Brief Report

Prediction of Survival in Asian Patients Hospitalized With Heart Failure: Validation of the OPTIMIZE-HF Risk Score

JONATHAN YAP, MBBS, MRCP,[1] FANG YI LIM, MBBS,[1] SHAW YANG CHIA,[1] JOHN CARSON ALLEN Jr, PhD,[1,2] FAZLUR REHMAN JAUFEERALLY, MBBS, MRCP,[2,3] MICHAEL ROSS MACDONALD, MBBS, MRCP,[4] PING CHAI, MBBS, MRCP,[5] SEET YOONG LOH, MBBS, MRCP,[6] PATRICK LIM, MBBS, MRCP,[7] MA WAI WAI ZAW, MBBS,[1] LOUIS TEO, MBBS, MRCP,[1] DAVID SIM, MBBS, MRCP,[1] AND CAROLYN S.P. LAM, MBBS, MS, PhD[1,2]

Singapore

ABSTRACT

Background: Risk scores predicting in-patient mortality in heart failure patients have not been designed specifically for Asian patients. We aimed to validate and recalibrate the OPTIMIZE-HF risk model for in-hospital mortality in a multiethnic Asian population hospitalized for heart failure.

Methods and Results: Data from the Singapore Cardiac Databank Heart Failure on patients admitted for heart failure from January 1, 2008, to December 31, 2013, were included. The primary outcome studied was in-hospital mortality. Two models were compared: the original OPTIMIZE-HF risk model and a modified OPTIMIZE-HF risk model (similar variables but with coefficients derived from our cohort). A total of 15,219 patients were included. The overall in-hospital mortality was 1.88% (n = 286). The original model had a C-statistic of 0.739 (95% CI 0.708−0.770) with a good match between predicted and observed mortality rates (Hosmer-Lemeshow statistic 13.8; $P = .086$). The modified model had a C-statistic of 0.741 (95% CI 0.709−0.773) but a significant difference between predicted and observed mortality rates (Hosmer-Lemeshow statistic 17.2; $P = .029$). The modified model tended to underestimate risk at the extremes (lowest and highest ends) of risk.

Conclusions: We provide the first independent validation of the OPTIMIZE-HF risk score in an Asian population. This risk model has been shown to perform reliably in our Asian cohort and will potentially provide clinicians with a useful tool to identify high-risk heart failure patients for more intensive management. (*J Cardiac Fail 2019;25:571−575*)

Key Words: Heart failure, in-hospital mortality, risk score.

Heart failure is a leading cause of hospitalization worldwide[1,2] including in Asia,[3] portending a significant risk of in-hospital mortality.[1,4] The ability to accurately predict outcomes enables physicians to risk stratify patients, identifying those at higher risk, providing appropriate individualized care, and thereby improving outcomes while ensuring optimal allocation of limited resources. This will also allow for better communication with patients and families on the projected trajectory of disease.

Among various risk scores formulated to predict in-hospital mortality,[5−9] the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) clinical model has one of the largest derivation cohorts to date of ∼38,000 inpatients, consists of readily available clinical variables, and has performed well, with a published C-statistic of 0.75 in both derivation and validation cohorts.[4] The cohort was composed largely of white and black Americans (>90%), with no validation studies performed in an Asian cohort. Multiple studies have highlighted how race affects mortality in heart failure patients.[10,11] We aimed, therefore, to validate and recalibrate the OPTIMIZE-HF risk model for inpatient

From the [1]Department of Cardiology, National Heart Centre Singapore, Singapore; [2]Duke-NUS Medical School, Singapore; [3]Department of Internal Medicine, Singapore General Hospital, Singapore; [4]Department of Cardiology, Changi General Hospital, Singapore; [5]Department of Cardiology, National University Heart Centre, National University Hospital, Singapore; [6]Department of Cardiology, Tan Tock Seng Hospital, Singapore and [7]Department of Cardiology, Khoo Teck Puat Hospital, Singapore.

Manuscript received August 15, 2018; revised manuscript received January 8, 2019; revised manuscript accepted February 20, 2019.

Reprint requests: Dr Jonathan Yap, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609. Tel: +65 67048965; Fax: +65 68449069. E-mail: jonyap@yahoo.com

See page 575 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.02.016

mortality in a multiethnic Asian population hospitalized for heart failure.

