; Hospitalization; Risk prediction

Received: 26 August 2020; Revised: 7 October 2020; Accepted: 29 October 2020

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Introduction

Patients hospitalized for heart failure (HF) represent a high-risk group faced with a 25% risk of readmission and a 4% risk of death within a month of discharge.¹ Hospitalizations and readmissions account for 70% of the costs of HF care.¹ Among prognostic models developed to assess risk in HF, only a small minority have been derived among hospitalized² patients, and most have used administrative datasets^{3,4} rather than clinical variables at the point of care.

The LE index—a sum of Length of hospital stay and number of Emergency department visits in the preceding 6 months—computed at the point of care on the day of hospital discharge predicts 30 day composite all-cause readmission or death with a 21% increase in risk per LE increment and with modest discrimination.⁵ N-terminal pro-B type natriuretic peptide (NT-proBNP), a prognostic biomarker in HF⁶ may improve performance of the LE risk prediction index when measured on admission or discharge. The change in NT-proBNP concentrations from admission

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to discharge may also serve as an indicator of risk in the month following hospitalization. 6

In this sub-study of the Patient Centered Transitions in Heart Failure (PACT-HF) randomized trial,^{7,8} we assess whether admission, discharge, or change in NT-proBNP from admission to discharge improves performance of the LE risk prediction index among patients hospitalized for HF. We develop and internally validate a simple clinical scoring system based on the LE index and NT-proBNP concentrations to predict the risk of 30 day composite all-cause readmission or death and 30 day all-cause readmission.

Methods

Study population

The patients in this study were a subset enrolled in the PACT-HF multicentre cluster randomized trial^{7,8} who received

transitional care services during and after their hospitalization, and had NT-proBNP measured at hospital admission or discharge (*Figure 1*). The trial complied with the Declaration of Helsinki and was approved by the Research Ethics Boards of all participating institutions with a waiver for written consent but with informed verbal consent. The trial included adult patients with an admission diagnosis of HF, confirmed using the validated Boston criteria⁹ or using either BNP or NT-proBNP concentrations. We excluded patients who did not meet diagnostic criteria for HF, who were previously admitted for HF during the study period, who died during hospitalization, or who were discharged to other hospitals.

Data collection

We obtained patient clinical characteristics via review of hospital charts and from administrative databases accessed at ICES. Research personnel computed the LE index at the time

FIGURE 1 Flow diagram of the study participants. Of a total of 2494 patients in the PACT-HF trial, 772 with NT-proBNP measured at admission or discharge were included in the sub-study. NT-proBNP was measured with a point-of-care device whose upper limit of detection was 9000 pg/mL.



of discharge and measured NT-proBNP levels at admission and discharge during the index hospitalization using the Cobas H 232[©] point-of-care NT-proBNP testing kits supplied by Roche diagnostics.¹⁰ We identified inpatient services utilized using the Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD) and deaths using the Ontario Registered Persons Database (ORPD). The datasets were linked with unique identifiers and were retrieved and analysed at ICES.

Outcomes

The primary outcome was 30 day composite all-cause readmission or death. The secondary outcome was 30 day all-cause readmission.

Statistical analysis

Of the 772 patients, 182 (23.6%) had either missing admission or missing discharge NT-proBNP values (but not both). We imputed missing admission or discharge NT-proBNP values using multiple imputation. We selected candidate variables by matrix analysis¹¹ and included sex, weight, creatinine, history of atrial fibrillation, LVEF, discharge or admission NTproBNP, and whether or not the patient was receiving diuretics, beta-blockers, ACE inhibitors, or mineralocorticoid receptor antagonists. We summarized continuous variables using means (SD) and medians (IQR) and categorical variables using numbers and percentages. We compared continuous variables using the Student's *t*-test or Wilcoxon two-sample test based on the distribution and categorical variables using the χ^2 or Fisher's exact test.

We fitted log₁₀-binomial regression models with the LE index as the predictor and either 30 day composite all-cause readmission or death or 30 day all-cause readmission as the outcome with the percentage change in NT-proBNP from admission to discharge or either log₁₀-admission or log₁₀-discharge NT-proBNP as a continuous covariate. We adjusted all models for post-discharge home care or HF clinic services to account for differences in post-discharge care. We assessed risk with risk ratios (RR) and 95% confidence intervals (CI). We assessed risk discrimination using the C-statistic and net reclassification index (NRI). The net reclassification index was calculated relative to the LE index. We assessed model goodness of fit with the Brier score, 12 in which a score of zero indicates perfect accuracy, while a score of one indicates that the model is wholly inaccurate. We internally validated the models using bootstrapping with replacement from the original sample for 100 runs and computed the optimistic C-statistic and NRI. We computed the additional points for the LE index to derive the LENT index based on the coefficient estimates obtained from the models. The predicted risk probability to each score of the LENT index were estimated.

