Profiles of heart failure in the western region of Nepal: prognostic implications of the MELD-XI score

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Abstract

Background: The demographic profile of heart failure (HF) is important to understand for its effective management and liver dysfunction has got prognostic impact on its outcome. We aimed to look for the demographic profile of HF and find out the predictive role of model for end-stage liver disease-XI (MELD-XI) score such that its prognostic implications in HF could be determined in the western Nepal.

Methods: Among 264 consecutive hospitalized HF patients, demographic profile was recorded prospectively and the patients were followed up till 3 months with recording of the composite end-points, which were defined as adverse outcomes measured in terms of all-cause death and hospital re-admission. The MELD-XI score was calculated as 11.76 (loge creatinine)+5.112 (loge total bilirubin)+9.44 and its predictive role in the adverse outcomes in HF was determined.

Results: Among 264 patients, the causes of HF were ischemic (29.5%), hypertensive (24.6%), dilated cardiomyopathy (21.6%), cor-pulmonale (15.5%) and valvular (8.7%), and 27.7% patients had adverse outcomes (re-admission 20.1% and all-cause death 7.6%). The prevalence of history of hypertension and diabetes in HF was 54.2% and 14.8%, respectively. The overall mean MELD-XI score was 10.8 (±2.1; range 6.3-18.8); the mean score was <10 in patients with no adverse outcome, >13 in patients with adverse outcome and >15 in patients who died. In univariate analysis, the MELD-XI score was found to be a significant predictor of adverse outcomes in HF with adjusted R² of 0.928 (P<0.001). The logistic regression analysis showed that the adverse outcome of HF could be predicted by the combination of MELD-XI score, ejection fraction, New York Heart Association functional class and age (Nagelkerke’s pseudo R² 0.935) with beta coefficient of MELD-XI being 3.79 (p<0.001) and that of ejection fraction being -0.19 (P 0.009); the Hosmer-Lemshow test showed p value of 1.0 (chi-square value of 0.494) indicating the goodness of fit for our logistic regression model. The area under receiver operating curve of MELD-XI score for adverse outcomes in HF was 0.993 (P<0.001).

Conclusion: Ischemic and hypertensive heart diseases were the common causes of HF in western region of Nepal. The MELD-XI score was an excellent predictor of hospital re-admission and all-cause death in the patients of HF and could be an important prognostic tool in the patients of HF. Further study with a large sample is required to establish the predictive role of increased MELD-XI score on adverse outcome of HF.

Keywords: Predictor, MELD-XI score, heart failure, Nepal

Introduction

Heart failure (HF) is a common clinical condition caused by cardiac dysfunction, and is associated with high morbidity and mortality [1-4]. It is estimated that 26 million people have HF worldwide [5], and is widespread in aging populations across the world [6]. The HF is a highly lethal disease, with a median survival time of 1.7 years in men and 3.2 years in women and a 5-year survival rate of 25% in men and 38% in women [7]. Sophisticated scoring models have been devised for the prediction of the outcome of HF such as Heart Failure Survival Score (7 variables: clinical findings, laboratory parameters and specific medical therapy) [8] and the Seattle Heart Failure Model (24 variables: clinical findings, laboratory parameters, specific medical and device therapy) [9]. Another scoring system has studied the predictors of mortality of HF, which can be quantified in an integer score [10].
The models have categorized the HF patients into low-, medium- or high-risk groups based upon the points obtained in the scoring system. The medium-risk category has been the most difficult group for the prediction of outcome. One of the methods for predicting the outcome of HF could be the application of model for end-stage liver disease (MELD) score used in the liver disease patients [11]. As hepatic congestion is one of the systemic effects of HF, hepatic dysfunction can identify a HF patient population at risk for worse outcomes, particularly death. Since the HF patients are likely to be receiving oral anticoagulants and MELD scoring system includes INR as one of the variables, the other alternative scoring system MELD-XI (MELD-excluding INR) would be more valuable in predicting the outcome of HF patients. We aimed to look for the demographic profile of HF and find out the predictive role of model for end-stage liver disease-XI (MELD-XI) score such that its prognostic implications in HF could be determined in the western Nepal.