Materials and Methods

Singapore has a multiracial population of 5.31 million, comprising 74% Chinese, 13% Malay, and 9% Indian,[12] with public hospitals providing 80%−90% of tertiary care.[13] The Singapore Cardiac Databank Heart Failure (SCDB-HF) registry is a national registry that has prospectively collated data on all consecutive patients ≥21 years of age admitted to public hospitals for heart failure since January 1, 2008, including details on demographics, medical history, clinical characteristics, investigation results, treatment, and discharge outcomes.[14] Details of the registry has previously been published.[14] Trained coordinators collected data with the use of a standardized case report form and entered these findings into an electronic database, which underwent internal and external validation. Registry participation was independent from medical care received. The study was approved by the Institutional Ethics Review Board. Consecutive unique patients who were admitted to the SCDB-HF registry from January 1, 2008, to December 31, 2013, were included in the present study. See Supplemental Fig. 1 for the flow chart of patient selection.

Outcomes

The primary outcome measure was in-hospital mortality.

Statistical Analysis

Baseline characteristics of study patients were summarized as frequencies and percentages for categoric variables and mean ± SD for continuous variables. Univariate and multivariate analyses were performed with the use of a logistic regression model to determine the independent predictors of in-hospital mortality in the derivation cohort. Odds ratios (ORs) and 95% confidence intervals (CIs) were presented.

Two models were assessed. The first model was the original OPTIMIZE-HF model with its published variables (age, heart rate, systolic blood pressure, sodium, creatinine, primary cause of admission (heart failure vs others), left ventricular ejection fraction (<40% vs ≥40%), and coefficients.[4] The second model (modified OPTIMIZE-HF model) used the same candidate variables as the OPTIMIZE-HF model, but used coefficients for in-hospital mortality derived from our cohort. The primary cause of admission in our cohort was heart failure.

Values predicted by the model belong to a range from 0 to 1, and represent the probability of the in-hospital mortality. The model is as follows:

$$p = \frac{1}{1 + e^{-y}}$$

where p is the predicted probability of in-hospital mortality, e is a base of natural logarithm, and y is a linear combination of x_i variables and their estimators b_i included in the model:

$$y = b_0 + b_1x_1 + b_2x_2 + \ldots + b_nx_n$$

For binary predictors (eg. LVEF <40%), $x_i = 1$ if it is present and 0 if it is absent.

The C-statistic measures how well the model can discriminate between observations at different levels of the outcome. The C-statistic and its 95% CI were calculated. The Hosmer and Lemeshow test evaluates the goodness-of-fit of the model to assess if the model is well calibrated such that probability predictions from the model reflect the occurrence of events in the data. Bar graphs showing the visual plots of the cumulative expected versus observed events across the various spectrums of risk were obtained. Both tests were used to compare the accuracy of the models. Bootstrapping was performed to internally validate the modified OPTIMIZE-HF model,[15] with the C-statistic and Hosmer and Lemeshow test similarly calculated for the validation sample derived by bootstrapping for the modified OPTIMIZE-HF model. Bootstrap estimation was adopted to obtain bias-corrected coefficients and CIs in each step. A total of 7610 (50%) random samples of the cohort were used to define the 95% centiles for model performance parameters. All 2-sided P values of <.05 were considered to be statistically significant. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used to conduct the analyses.

Results

A total of 15,219 (mean age 70 ± 13 years; 8480 (55.7%) male) patients were included. Table 1 presents the demographics and clinical characteristics of patients in each cohort.

Outcomes and Predictors

The overall in-hospital mortality rate was 1.88% (n = 286). The mean length of stay was 5.7 ± 6.6 days. A total of 568 patients (3.7%) required intensive care unit admission. Table 2 presents the results of the multivariate analysis using the variables in the original OPTIMIZE HF model for in-hospital mortality.

The final equation for the modified OPTIMIZE HF model is as follows:

$$\begin{aligned} y = {} & 2.7972 + (0.033 \times \text{Age}) + (0.00845 \times \text{Heart Rate}) \\ & - (0.0248 \times \text{Systolic Blood Pressure}) - (0.0527 \\ & \times \text{Sodium}) + (0.2782 \times \text{Creatinine}) + (0.2148 \\ & \times \text{LVEF} < 40\%) \end{aligned}$$

Table 1. Demographics and Clinical Characteristics of Study Population (n = 15,219)