We conducted analyses using SAS Version 9.4 for UNIX (SAS Institute Inc, Cary, NC, USA) and set the nominal significant level for testing at 5%.

We proposed a new scoring system based on the beta coefficients from the regression models with the LE index and log-transformed admission or discharge NT-proBNP values (Supporting Information, *Table S1*). The probability of 30 day outcomes associated with each point was calculated using previously published methods.¹³

Results

Study population

The baseline characteristics of the 772 patients in the derivation cohort are presented in *Table 1*, which details a fairly typical higher risk population of hospitalized HF patients. The mean age (SD) of the patients was 77.0 (12.4) years, and 49.9% were female. The mean (SD) left ventricular ejection fraction (LVEF) was 48% (14.5). Among the patients in this study, 49.1% had diabetes, 42.1% had hypertension, and 31.3% previously underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). All of the patients in this study received in-hospital transitional care services, and 46.8% were referred for home care or HF clinic services after discharge.

Outcomes

Of the 772 patients in the derivation cohort, 163 (21.1%) were readmitted or died within 30 days of discharge and 157 (20.3%) were readmitted within 30 days of discharge. At baseline, the mean (SD) LE index was 7.4 (2.1) for patients who were readmitted or died within 30 days, and 6.5 (1.8) for patients who were neither readmitted nor died within 30 days (*Table 1*).

30 day all-cause readmission or death

Each increment in the LE index was associated with a 25% increased risk of 30 day composite all-cause readmission or death (RR 1.25; 95% CI 1.16, 1.35 per unit) with moderate discrimination (C-statistic 0.63; 95% CI 0.58, 0.68). The LE index was well calibrated for 30 day composite all-cause readmission or death (Brier score 0.16). On its own, log_{10} -admission NT-proBNP had suboptimal discrimination for 30 day composite all-cause readmission or death (C-statistic 0.58; 95% CI 0.53, 0.63), as did log_{10} -discharge NT-proBNP (C-statistic 0.57; 95% CI 0.52, 0.62) (*Table 2*).

After adjusting for the LE index, every 10-fold increase in admission NT-proBNP was associated with a 48% increased

	Readmitted or dead in 30 days $(N = 163)$	Neither readmitted nor dead in 30 days $(N = 609)$	<i>P-</i> value
Demographics			
Age (year), mean (SD)	77.4 (12.5)	76.9 (12.4)	0.68
Sex, n (%)			
Male	81 (49.7)	306 (50.2)	0.90
Female	82 (49.3)	303 (49.8)	
Resides in long-term care, n (%)	15 (9.2)	38 (6.2)	0.51
Co-morbidities			
LV ejection fraction, mean (SD)	48.5 (14.4)	47.9 (14.5)	0.61
Hypertension, n (%)	65 (39.9)	260 (42.7)	0.52
Diabetes, n (%)	79 (48.5)	300 (49.3)	0.86
Diabetes with end organ damage, n (%)	76 (46.6)	281 (46.1)	0.91
Prior PCI or CABG, n (%)	64 (39.3)	178 (29.2)	0.01
Chronic pulmonary disease, n (%)	22 (13.5)	74 (12.2)	0.64
Dementia, n (%)	12 (7.4)	28 (4.6)	0.16
Cancer (anv), n (%)	8 (4.9)	12 (2.0)	0.04
Resource utilization			
Acuity of admission (via emergency department), n (%)	161 (98.8)	607 (99.7)	0.16
Number of ED visits in preceding 6 months, mean (SD)	3.2 (2.7)	2.2 (1.6)	<0.01
Estimated risk			
LE index, mean (SD)	7.4 (2.1)	6.5 (1.8)	< 0.01
Admission NT-proBNP (pg/mL), median (IQR)	4569 (2686, 10 030)	3702 (1970, 6821)	< 0.01
Discharge NT-proBNP (pg/mL), median (IQR)	2631 (1285, 4880)	2073 (1057, 3630)	0.02