Methods
A total of 264 consecutive patients presented with HF in Manipal Teaching Hospital, Pokhara, a tertiary referral hospital of the western region of Nepal, were enrolled in the study. The HF was diagnosed according to the Framingham criteria for the diagnosis of heart failure which consist of the concurrent presence of either 2 major criteria or 1 major and 2 minor criteria [7]. The New York Heart Association (NYHA) classification system was also used to categorize HF on a scale of I to IV NYHA [12].

Demographic profile of the patients was recorded prospectively. The patients were followed up till 3 months with recording of the composite end-points, which were defined as adverse outcomes measured in terms of all-cause death and hospital re-admission. Echocardiography, electrocardiography (ECG), chest X-ray, laboratory parameters (white blood count, hemoglobin, random blood sugar, blood urea, serum creatinine, sodium, potassium, total cholesterol, total bilirubin, aminotransferase, proteinurea) and other necessary investigations were done to define the characteristics of HF. The causes of HF were determined and the medical history including hypertension, diabetes, chronic obstructive pulmonary disease (COPD), sepsis or clinically relevant infection, prior myocardial infarction (MI), smoking and alcohol consumption was recorded.

The HF caused by ischemic heart disease was diagnosed by the clinical features of HF supported by the past history of MI, ischemic changes in ECG and regional wall motion abnormality in Echocardiogram. The hypertensive heart disease was regarded as a cause of HF when hypertension was the sole cause of HF supported by features of left ventricular hypertrophy in ECG and Echocardiogram. When hypertension was associated with other medical conditions causing HF such as ischemic heart disease, then hypertension was recorded as a co-existing medical history. Dilated cardiomyopathy (DCM), cor-pulmonale and valvular heart disease were also diagnosed on the basis of specific Echocardiographic features of the respective diseases. The secondary causes of DCM were excluded after a thorough investigation.

The cause of sepsis or clinically relevant infection was documented based upon the growth of microorganism in the blood or sputum or urine. The alcohol consumption was regarded as significant based upon the CAGE criteria [13].

The informed consent was taken from the patient and the study protocol was approved by the Institutional Review Board of the hospital.

Liver dysfunction was looked for in each patient of HF. The MELD score was not calculated in the HF patients because it required International Normalized ratio (INR) for its final result, but most of the patients with HF were having anticoagulants; so, the interpretation of INR would not be accurate. Hence, MELD-XI score (function of serum creatinine and total bilirubin, excluding INR), calculated as 11.76 (log, creatinine) +5.112 (log, total bilirubin)+9.44, was determined in the HF patients, because the study has showed that MELD-XI, despite omission of INR, is nearly as accurate as MELD in predicting short-term survival in cirrhosis [14].

All the variables were taken at the time of initial presentation of the patient to predict the adverse outcomes in HF. The statistical analysis was done with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). The P value of less than 0.05 was considered statistically significant.

Results
Among 264 HF patients [male 40.5% and female 59.5%; overall mean age 63.7 years ±15.5; range 14-92]), the mean age in male and female was 66.2 years ±14.5; range 21-92) and 61.9 years ±15.5; range 14-92), respectively. The distribution of the clinical characteristics of Framingham criteria of HF and NYHA functional classification of HF is shown in Tables 1 and 2.

The causes of HF were ischemic heart disease (29.5%), hypertensive heart disease (24.6%), dilated cardiomyopathy (21.6%), cor-pulmonale (15.5%) and valvular heart disease (8.7%) (Table 3). More than half (54.2%) of patients with HF had a history of hypertension which was more in male patients [P=0.005; odds ratio (OR) 1.5; 95% confidence interval (CI) 1.1-2.1], but among hypertensive patients, more female patients developed hypertensive heart disease leading to HF than male patients (P=0.002; OR 2.9; 95% CI 1.5-5.8); 31.8% of male patients developed hypertensive heart disease among 69 male hypertensive patients, and 58.1% of female patients developed hypertensive heart disease among 74 female hypertensive patients.