Characteristic	Value
Demographics	
Age, y	70.0 (13.0)
Male	8480 (55.7%)
Race	
Chinese	10310 (67.7%)
Malay	2960 (19.4%)
Indian	1506 (9.9%)
Others	443 (2.9%)
Clinical characteristics	
Prior coronary artery disease	6230 (40.9%)
Prior myocardial infarction	2546 (16.7%)
Atrial fibrillation	3631 (23.9%)
Hypertension	11705 (76.9%)
Hyperlipidemia	9799 (64.4%)
Diabetes mellitus	8043 (52.8%)
Stroke	2331 (15.3%)
Peripheral vascular disease	862 (5.7%)
Chronic obstructive pulmonary disease	1654 (10.9%)
Ever smoker	5459 (35.9%)
Heart rate, beats/min	89.8 (22.8)
Systolic blood pressure, mm Hg)	143.9 (29.9)
Diastolic blood pressure, mm Hg	78.7 (18.6)
Left ventricular ejection fraction	
≥50%	5834 (38.3%)
40%−49%	1993 (13.1%)
30%−39%	2739 (18.0%)
<30%	4653 (30.6%)
QRS duration, ms	100.9 (24.5)
Creatinine, mg/dL	1.6 (1.3)
Sodium, mmol/L)	136.8 (4.9)
Potassium, mmol/L)	4.2 (0.8)
Hemoglobin, g/dL)	12.2 (4.2)
Chronic medications	
Angiotensin-converting enzyme inhibitor (ACEI)	5483 (36.0%)
Angiotensin II receptor blocker (ARB)	2904 (19.1%)
ACEI/ARB	8195 (53.8%)
Beta-blocker	8844 (58.1%)
Spironolactone/aldosterone antagonist	1232 (8.1%)
Nitrate	3775 (24.8%)
Diuretic	6903 (45.4%)
Digoxin	2378 (15.6%)
Aspirin	7042 (46.3%)
Clopidogrel	2244 (14.7%)
Warfarin	1797 (11.8%)
Statins	9749 (64.1%)

Values are presented as mean (SD) or n (%).

Performance of the Different Predictive Models

Regarding the original OPTIMIZE-HF model, the C-statistic for in-hospital mortality was 0.739 (95% CI 0.708−0.770). There was a good match between predicted and observed mortality rates in the derivation cohort (Hosmer-Lemeshow statistic 13.8; $P = .086$; Fig. 1a).

Table 2. Multivariable Model for In-Hospital Mortality

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value
Age	1.034 (1.023−1.044)	<.001
Heart rate	1.008 (1.003−1.014)	.001
Systolic blood pressure	0.976 (0.971−0.980)	<.001
Sodium level	0.949 (0.929−0.968)	<.001
Creatinine level	1.321 (1.248−1.397)	<.001
Left ventricular ejection fraction <40%	1.240 (0.967−1.588)	.090

Regarding the modified OPTIMIZE-HF model, the C-statistic obtained was 0.741 (95% CI 0.709−0.773). There was not a good match between predicted and observed mortality rates (Hosmer-Lemeshow statistic 17.2; $P = .029$). The modified model tended to underestimate risk at the extremes (lowest and highest ends) of risk (Fig. 1b). Internally validating the modified model via bootstrapping, a C-statistic of 0.761 (95% CI 0.719−0.804) was obtained and there was not a good match between predicted and observed mortality rates (Hosmer-Lemeshow statistic = 43.6; $P < .001$).

Discussion

The present study tested the validity of the OPTIMIZE-HF risk score, which was derived largely from a population of white and black Americans, in a large multiethnic Asian cohort. The OPTIMIZE-HF investigators previously validated their model in Western cohorts,[4] but data in Asian populations are lacking. To our knowledge, this is the first independent study validating the OPTIMIZE-HF risk score in an Asian population.

Ethnic differences affect heart failure outcomes. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, black patients had higher mortality than white patients.[10] In the ADHERE International−Asia Pacific (ADHERE-AP) registry, Asian patients presented at a median age of 67 years compared with 75 years for Western patients in the original ADHERE registry.[16] In our cohort, the mean age of presentation was 70 years, which was fairly similar to ADHERE-AP. In the ADHERE-AP registry, mean length of stay was 6 days, which was similar to our cohort but longer than that in the ADHERE registry, which was 4.2 days.[16] In addition, Asian patients had a higher in-hospital mortality rate of 4.8% in the ADHERE-AP registry compared with 3.2% in the ADHERE registry.[16] Interestingly, in-hospital mortality was 1.88% in our cohort. This lower mortality rate may reflect improvements in heart failure management and outcomes over time, because our patients were recruited in 2008−2013 whereas those in the ADHERE databases were recruited in 2005−2008.