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risk of 30 day composite all-cause readmission or death (RR 1.48; 95% CI 1.10, 1.99), and every 10-fold increase in discharge NT-proBNP was associated with a 56% increased risk of 30 day composite all-cause readmission or death (RR 1.56; 95% CI 1.08, 2.25). The addition of admission or discharge NT-proBNP to the LE index correctly reclassified 12% or 20% of events, respectively, and 7% or 1% of nonevents, respectively. Risk classification for 30 day composite all-cause readmission or death was significantly improved with log₁₀-admission (NRI 0.19; 95% CI 0.02, 0.36) and log₁₀-discharge NT-proBNP (NRI 0.21; 95% CI 0.04, 0.38) relative to the LE index alone. In contrast, the percentage change in NT-proBNP from admission to discharge was not associated with increased risk of 30 day composite all-cause readmission or death (RR 1.00, 95% CI 1.00, 1.00; NRI 0.07; 95% CI -0.10, 0.23; Brier score 0.16) relative to the LE index (Table 2).

30 day all-cause readmission

After adjusting for post-discharge transitional care services that were delivered during the trial, increments in the LE index were associated with a 26% increased risk of 30 day all-cause readmission (RR 1.26; 95% Cl 1.16, 1.36 per unit) with moderate discrimination (C-statistic 0.63; 95% Cl 0.58, 0.68). The LE index was well calibrated for 30 day all-cause readmission (Brier score 0.15). The log₁₀-admission NT-proBNP poorly predicted 30 day all-cause readmission on its own (C-statistic 0.58; 95% Cl 0.53, 0.63). The log₁₀-discharge

NT-proBNP performed similarly for 30 day all-cause readmission (C-statistic 0.57; 95% CI 0.52, 0.63) (*Table 2*).

After adjusting for the LE index, each 10-fold increase in admission NT-proBNP was associated with a 43% increased risk of 30 day all-cause readmission (RR 1.43; 95% CI 1.06, 1.93), and each 10-fold increase in discharge NT-proBNP was associated with a 55% increased risk of 30 day all-cause readmission (RR 1.55; 95% CI 1.06, 2.25). Log₁₀-discharge NT-proBNP significantly improved risk classification with the LE index for 30 day all-cause readmission (NRI 0.20; 95% CI 0.03, 0.37 compared with the LE index); log₁₀-admission NT-proBNP improved risk classification without statistical significance (NRI 0.15; 95% CI -0.03, 0.32 compared with the LE index). The addition of admission or discharge NT-proBNP to the LE index correctly reclassified 8% or 20% of events, respectively, and 6% or 0% of non-events, respectively. After adjusting for the LE index, the percentage change in NT-proBNP from admission to discharge was not associated with 30 day all-cause readmission (RR 1.00; 95% CI 1.00, 1.00; NRI 0.04; 95% CI -0.13, 0.21; Brier score 0.15) (Table 2).

LENT index scoring system

The scoring system for the LENT index, ranging from 2 to 13, and the option of using admission or discharge NT-proBNP values to compute the LENT indices is depicted in the

Predictors	Relative risk (95% Cl) ^a	C-statistic (95% CI) ^a	Optimism adjusted C-statistic (95% CI) ^b	Brier score ^c	NRI (95% CI) ^d	Optimistic NRI (95% CI) ^d
30 day composite all-cause re	eadmission or death					
LE index	1.25 (1.16, 1.35)	0.63 (0.58, 0.68)	0.63 (0.59, 0.68)	0.16		
LE + admission NT-proBNP ^e	1.48 (1.10, 1.99)	0.64 (0.59, 0.69)	0.64 (0.59, 0.69)	0.16	0.19 (0.02, 0.36)	0.16 (0.00, 0.34)
LE + discharge NT-proBNP ^e	1.56 (1.08, 2.25)	0.64 (0.59, 0.69)	0.64 (0.60, 0.69)	0.16	0.21 (0.04, 0.38)	0.19 (0.02, 0.37)
LE + % change in NT-proBNP	1.00 (1.00, 1.00)	0.63 (0.58, 0.68)	0.63 (0.59, 0.69)	0.16	0.07 (-0.10, 0.23)	0.06 (-0.13, 0.17)
30 day all-cause readmission						
LE Index	1.26 (1.16, 1.36)	0.63 (0.58, 0.68)	0.64 (0.59, 0.69)	0.15		Ι
LE + admission NT-proBNP ^e	1.43 (1.06, 1.93)	0.64 (0.59, 0.69)	0.64 0.60, 0.69)	0.15	0.15 (-0.03, 0.32)	0.15 (0.00, 0.33)
LE + discharge NT-proBNP ^e	1.55 (1.06, 2.25)	0.64 (0.59, 0.69)	0.64 (0.60, 0.69)	0.15	0.20 (0.03, 0.37)	0.18 (0.00, 0.37)
LE + % change in NT-proBNP	1.00 (1.00, 1.00)	0.63 (0.58, 0.68)	0.64 (0.59, 0.69)	0.15	0.04 (-0.13, 0.21)	0.04 (-0.15, 0.17)
^a Adjusted for post-discharge se	ervices. The C-statistic is a me	asure of discrimination fro	om 0 to 1 with higher scores indic	ating stronger di	scrimination.	
² The optimism adjusted C-stat	istic is the result of internal va	alidation by bootstrapping	g with 100 samples.			
^c The Brier score is a measure o	f model accuracy from 0 to 1	, with lower scores indicat	ting higher accuracy.			