All patients with cor-pulmonale causing HF had chronic obstructive lung disease; moreover, all valvular heart disease patients with HF in the current study population were rheumatic in origin. The prevalence of diabetes in HF was 14.8%. The prevalence of atrial fibrillation was more in male [P=0.023 (OR 1.5; 95% CI
Table 1. Distribution of components of Framingham criteria for a diagnosis of HF.

| Major criteria                                      | Number (%) (n=264) | Minor criteria                                      | Number (%) (n=264) |
|-----------------------------------------------------|--------------------|-----------------------------------------------------|--------------------|
| Paroxysmal nocturnal dyspnea                        | 111 (42%)          | Nocturnal cough                                      | 134 (50.8%)        |
| Weight loss of 4.5 kg in 5 days in response to treatment of HF | 10 (2.6%)          | Dyspnea on ordinary exertion                         | 224 (84.8%)        |
| Neck vein distention                                | 170 (64.4%)        | A decrease in vital capacity by one third the maximal value recorded | 75 (28.4%)        |
| Rales                                               | 188 (71.2%)        | Pleural effusion                                     | 35 (13.3%)         |
| Acute pulmonary edema                               | 20 (7.6%)          | Tachycardia >120 bpm                                 | 40 (15.2%)         |
| Hepatocjugular reflux                               | 162 (61.4%)        | Bilateral ankle edema                                | 210 (79.5%)        |
| S3 gallop                                           | 60 (22.7%)         | --                                                  | --                 |
| Central venous pressure greater than 16 cm water    | 22 (8.3%)          | --                                                  | --                 |
| Circulation time of more than 25 seconds            | 35 (13.3%)         | --                                                  | --                 |
| Radiographic cardiomegaly                           | 161 (70%)          | --                                                  | --                 |
| Pulmonary edema, visceral congestion or cardiomegaly at autopsy | --                | Autopsy not performed                               | --                 |

Table 2. Distribution of HF patients according to the NYHA functional class.

| NYHA functional class at presentation | Male (n=264) | Female (n=264) | Total (n=264) | P value (by chi-square test) |
|---------------------------------------|--------------|----------------|--------------|-----------------------------|
| I                                     | 6 (5.6%)     | 6 (3.8%)       | 12 (4.5%)    | --                          |
| II                                    | 16 (15%)     | 27 (17.2%)     | 43 (16.3%)   | --                          |
| III                                   | 24 (22.4%)   | 35 (22.3%)     | 59 (22.3%)   | 0.886                       |
| IV                                    | 61 (57%)     | 89 (56.7%)     | 150 (56.8%)  | --                          |

Table 3. Distribution of causes of HF according to the gender.

| Causes of HF                      | Male (n=107) | Female (n=157) | Total (n=264) | P value (by chi-square test) |
|-----------------------------------|--------------|----------------|--------------|-----------------------------|
| Ischemic heart disease            | 40 (37.4%)   | 38 (24.2%)     | 78 (29.5%)   | --                          |
| Hypertensive heart disease        | 22 (20.6%)   | 43 (27.4%)     | 65 (24.6%)   | --                          |
| Dilated cardiomyopathy            | 23 (21.5%)   | 34 (21.7%)     | 57 (21.6%)   | 0.203                       |
| Cor-pulmonale due to COPD         | 14 (13.1%)   | 27 (17.2%)     | 41 (15.5%)   | --                          |
| Valvular heart disease            | 8 (7.5%)     | 15 (9.6%)      | 23 (8.7%)    | --                          |

1.1-2.0)], whereas that of sepsis or clinically relevant infections such as urinary and respiratory tract infection were more in female [P=0.034 (OR 1.3; 95% CI 1.0-1.5)]. The distribution of medical history in the patients of HF is shown in Table 4. The characteristics including vital signs and laboratory parameters of the patients of HF are shown in Table 5.

In female, the left ventricular internal diameter in diastole (LVIDd) was more likely to be less than 6.5 cm, but when LVIDd was more than 6.5 cm, it was more prevalent in male (p=0.008). The distribution of Echocardiographic parameters in the patients of HF is shown in Table 6.

After a mean follow-up of 3 months, 70 patients (27.7%) had adverse outcome (re-admission 20.1% and all-cause death 7.6%). The overall mean MELD-XI score in HF patients was 10.8 (±2.1; range 6.3-18.8); the score was 9.7 (±0.9; range 6.3-12.4) in HF patients with no adverse outcome, 13.7 (±1.6; range 10.3-18.8) in HF patients with adverse outcome and 15.5 (±1.5; range 13.5-18.8) in HF patients who died. The distribution of MELD-XI score among male and female patients were similar (P>0.05). The distribution of MELD-XI score in the patients of HF is shown in Table 7.