Recognizing the attendant differences between various ethnicities and cohorts highlights the importance of validating the OPTIMIZE-HF risk score in an Asian cohort. In the present study, the original OPTIMIZE-HF risk score provided accurate prediction of in-hospital mortality in a multiethnic Asian cohort comprising predominantly of Chinese, Malay, and Indian patients, with a C-statistic of 0.739. There was no significant difference between predicted and observed probabilities. To improve the risk model, different coefficients for the same OPTIMIZE-HF variables were derived from our Asian cohort. The modified OPTIMIZE-HF model had a fairly similar C-statistic of 0.741, but significant difference between predicted and observed probabilities were noted. The modified model tended to underestimate risk at the extremes (lowest and highest ends) of risk. In part, this may be due to the lower event rates in our

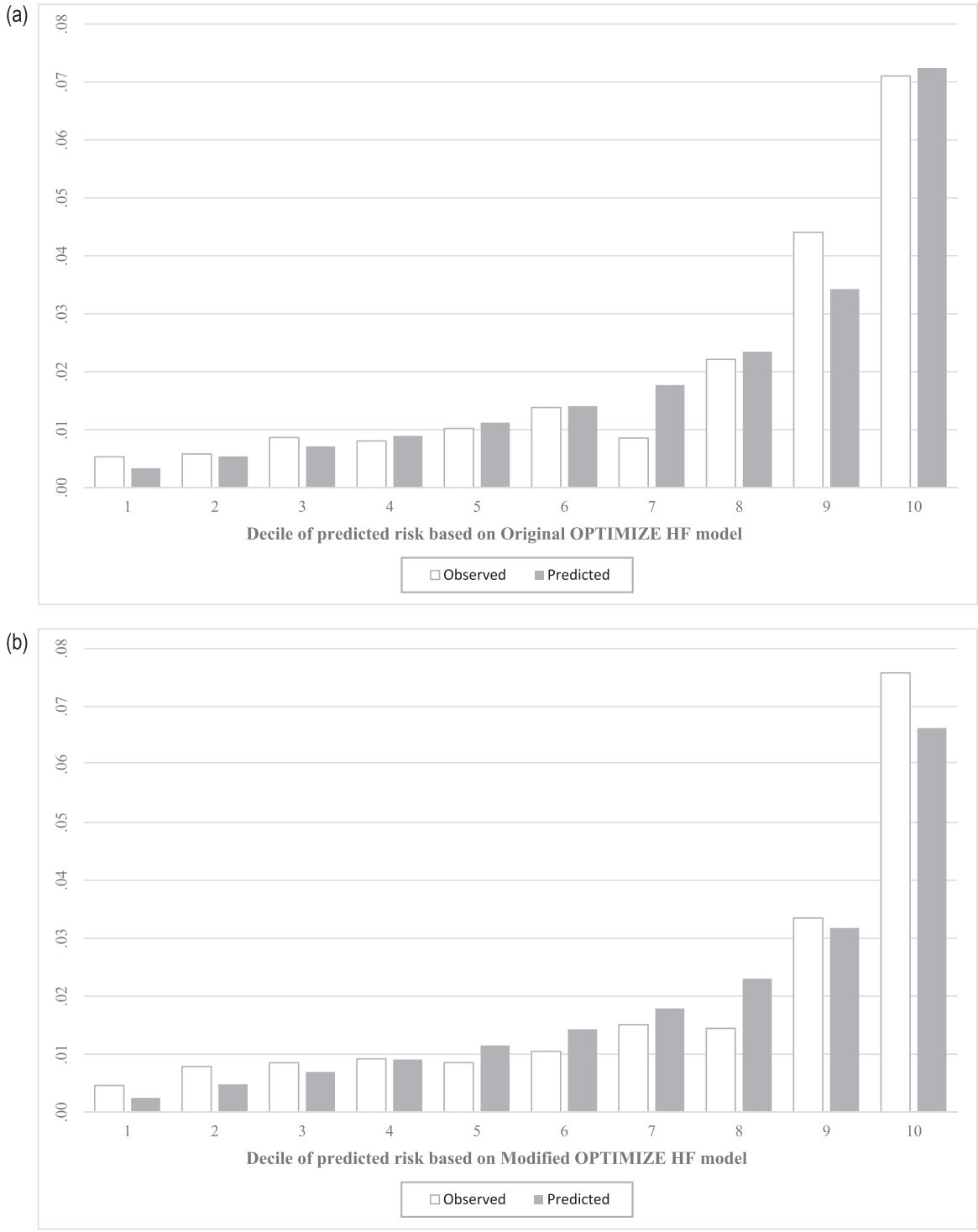

Fig. 1. Observed vs predicted in-hospital mortality in (a) the original OPTIMIZE-HF model and (b) the modified OPTIMIZE-HF model. The horizontal axis shows grouping by deciles of risk determined with the use of the respective risk models. The vertical axis shows actual observed versus predicted mortality.

cohort (in-hospital mortality of 1.88% vs 3.8% in the OPTIMIZE-HF cohort4).

The performance of the original OPTIMIZE-HF model in our Asian cohort compares favorably with the existing literature. The OPTIMIZE-HF investigators previously applied their model to Western patient populations from the ADHERE and the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) databases to obtain C-statistics of 0.746 and 0.756, respectively.[4] These are fairly similar to our C-statistic of 0.739. Other well known risk scores, such as the Get With the Guidelines−Heart Failure model,[5] also

achieved a similar C-statistic of ~0.75. In the ADHERE risk model, a simple model involving 4 variables (urea, age, systolic blood pressure, and age) achieved a C-statistic of only ~0.67−0.69, whereas a more complicated model consisting of 28 variables achieved a C-statistic of about 0.76.[6]

Study Limitations

Several limitations exist. First, bias may have arisen from missing data but only ~10% of cases were excluded from analysis owing to missing OPTIMIZE-HF variables (Supplemental Fig. 1). Although we examined in-hospital mortality in 3 major Asian ethnicities (Chinese, Malay, and Indian) in Singapore, these populations may not be fully representative of their counterparts in other countries and of other Asian ethnicities. Finally, only in-hospital mortality was assessed. Other clinically important outcomes, such as postdischarge mortality and rehospitalizations, will be the work of future studies.