^dThe NRI is the net reclassification index from 0 to 1, with higher scores indicating a greater incremental value.

^eAdmission and discharge natriuretic peptide values were log₁₀-transformed

Table 2 LE and NT-proBNP as predictors of 30 day outcomes following hospitalization for HF: derivation sample (n = 772)

30 day all-cause readmission or death The admission and discharge LENT indices offered moderate

graphical abstract. The distribution of the LENT index is

depicted in Figure 2.

The admission and discharge LENT indices offered moderate discrimination for 30 day composite all-cause readmission or death (C-statistic 0.64; 95% CI 0.59, 0.69 for both) with good calibration (Brier score 0.16 for both). The corresponding predicted probabilities of 30 day composite all-cause readmission or death is shown in the graphical abstract. Using admission NT-proBNP, the lowest and highest possible LENT score was associated with a mean probability (SD) of 0.05 (0.00) and 0.51 (0.01), respectively, for 30 day readmission or death. Using discharge NT-proBNP, the lowest and highest LENT score was associated with a mean probability (SD) of 0.06 (0.00) and 0.53 (0.01), respectively, for 30 day readmission or death (*Figure 3*, Supporting Information, *Table S2*).

FIGURE 2 The distribution of LENT index scores in the cohort of patients hospitalized for HF. The distribution of admission and discharge LENT scores was similar.



FIGURE 3 The predicted probability of 30 day composite all-cause readmission or death in patients hospitalized for HF. The LENT indices demonstrate a continuum of risk, with higher scores associated with an increased risk of 30 day composite all-cause readmission or death.



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30 day all-cause readmission

The admission and discharge LENT indices offered moderate discrimination for 30 day all-cause readmission (C-statistic 0.64; 95% CI 0.59, 0.69 for both) with good calibration (Brier score 0.15 for both). Using admission NT-proBNP, the lowest and highest possible LENT score was associated with a probability (SD) of 0.06 (0.00) and 0.46 (0.01), respectively, for 30 day readmission. The LENT index using discharge NT-proBNP offered similar results, with the lowest and highest scores associated with a probability (SD) of 0.06 (0.00) and 0.48 (0.01), respectively, for 30 day readmission (Figure 4, Supporting Information, Table S3).

Internal validation

30 day all cause readmission or death

In the internal validation with 100 bootstrap samples, the LE index had moderate discrimination for 30 day composite

FIGURE 4 The predicted probability of 30 day all-cause readmission in patients hospitalized for HF. The LENT indices demonstrate a continuum of risk, with higher scores associated with an increased risk of 30 day all-cause readmission.



all-cause readmission or death (optimistic C-statistic 0.63; 95% CI 0.59, 0.68). Risk classification for 30 day composite all-cause readmission or death was improved with the LENT index using admission NT-proBNP (optimistic NRI 0.16; 95% CI 0.00, 0.34; optimistic C-statistic 0.64; 95% CI 0.60, 0.69) and discharge NT-proBNP (optimistic NRI 0.19; 95% CI 0.02, 0.37; optimistic C-statistic 0.64; 95% CI 0.59, 0.69).