The univariate analysis showed that MELD-XI score was a significant predictor of hospital re-admission and all-cause death with adjusted R² 0.928 (P<0.001). The logistic regression analysis showed that the adverse outcome of HF could be predicted by the combination of MELD-XI score [B coefficient 3.79, odds ratio (OR) 44.02, 95% confidence interval (CI) 9.44-205.25; P<0.001], ejection fraction [B coefficient -0.19, OR 0.83, 95% CI 0.72-0.95; P 0.009], NYHA functional class [P>0.05] and age [P>0.05] with Nagelkerke’s pseudo R² of 0.935 (Cox and Snell pseudo R² of 0.648) and P value of Omnibus test of model coefficient being <0.001; the Hosmer-Lemshow test showed p value of 1.0 (chi-square value of 0.494) indicating the goodness of fit for our logistic regression model. However, other variables, taken from the demographic profiles, were not statistically significant to predict the adverse outcomes of HF. Logistic regression analysis for the prediction of adverse
outcome of HF is shown in Table 8. The area under receiver operating curve for adverse outcome with MELD-XI score was 0.993 (P<0.001), which showed that the increasing level of MELD-XI score had an excellent correlation with the adverse outcomes of HF.

Discussion
It has been reported that a relative risk reduction of HF of 29% to over 50% occurs after the treatment of hypertension [15,16]. Our study showed that more than half of HF patients had history of hypertension, and hence, the proper treatment of hypertension could control the increasing burden of HF in Nepal.

It is believed that coronary artery disease (CAD) is the underlying cause in approximately two thirds of patients with HF and low EF [17]. The study done in US and Italy showed ischemic heart disease as the commonest cause of HF in 62% and 40%, respectively [18,19]. Even in the patients of HF with

Table 4. Prevalence of medical history in the patients of HF.

| Medical history                          | Male (n=107) | Female (n=157) | Total (n=264) | P value (by chi-square test) |
|-----------------------------------------|--------------|----------------|---------------|-----------------------------|
| Hypertension                            | 69 (64.5%)  | 74 (47.1%)     | 143 (54.2%)   | 0.005 (OR for male 1.5; 95% CI 1.1-2.1) |
| Sepsis or clinically relevant infection | 23 (21.7%)   | 53 (33.8%)     | 76 (28.9%)    | 0.034 (OR for female 1.3; 95% CI 1.0-1.5) |
| Atrial fibrillation                     | 30 (28.3%)   | 26 (16.6%)     | 56 (21.3%)    | 0.023 (OR for male 1.5; 95% CI 1.1-2.0) |
| COPD                                    | 15 (14.2%)   | 30 (19.1%)     | 45 (17.1%)    | 0.295                       |
| Diabetes                                | 11 (10.4%)   | 28 (17.8%)     | 39 (14.8%)    | 0.095                       |
| Prior MI                                | 17 (16%)     | 13 (8.3%)      | 30 (11.4%)    | 0.052 (OR for male 1.5; 95% CI 1.0-2.1) |
| Smoker                                  | 73 (68.2%)   | 105 (66.9%)    | 178 (67.4%)   | 0.819                       |

Table 5. Characteristics including vital signs and laboratory parameters of the patients of HF.

| Vital signs and laboratory data at presentation | Male (n=107) | Female (n=157) | Total (n=264) |
|-------------------------------------------------|--------------|----------------|---------------|
| SBP (mean; mm Hg)                               | 107.7        | 105.1          | 106.2         |
| HR (mean; beats/minute)                         | 110.6        | 106.7          | 108.3         |
| WBC (mean; /cmm)                                | 10269.7      | 10569.3        | 10447.4       |
| Hb (mean; g/dl)                                 | 12.8         | 12.8           | 12.8          |
| RBS (mean; mg/dl)                               | 118.3        | 116.2          | 117.1         |
| Blood urea (mean; mg/dl)                        | 46.6         | 43.3           | 44.6          |
| Serum creatinine (mean; mg/dl)                  | 1.4          | 1.4            | 1.4           |
| Na+ (mean; mmol/l)                              | 139.2        | 138.4          | 138.7         |
| K+ (mean; mmol/l)                               | 4.1          | 4.6            | 4.4           |
| Total cholesterol (mean; mg/dl)                 | 175.4        | 179.3          | 177.7         |
| Bilirubin (mean; mg/dl)                         | 1.2          | 1.0            | 1.1           |
| AST (mean; U/l)                                 | 72.7         | 55.5           | 62.5          |
| ALT (mean; U/l)                                 | 62.0         | 50.5           | 55.2          |
| Proteinuria                                    | 26           | 28             | 54            |