Conclusion

We provide the first independent validation of the OPTIMIZE-HF risk in an Asian population. This risk model was shown to perform reliably in our Asian cohort and will potentially provide clinicians with a useful tool to identify high-risk heart failure patients for more intensive management.

Disclosures

None.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.cardfail.2019.02.016.

References

1. Passantino A, Monitillo F, Iacoviello M, Scrutinio D. Predicting mortality in patients with acute heart failure: Role of risk scores. World J Cardiol 2015;7:902–11.
2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123–33.
3. Lam CS. Heart failure in southeast Asia: facts and numbers. ESC Heart Failure 2015;2:46–9.
4. Abraham WT, Fonarow GC, Albert NM, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 2008;52:347–56.
5. Peterson PN, Rumsfeld JS, Liang L, et al. 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.
6. Fonarow GC, Adams Jr KF, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293:572–80.
7. O'Connor CM, Mentz RJ, Cotter G, et al. The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction. Eur J Heart Fail 2012;14:605–12.
8. Auble TE, Hsieh M, Gardner W, et al. A prediction rule to identify low-risk patients with heart failure. Acad Emerg Med 2005;12:514–21.
9. Lee DS, Stitt A, Austin PC, et al. Prediction of heart failure mortality in emergent care: a cohort study. Ann Intern Med 2012;156:767–75. w-261, w-2.
10. Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. N Engl J Med 1999;340:609–16.
11. Mentz RJ, Roessig L, Greenberg BH, et al. Heart failure clinical trials in east and southeast Asia: understanding the importance and defining the next steps. JACC Heart Fail 2016;4:419–27.
12. Singapore Department of Statistics. Monthly digest of statistics Singapore. February 2013. https://www.singstat.gov.sg.
13. Ministry of Health. Admissions and outpatient attendances. 2015. https://www.moh.gov.sg/resources-statistics/singapore-health-facts/admissions-and-outpatient-attendances. Accessed 31 December 2015.
14. Yap J, Sim D, Lim CP, et al. Predictors of two-year mortality in Asian patients with heart failure and preserved ejection fraction. Int J Cardiol 2015;183:33–8.
15. Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
16. Atherton JJ, Hayward CS, Wan Ahmad WA, et al. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International−Asia Pacific). J Card Fail 2012;18:82–8.