30 day all cause readmission

In the internal validation with 100 bootstrap samples, the LE index had moderate discrimination for 30 day all-cause readmission (optimistic C-statistic 0.64; 95% CI 0.59, 0.69). Relative to the LE index, risk classification for 30 day all-cause readmission was improved with the LENT index using admission (optimistic NRI 0.15; 95% CI 0.00, 0.33; optimistic C-statistic 0.64; 95% CI 0.60, 0.69) and discharge NT-proBNP (optimistic NRI 0.18; 95% CI 0.00, 0.37; optimistic C-statistic 0.64; 95% CI 0.60, 0.69).

Discussion

In this multicentre study of patients being discharged after hospitalization for HF, we derived a risk index that predicts 30 day clinical outcomes using only length of stay, number of ED visits in the preceding 6 months, and admission or discharge NT-proBNP (*Figure 5*). Ten-fold increases in NT-proBNP were associated with increased risk of 30 day composite all-cause readmission or death and 30 day all-cause readmission relative to the LE index, a simple bedside index which compares favourably to more complex risk prediction models in HF.⁵ The 3-variable LENT index correctly identified a greater proportion of both events and non-events in patients hospitalized for HF relative to the LE index.

The simplicity of the LENT index and its derivation at the bedside offer major advantages over existing risk prediction





models. The LENT index does not require adjustment for baseline or clinical characteristics, improving its generalizability and ease-of-use in clinical practice without sacrificing performance; in our previous comparison of the LE index⁵ with the more complex LACE index (which includes additional variables for acuity of presentation and Charlson co-morbidity),¹⁴ we found no difference in risk discrimination between the two for the outcome of 30 day composite all-cause readmission or death. Like the LACE index, a majority of validated risk prediction models in HF are derived and validated in administrative claims databases and use large numbers of variables that make computation difficult and limit their utility at the point of care. For example, the Medicare-endorsed readmission risk score (RRS) includes 37 variables from an administrative claims database, and the Get With The Guidelines risk calculator includes up to 28 points each for categories of age, blood pressures, and BUN.³

The discrimination of the LE index and the LENT index was similar; however, the net reclassification index improved with the addition of NT-proBNP to the LE index. These disparate findings can be explained by the limitations of using the difference in C-statistics to assess the incremental value of predictors. The C-statistic is defined as the probability that for a given predictive model, individuals with an event will have a higher predicted risk than those who do not experience an event; it is not the probability that individuals are correctly classified as high or low risk.¹⁵ By contrast, the NRI is the sum of the percentage of events and non-events correctly reclassified less the percentage of events and non-events incorrectly reclassified by the addition of a predictor to a model.¹⁶ This distinction is clinically relevant; if a patient is reclassified as having higher or lower risk by adding a predictor to a basic model, clinicians can allocate postdischarge resources and formulate follow-up care plans accordingly.17

To date, there are no risk models that predict 30 day composite all-cause readmission or death or 30 day all-cause readmissions in patients admitted for HF with C-statistics >0.65, which reveals the challenges of predicting readmission, in particular. The LENT index had moderate discrimination (C-statistic 0.64; 95% CI 0.59, 0.69 for 30 day composite all-cause readmission and death and for 30 day all-cause readmission) that is comparable or better than other models such as the RRS, validated in a separate sample (C-statistic 0.62; 95% CI 0.55, 0.68 for 30 day composite all-cause readmission or death; C-statistic 0.61; 95% CI 0.55, 0.67 for 30 day all-cause readmission).¹⁴ In a study of 59 652 patients admitted for HF, a model containing length of stay, age, Charlson co-morbidity index, and emergency visits offered modest discrimination for 30 day composite readmission or death (C-statistic 0.61).¹⁸ Similarly, in a study of 24 326 patients admitted for HF, a more complicated model consisting of discharge BNP, co-morbidities, patient

demographics, and year hospitalized achieved moderate discrimination for 30 day all-cause readmission (C-statistic 0.63).¹⁹

The discrimination of models for all-cause readmission is typically lower than that of HF-specific readmission,²⁰ as up to 65% of readmissions after HF hospitalization are for reasons other than HF.²¹ Readmission may be more difficult to predict in HF than mortality due to unaccounted for patient-level and health systems variables that are challenging to measure and incorporate in risk prediction models.²²

Both admission and discharge NT-proBNP added incremental value to the LE index for predicting 30 day all-cause readmission or death, but on their own, were suboptimal in predicting risk or discriminating between risk groups. NTproBNP, a biomarker that is sensitive to changes in LV filling pressure, may be more useful in predicting HF-specific, rather than all-cause, endpoints. While NT-proBNP has previously been shown to add incremental value to clinical risk prediction models,¹⁹ there are few studies on its utility for 30 day outcomes. Our study is one of the first to combine NT-proBNP with simple variables based on health care utilization to predict 30 day all-cause readmission or death.