The distribution of laboratory parameters were similar among male and female groups (P value>0.05 in all cases).

Table 6. Distribution of echocardiographic parameters in the patients of HF.

| LVIDd (cm) | Male (n=107) | Female (n=157) | Total (n=264) | P value (by chi-square test) |
|------------|--------------|----------------|---------------|-----------------------------|
| <5.5       | 14 (13.1%)   | 32 (20.4%)     | 46 (17.4%)    | --                          |
| 5.5-6.4    | 52 (48.6%)   | 94 (59.9%)     | 146 (55.3%)   | 0.008                       |
| 6.5-7.5    | 35 (32.7%)   | 28 (17.8%)     | 63 (23.9%)    | --                          |
| >7.5       | 6 (5.6%)     | 3 (1.9%)       | 9 (3.4%)      | --                          |

| PASP (mm Hg) | Male (n=107) | Female (n=157) | Total (n=264) | P value (by chi-square test) |
|--------------|--------------|----------------|---------------|-----------------------------|
| <30          | 31 (29%)     | 39 (24.8%)     | 70 (26.5%)    | --                          |
| 30-49        | 65 (60.7%)   | 96 (61.1%)     | 161 (61%)     | --                          |
| 50-74        | 5 (4.7%)     | 11 (7%)        | 16 (6.1%)     | 0.759                       |
| ≥75          | 6 (5.6%)     | 11 (7%)        | 17 (6.4%)     | --                          |

| EF % | Male (n=107) | Female (n=157) | Total (n=264) | P value (by chi-square test) |
|------|--------------|----------------|---------------|-----------------------------|
| ≥50 | 5 (4.7%)     | 6 (3.8%)       | 11 (4.2%)     | --                          |
| 40-49| 63 (58.9%)   | 106 (67.5%)    | 169 (64%)     | --                          |
| 30-39| 22 (20.6%)   | 28 (17.8%)     | 50 (18.9%)    | 0.500                       |
| <30 | 17 (15.9%)   | 17 (10.8%)     | 34 (12.9%)    | --                          |

LVIDd left ventricular internal diameter in diastole, PASP Pulmonary artery systemic arterial pressure, EF ejection fraction.
preserved EF, whom there is less often a history of prior MI, CAD has been documented on angiography or autopsy [20-22]. One study done in Bharatpur, Nepal showed that the causes of HF were CAD (36.5%), rheumatic heart disease (25.5%), dilated cardiomyopathy (14.5%), cor-pulmonale (12.2%), hypertensive heart disease (8.6%), and congenital heart disease 2.7% [23]. In our study done in western region of Nepal, the ischemic heart disease (29.5%) was still the commonest cause of HF followed by hypertensive heart disease (24.6%).

Our study showed that among hypertensive patients, more female patients developed hypertensive heart disease leading to HF; this could be because the female patients were not compliant with the prescribed anti-hypertensive drugs and had more uncontrolled hypertension in comparison to the male patients.

The mean age of presentation of HF in our study was 63.7 years, and this was comparable to the mean age (57 years) of HF patients of Bharatpur, Nepal [23]. The mean age of presentation of HF in Nepal was still less than that in the developed world, as shown in a study done in Minnesota, where the mean age of patients with HF was 77 years [24], but it was more than that in African country, as shown in a study done in Ghana, where the mean age was 42 years [25].

The reason for increased number of ischemic heart disease causing HF in our study could be because of the high percentage of patients consuming tobacco products, as evidenced by a fact that 67.4% of HF patients in our study were smokers. The epidemiology of developing countries such as South Asian region has shown that recently the burden of CAD has been increasing in this region [26], and this could be due to increasing consumption of tobacco product [27].