Our study has multiple strengths. This was a pragmatic, multicentre trial with broad inclusion criteria, resulting in a study sample representative of real-world patients hospitalized for HF: elderly, multi-morbid, and an equal distribution of male and female patients. The diagnosis of HF was confirmed by a research nurse using the validated Boston criteria, rather than administrative data in which diagnoses may be misclassified.²³ All patients received standard post-discharge services, and we adjusted the regression models for level of transitional care support, which can impact 30 day outcomes but which are typically not accounted for in other risk prediction models. We internally validated our risk index via bootstrapping. The LENT index can be easily computed at the bedside without chart review, improving its clinical utility.

Limitations

A major limitation of this study was the lack of a complete range of NT-proBNP values due to technical limitation of point-of-care devices. Values higher than 9000 μ g/mL were recorded as ">9000" on the devices and analysed as 9000. It is possible that a complete range would have yielded a LENT index with a better performance than observed in the study. The performance of the LENT index will require testing in an external validation cohort using devices that can capture a broader range of NT-proBNP values. Furthermore, the 30 day all-cause mortality rate observed was lower than expected.² However, as discrimination for mortality is typically better than for readmission, the discrimination of the LENT index for 30 day composite all-cause readmission or death is likely underestimated due to the low mortality. Finally, the LENT index was derived among hospital inpatients, and its performance among those in ambulatory day hospital or home intravenous diuretic programmes is unclear.

Conclusions

The point-of-care LENT index—based on length of hospital stay, number of ED visits in preceding 6 months, and either admission or discharge NT-proBNP levels—is a practical and reliable means of estimating the risk of 30 day composite all-cause readmission or death or 30 day all-cause readmission following hospitalization for HF. The performance of this simple index is comparable with more complex risk prediction models derived from administrative datasets and may improve the ability of clinicians to identify high-risk patients and allocate resources accordingly.

Data availability statement

The data have been transferred to and are stored at a provincial research centre (ICES) that links the clinical trial participant data to clinical outcomes using encrypted identifiers. The data are bound by agreements, and the linked individual-level data cannot be transferred outside of ICES. The aggregate data underlying this article are available in the article and in the supporting information.

Conflict of interest

Dr. Van Spall has received an educational grant from Roche Diagnostics and is supported by a career award from Hamilton Health Sciences and McMaster University. Dr. Januzzi has received consulting income from Roche Diagnostics and has received research funding from Abbott Diagnostics and Novartis Pharmaceuticals. Dr. Ko is supported by a Clinician Scientist Award from the Heart and Stroke Foundation of Canada. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Funding

This work was funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC) grant 6686 and Canadian Institutes of Health Research grant 135917 held by Dr. Van Spall. Research support for point-of-care NT-proBNP testing devices was provided by Roche Diagnostics. The work was supported by ICES, which is funded by an annual grant from the MOHLTC. Parts of this material are based on data and information compiled and provided by the MOHLTC and the Canadian Institute for Health Information (CIHI). The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Author contributions

H.V. conceived the study idea, obtained funding, led the conduct of the study, informed the analytic plan, interpreted the results, and drafted and edited the manuscript. S.L. informed the analytic plan, and U.O. performed the statistical analysis. S.L. and T.A. interpreted the results and drafted portions of the manuscript. All authors edited the manuscript and approved the final version. H.V. assumes responsibility for the scientific integrity of this work.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

 Table S1. The beta coefficients for the admission and discharge NT-pro-BNP derived LENT index for 30-day clinical outcomes.

Table S2. The predicted probability of 30-day composite all-cause readmission or death in patients admitted for HF by LENT index score, derived using admission or discharge NT-proBNP.

Table S3. The predicted probability of 30-day all-cause readmission in patients admitted for HF by LENT index score, derived using admission or discharge NT-proBNP.

References

 Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, López-Sendón J. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Hear Fail* 2014; 1: 110–145.

 Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D. Predicting mortality among patients hospitalized for heart failure derivation and validation of a clinical model. *JAMA* 2003; **290**: 2581–2587.

 Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, Fonarow GC, Masoudi FA, American Heart Association Get With the Guidelines-Heart Failure Program. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 25–32.

- Krumholz HM, Wang YY, Mattera JA, Wang YY, Han LF, Ingber MJ, Roman S, Normand SLT. An administrative claims model suitable for profiling hospital performance based on 30-day mortality rates among patients with heart failure. *Circulation* 2006; **113**: 1693–1701.
- 5. Van Spall HGC, Lee SF, Averbuch T, Erbas Oz U, Perez R, Maingi M, Heffernan M, Mitoff P, Tjandrawidjaja M, Zia M, Simek K, Porepa L, Panju M, Ko D, Connolly S. All you need is LE: utility of an abbreviated LACE score in predicting 30-day outcomes among patients hospitalized for heart failure (HF). Eur Heart J 2018; **39**: 6544.
- Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S. Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation* 2004; 110: 2168–2174.
- 7. Van Spall HGC, Lee SF, Xie F, Ko DT, Thabane L, Ibrahim Q, Mitoff PR, Heffernan M, Maingi M, Tjandrawidjaja MC, Zia MI, Panju M, Perez R, Simek KD, Porepa L, Graham ID, Haynes RB, Haughton D, Connolly SJ. Knowledge to action: rationale and design of the Patient-Centered Care Transitions in Heart Failure (PACT-HF) stepped wedge cluster randomized trial. Am Heart J 2018; **199**: 75–82.
- Van Spall HGC, Lee SF, Xie F, Erbas Oz U, Perez R, Mitoff PR, Maingi M, Tjandrawidjaja MC, Heffernan M, Zia MI, Porepa L, Panju M, Thabane L, Graham ID, Haynes RB, Haughton D, Simek

KD, Ko DT, Connolly SJ. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure. The PACT-HF randomized clinical trial. *JAMA* 2019; **321**: 753–761.

- Carlson KJ, Lee DCS, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. J Chronic Dis 1985; 38: 733–739.
- 10. Roche Diagnostics. Cobas H 232 User's manual. 2016.
- Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials—A practical guide with flowcharts. BMC Med Res Methodol 2017; 17: 1–10.
- Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Obuchowski N, Pencina MJ, Gonen M, Pencina MJ, Kattan MW. Assessing the performance of prediction models: A framework for some traditional and novel measures. *Epidemiology* 2010; 21: 128–138.
- Sullivan LM, Massaro JM Sr. RBDA. Tutorial in biostatistics. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004; 23: 1631–1660.
- 14. Yazdan-Ashoori P, Lee SF, Ibrahim Q, Van Spall HGC. Utility of the LACE index at the bedside in predicting 30-day readmission or death in patients hospitalized with heart failure. *Am Heart J* 2016; **179**: 51.
- Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007; 115: 928–935.
- Pencina M, D'Agostino R Sr, D'Agostino R Jr, Vasan R. Evaluating the added predictive ability of a new marker: from area under the ROC curve to

reclassification and beyond. Stat Med 2008; 27: 157–172.

- Vickers AJ, Cronin AM, Begg CB. One statistical test is sufficient for assessing new predictive markers. *BMC Med Res Methodol* 2011; 11: 1–7.
- 18. Au AG, McAlister FA, Bakal JA, Ezekowitz J, Kaul P, Van Walraven C. Predicting the risk of unplanned readmission or death within 30 days of discharge after a heart failure hospitalization. Am Heart J 2012; 164: 365–372.
- Flint KM, Allen LA, Pham M, Heidenreich PA. B-type natriuretic peptide predicts 30-day readmission for heart failure but not readmission for other causes. J Am Heart Assoc 2014; 3: 1–9.
- Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, Woodward M, Patel A, McMurray J, MacMahon S. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Hear Fail 2014; 2: 440–446.
- Dharmarajan K, Lin Z, Ross JS, Horwitz LI, Barreto-filho A, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA* 2015; 309: 355–363.
- 22. Hammill BG, Curtis LH, Fonarow GC, Heidenreich PA, Yancy CW, Peterson ED, Hernandez AF. Incremental value of clinical data beyond claims data in predicting 30-day outcomes after heart failure hospitalization. *Circ Cardiovasc Qual Outcomes* 2011; 4: 60–67.
- McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and metaanalysis. *PLoS ONE* 2014; 9: 8.