Another potential cause for increasing incidence of ischemic heart disease and hypertension causing HF in Nepal could be because of the “westernization” of the life style of people in developing world like Nepal, which has recently witnessed increasing prevalence of diseases of affluent society such as diabetes [28]. The contribution of valvular heart disease (rheumatic heart disease) for the HF, which was presumed to be the commonest cause of HF in developing countries like Nepal, was only the fifth common cause of HF, after ischemic heart disease, hypertensive heart disease, dilated cardiomyopathy and cor-pulmonale in our study. There might still be large number of undiagnosed HF patients with rheumatic valvular heart disease in the rural area of Nepal, hence giving the picture of decreased number of valvular heart disease population in our study done in western region of Nepal. The variation in the frequencies of causes of heart failure could be due to the difference in the study population according to the geographical location.

Recently, the study has found that the liver dysfunction is frequent in HF and is characterized by a predominantly cholestatic enzyme profile that is associated with disease severity and prognosis [29]. Moreover, renal dysfunction has also been found to be common in the HF patients and indicates a poor prognosis [30]. Thus, both of liver and renal dysfunctions can have a direct effect on morbidity and mortality in the patients of HF. The scoring system, which uses only these parameters, has been utilized by MELD-XI scoring system and has been applied in patients surviving after Fontan surgery to predict the sudden death, death from HF or cardiac transplantation [31].

One study has looked for the effect of liver dysfunction on outcomes after ventricular assist device implantation and found that the MELD-XI was a viable alternative for assessing liver dysfunction in heart failure patients on oral anti-coagulation [32].

Another study has found that the MELD scoring system was an important predictor of the composite end points such as death/heart transplantation/ventricular assist device requirement in HF patients [33].

The MELD score has been found to be valuable to predict...
the operative mortality among patients who undergo heart transplantation [34]. The MELD score has also been used for prediction in patients undergoing tricuspid valve surgery [35].

Our study is the first one to look for MELD-XI scoring system in the adverse outcomes in the patients of HF from Asian region. We found that the mean MELD-XI score was significantly high in the patients of HF with adverse effect (mean score more than 13) and with all-cause mortality (mean score more than 15) in comparison to the patients of HF without adverse effect (mean score less than 10). Our study showed that the MELD-XI score was a significant predictor of hospital re-admission and all-cause death and had an excellent correlation with those adverse outcomes of HF. Hence, we propose that MELD-XI score could be an important prognostic tool to identify a HF patient at risk for worse outcomes determined by hospital re-admission and or all-cause death.

Our study was not without limitations. This study was limited by the relatively small sample size of patients (n=264) with HF. Coronary angiography could not be done for the diagnosis for coronary artery disease because of the unstable condition of the HF patients. While analyzing the MELD-XI score in adverse outcome of HF patients, the survival analysis could not be done because of the lack of prolonged follow-up of the patients. Nevertheless, the finding of the current study is robust in determining the predictive role of MELD-IX in the hospital re-admission and all-cause death in HF patients.

**Conclusion**

Our study clearly demonstrated that the ischemic and hypertensive heart disease were the leading causes of HF in the western region of Nepal. The MELD-XI score was an excellent predictor of hospital re-admission and all-cause death in the patients of HF and could be an important prognostic tool in the patients of HF. Further study with a large sample is required to establish the predictive role of increased MELD-XI score on adverse outcome of HF.

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

| Authors' contributions | UKS | VMA | RB | BB | DP | SG |
|------------------------|-----|-----|----|----|----|----|
| Research concept and design | ✓   | ✓   | ---| ---| ---| ---|
| Collection and/or assembly of data | ✓   | ✓   | ✓  | ✓  | ✓  | ✓  |
| Data analysis and interpretation | ✓   | ---| ---| ---| ---| ---|
| Writing the article | ✓   | ---| ---| ---| ---| ---|
| Critical revision of the article | ✓   | ---| ---| ---| ---| ---|
| Final approval of article | ✓   | ✓   | ✓  | ✓  | ✓  | ✓  |
| Statistical analysis | ✓   | ---| ---| ---| ---| ---|

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